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AMAÇ VE KAPSAM

Türk Yoğun Bakım Dergisi (eski adı Türk Yoğun Bakım Derneği Dergisi ISSN: 2146-6416), Türk Yoğun Bakım Derneği'nin süreli yayın organı olup yoğun bakım içerikli, yayın dili Türkçe ve İngilizce olan, bağımsız ve önyargısız hakemlik ilkelerine dayanan ulusal, periyodik bir dergidir. Türk Yoğun Bakım Dergisi Mart, Haziran, Eylül, Aralık aylarında olmak üzere yılda dört sayı çıkar. Ayrıca yılda bir kez özel sayı yayınlanır.

Türk Yoğun Bakım Dergisi'nin hedefi nitelikli, sürekli ve yoğun bakım konusunda özgün bir periyodik olarak klinik ve bilimsel açıdan en üst düzeyde derlemeler, olgu sunumları ve araştırmalar yayınlamaktır. Dergi, yoğun bakım alanı ile ilgili olan hekimler, anestezistler, cerrahlar, pediatristler ve bu alanla ilgili diğer uzmanlara yöneliktir.

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Açık Erişim, "[hakem değerlendirmesinden geçmiş bilimsel literatürün], İnternet aracılığıyla; finansal, yasal ve teknik engeller olmaksızın, serbestçe erişilebilir, okunabilir, indirilebilir, kopyalanabilir, dağıtılabilir, basılabilir, taranabilir, tam metinlere bağlantı verilebilir, dizinlenebilir, yazılıma veri olarak aktarılabilir ve her türlü yasal amaç için kullanılabilir olması"dır. Çoğaltma ve dağıtım üzerindeki tek kısıtlama yetkisi ve bu alandaki tek telif hakkı rolü; kendi çalışmalarının bütünlüğü üzerinde kontrol sahibi olabilmeleri, gerektiği gibi tanınmalarının ve alıntılanmalarının sağlanması için, yazarlara verilmelidir.

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AIMS AND SCOPE

Turkish Journal of Intensive Care (formerly called Journal of the Turkish Society of Intensive Care ISSN: 2146-6416) is the periodical of the "Turkish Society of Intensive Care" and it covers subjects on intensive care, being published in Turkish and English languages, and is an independent national periodical based on unprejudiced peer-review principles. Turkish Journal of Intensive Care is regularly published four times a year; in March, June, September and December In addition, an annual special issue is published.

The aim of the Turkish Journal of Intensive Care is to publish original periodic research papers of highest scientific and clinical value on intensive care, reviews, case reports. It is directed towards for interested in intensive care, physicians, anesthesists, surgeons, pediatricians, and any other specialists concerned with these fields.

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Türk Yoğun Bakım Dergisi, Türk Yoğun Bakım Derneği'nin yayın organıdır. Dergi dört ayda bir (Nisan, Ağustos, Aralık) yayınlanan bağımsız, uluslararası hakemli bir dergidir.

Türk Yoğun Bakım Dergisi'ne gönderilen yazılar çift-kör hakemliğe tabi tutulur. Dergi Türkçe ve İngilizce dillerinde makaleler yayınlar.

Türk Yoğun Bakım Dergisi'nin kısa adı "Turk J Intensive Care"dir. Kaynaklarda kullanılırken bu şekilde belirtilmelidir.

Yoğun bakım alanına ilişkin özgün deneysel ve klinik araştırmaları, olgu sunumlarını, yayın kurulu kararı ile istenmiş derlemeleri, editöryal yorumları, editöre mektupları ve ulusal yoğun bakım kongrelerinde sunulan bildiri özetlerini yayımlar. Dergide yayınlanacak yazıların seçimine temel teşkil eden hakem heyeti, dergide belirtilen danışmanlar ve gerekirse yurt içi/dışı otörler arasından seçilir.

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Türk Yoğun Bakım Dergisi makale başvuru ücreti ve ya makale işlem ücreti uygulamamaktadır.

Yazılar sadece online olarak kabul edilmektedir. Yazarların makale gönderebilmesi için web sayfasına (http://www.journalagent.com/tybdd/) kayıt olup şifre almaları gereklidir. Bu sistem online yazı gönderilmesine ve değerlendirilmesine olanak tanımaktadır.

Makale gönderimi yapılırken sorumlu yazarın ORCID (Open Researcher and Contributor ID) numarası belirtilmelidir. http://orcid.org adresinden ücretsiz olarak kayıt oluşturabilir.

Bu sistem ile toplanan makaleler International Committee of Medical Journal Editors (ICMJE), Index Medicus (Medline/PubMed) ve Ulakbim-Türk Tıp Dizini kurallarına uygun olarak sisteme alınmakta ve arşivlenmektedir.

Yayına kabul edilmeyen yazılar, sanatsal resimler hariç geriye yollanmaz.

Editör veya yardımcıları tarafından, etik kurul onayı alınması zorunluluğu olan klinik araştırmalarda onay belgesi (etik onay numarası ile birlikte), talep edilmektedir. Yazıların içeriğinden ve kaynakların doğruluğundan yazarlar sorumludur.

Yazarlar, gönderdikleri çalışmanın başka bir dergide yayınlanmadığı ve/veya yayınlanmak üzere incelemede olmadığı konusunda garanti vermelidir. Daha önceki bilimsel toplantılarda 200 kelimeyi geçmeyen özet sunumlarının yayınları, durumu belirtilmek koşulu ile kabul edilebilir. Tüm otörler bilimsel katkı ve sorumluluklarını bildiren toplu imza ile yayına katılmalıdırlar.

Hastalar mahremiyet hakkına sahiptirler. Belirleyici bilgiler, hasta isimleri ve fotoğraflar, bilimsel olarak gerekli olmayan durumlarda ve hasta (ebeveyn veya koruyucu) tarafından yayınlanmasına yazılı olarak bilgilendirilmiş bir onay verilmediği sürece yayınlanmamalıdır.

Bu amaçla, bilgilendirilmiş onay, hastanın yayınlanacak belirli bir taslağı görmesini gerektirir. Eğer gerekli değilse hastanın belirleyici detayları yayınlanmayabilir. Tam bir gizliliği yakalamak oldukça zordur ancak eğer bir şüphe varsa, bilgilendirilmiş onay alınmalıdır. Örneğin, hasta fotoğraflarında göz bölgesini maskelemek, yetersiz bir gizlilik sağlanmasıdır.

Yazarlar, takip edilen standartların, insan deneylerinden sorumlu komitenin (kurumsal ve ulusal) etik standartlarına ve 2013'de gözden geçirilmiş 1964 Helsinki Beyannamesine uygun olduğunu belirtmelidirler. Deney hayvanı ile olan çalışmalarda, yazarlar takip edilen standartların hayvan haklarına (laboratuvar hayvanlarının bakım ve kullanımı için rehber www.nap.edu/catalog/5140.html) uygun olduğunu ve hayvan etik komitesinin onayını aldıklarını belirtmelidirler. Etik kurul onayı ve bilgilendirilmiş onam formu alındığı araştırmanın "Gereç ve Yöntem" bölümünde belirtilmelidir.

Yazıların bilimsel ve etik sorumlulukları yazarlara, telif hakkı ise Türk Yoğun Bakım Dergisi'ne aittir. Yazıların içeriğinden ve kaynakların doğruluğundan yazarlar sorumludur. Yazarlar, yayın haklarının devredildiğini belirten onay belgesini (Yayın Hakları Devir Formu) yazıları ile birlikte göndermelidirler. Bu belgenin tüm yazarlar tarafından imzalanarak dergiye gönderilmesi ile birlikte yazarlar, gönderdikleri çalışmanın başka bir dergide yayınlanmadığı ve/veya yayınlanmak üzere incelemede olmadığı konusunda garanti vermiş, bilimsel katkı ve sorumluluklarını beyan etmiş sayılırlar.

Makale Değerlendirmesi

Dergiye yayımlanmak üzere gönderilen tüm yazılar 'iThenticate' programı ile taranarak intihal kontrolünden geçmektedir. İntihal taraması sonucuna göre yazılar red ya da iade edilebilir.

Tüm yazılar, editör ve ilgili editör yardımcıları ile en az iki danışman hakem tarafından incelenir. Yazarlar, yayına kabul edilen yazılarda, metinde temel değişiklik yapmamak kaydı ile editör ve yardımcılarının düzeltme yapmalarını kabul etmiş olmalıdırlar.

Makalelerin formatı Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication (http://www.icmje.org/) kurallarına göre düzenlenmelidir.

İncelemeye sunulan araştırmada olası bir bilimsel hata, etik ihlal şüphesi veya iddiasıyla karşılaşılırsa, bu dergi verilen yazıyı destek kuruluşların veya diğer yetkililerin soruşturmasına sunma hakkını saklı tutar. Bu dergi sorunun düzgün biçimde takip edilmesi sorumluluğunu kabul eder ancak gerçek soruşturmayı veya hatalar hakkında karar verme yetkisini üstlenmez.

Yayın Politikası ve Makale Yazım Kuralları aşağıda belirtilen maddeler "Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals (ICMJE Recommendations)" (2016, http://www.icmje.org/) temel alınarak hazırlanmıştır.

Araştırma makalelerinin hazırlığı, sistematik derleme, meta-analizleri ve sunumu ise uluslararası kılavuzlara uygun olmalıdır.

Randomize çalışmalar için; CONSORT (Moher D, Schultz KF, Altman D, for the CONSORT Group. The CONSORT statement revised recommendations for improving the quality of reports of parallel group randomized trials. JAMA 2001; 285:1987-91) (http://www.consort-statement.org/).

Sistematik derleme ve meta-analizlerin raporlamaları için; PRISMA [Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 2009; 6(7): e1000097] (http://www.prisma-statement.org/).

Tanısal değerli çalışmalar için; STARD (Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig LM, et al, for the STARD Group. Towards complete and accurate reporting of studies of diagnostic accuracy: the STARD initiative. Ann Intern Med 2003;138:40-4) (http://www.stard-statement.org/).

Gözlemsel çalışmalar için; STROBE (http://www.strobe-statement.org/).

Meta-analizleri ve gözlemsel çalışmaların sistematik derlemeleri için; MOOSE [Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting "Meta-analysis of observational Studies in Epidemiology" (MOOSE) group. JAMA 2000; 283: 2008-12].

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Yazının tümünün 5000 kelimeden az olması gerekmektedir. İlk sayfa hariç tüm yazıların sağ üst köşelerinde sayfa numaraları bulunmalıdır. Yazıda, konunun anlaşılmasında gerekli olan sayıda ve içerikte tablo ve şekil bulunmalıdır.

Başlık sayfası, kaynaklar, şekiller ve tablolar ile ilgili kurallar bu dergide basılan tüm yayın türleri için geçerlidir.

1) Başlık Sayfası (Sayfa 1)

Yazı başlığının, yazar(lar)ın bilgilerinin, anahtar kelimelerin ve kısa başlıkların yer aldığı ilk sayfadır.

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Türkçe ve İngilizce anahtar sözcükler ve kısa başlık da başlık sayfasında yer almalıdır.

Yazarların isimleri, hangi kurumda çalıştıkları ve açık adresleri belirtilmelidir. Yazışmaların yapılacağı yazarın adresi de ayrıca açık olarak belirtilmelidir. Yazarlarla iletişimde öncelikle e-posta adresi kullanılacağından, yazışmaların yapılacağı yazara ait e-posta adresi belirtilmelidir. Buna ek olarak telefon ve faks numaraları da bildirilmelidir.

Çalışma herhangi bir bilimsel toplantıda önceden bildirilen koşullarda tebliğ edilmiş ya da özeti yayınlanmış ise bu sayfada konu ile ilgili açıklama yapılmalıdır.

Yine bu sayfada, dergiye gönderilen yazı ile ilgili herhangi bir kuruluşun desteği sağlanmışsa belirtilmelidir.

2) Özet (Sayfa 2)

İkinci sayfada yazının Türkçe ve İngilizce özetleri (her biri için en fazla 200 sözcük) ile anahtar sözcükler belirtilmelidir.

Özet bölümü; Amaç, Gereç ve Yöntem, Bulgular, Sonuç şeklinde alt başlıklarla düzenlenir. Derleme, olgu sunumu ve eğitim yazılarında özet bölümü alt başlıklara ayrılmaz. Bunlarda özet bölümü, 200 kelimeyi geçmeyecek şekilde amaçlar, bulgular ve sonuç cümlelerini içermelidir.

Özet bölümünde kaynaklar gösterilmemelidir. Özet bölümünde kısaltmalardan mümkün olduğunca kaçınılmalıdır. Yapılacak kısaltmalar metindekilerden bağımsız olarak ele alınmalıdır.

3) Metin (Özetin uzunluğuna göre Sayfa 3 veya 4'den başlayarak)

Metinde ana başlıklar şunlardır: Giriş, Gereç ve Yöntem, Bulgular, Tartışma.

Giriş bölümü, çalışmanın mantığı ve konunun geçmişi ile ilgili bilgiler içermelidir. Çalışmanın sonuçları giriş bölümünde tartışılmamalıdır.

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Bulgular bölümü de çalışmanın tekrar edilebilmesine yetecek ayrıntıları içermelidir.

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c) Kitap Bölümü: Porter RJ, Meldrum BS. Antiepileptic drugs. In: Katzung BG, editor. Basic and clinical pharmacology. 6th ed. Norwalk, CN: Appleton and Lange; 1995. p. 361-80.

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e) Elektronik Formatta Makale: Morse SS. Factors in the emergence of infectious disease. Emerg Infect Dis [serial online] 1995 1(1):[24 screens]. Available from:s URL:http://www/cdc/gov/ncidoc/EID/eid.htm. Accessed December 25, 1999.

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ORIGINAL RESEARCH / *ÖZGÜN ARAŞTIRMA*

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Çağla Yazar,
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Tuğba Yanık Yalçın,
Pınar Zeyneloğlu

Evaluation of Sepsis and Extensively Drug Resistant Infections in Deceased Critically Ill Patients

Mortal Seyreden Kritik Hastalarda Çoklu İlaç Dirençli Enfeksiyonların ve Sepsisin Değerlendirilmesi

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ABSTRACT *Objective:* Sepsis due to the drug resistant infections is associated with the higher mortality rates in an intensive care unit (ICU). The aim of this study was to determine the demographic characteristics of the deceased critically ill patients, prevalence of the sepsis, and extensively drug resistant infectious-related (XDR) deaths within a year in the ICU.
Materials and Methods: The data of patients who died in the ICU between January 1, 2019 and 2020 was retrospectively analyzed.
Results: Out of 525 patients admitted to the ICU, 269 of them died. One hundred fifty-one of those deceased patients (56.1%) were in medical and 118 (43.9%) in the surgical ICU. Their mean age was 70.5±15 years and 126 (46.8%) of them were female. The mean Acute Physiology and Chronic Health Evaluation-II, Glasgow coma score, Sequential Organ Failure Assessment scores at ICU admission were 23.4±20.9, 9.8±4.4, and 8.2±3.6, respectively. A few reasons for the ICU admission were: respiratory failure (34.9%), neurologic dysfunction (19%), sepsis (17.8%), and cardiovascular failure (16%). Infection occurred in the 231 (85.9%) patients. Of the 109 (40.5%) deceased patients with the diagnosis of sepsis, 48 (40%) of them were admitted in the ICU with sepsis. The most common site of infection was the respiratory system (34.6%). Septic shock was seen in 170 patients (63.2%) and renal replacement therapy was needed in 61 (22.7%) of them. XDR developed in 34.6% of the deceased patients and was more frequent among those with an antibiotic usage before the ICU admission (p=0.02). The mean length of stay at hospital before the ICU admission and length of the ICU stay were 22±25.8 and 10.1±12.7 days, respectively. The number of the deceased medical patients were significantly higher than the surgical patients (p=0.018).
Conclusion: The deceased critically ill medical patients were higher than the surgical patients. A total of 40% of the deceased critically ill patients were diagnosed with a sepsis, and one third of them had XDR infection. XDR infections were more frequent among the patients with an antibiotic usage before the ICU admission.
Keywords: Extensively drug-resistant, sepsis, deceased critically ill patient, intensive care unit

ÖZ *Amaç:* İlaca dirençli enfeksiyonlara bağlı sepsis, yoğun bakım ünitesinde (YBÜ) yüksek mortalite oranları ile ilişkilidir. Bu çalışmanın amacı, YBÜ'de bir yıl içerinde ölen kritik hastaların demografik özelliklerinin, sepsis ve çoklu ilaç dirençli enfeksiyonlara bağlı (XDR) ölümlerin prevalansının belirlenmesidir.
Gereç ve Yöntem: 1 Ocak 2019-2020 tarihleri arasında YBÜ'de ölen hastaların verileri retrospektif olarak incelendi.
Bulgular: YBÜ'ye kabul edilen 525 hastadan 269'u öldü. Ölen hastaların 115'i (%56,1) dahili, 118'i (%43,9) cerrahi YBÜ'deydi. Yaş ortalamaları 70,5±15 yıl olup 126'sı (%46,8) kadındı. Yoğun bakıma yatışta ortalama Akut Fizyoloji ve Kronik Sağlık Değerlendirmesi-II, Glasgow koma skalası, Sıralı Organ Yetmezliği Değerlendirmesi skorları sırasıyla 23,4±20,9, 9,8±4,4 ve 8,2±3,6 idi. YBÜ'ye yatış nedenleri solunum yetmezliği (%34,9), nörolojik disfonksiyon (%19), sepsis (%17,8) ve kardiyovasküler yetmezlik (%16) idi. Enfeksiyon 231 (%85,9) hastada görüldü. Sepsis tanısı ile ölen 109 (%40,5) hastanın 48'i (%40) sepsis tanısı ile YBÜ'ye yatırıldı. En sık solunum sistemi enfeksiyonları saptandı (%34,6). Yüz yetmiş hastada (%63,2) septik şok görüldü ve bunların 61'inde (%22,7) renal replasman tedavisi gerekti. Ölen hastaların %34,6'sında XDR enfeksiyon gelişti ve YBÜ'ye yatmadan önce antibiyotik kullananlarda görülme sıklığı daha fazlaydı (p=0,02). YBÜ'ye

kabul edilmeden önceki ortalama hastanede kalış süresi ve YBÜ'de kalış süresi sırasıyla 22±25,8 ve 10,1±12,7 gün idi. Dahili YBÜ'de ölen hasta sayısı cerrahi YBÜ'de ölenlerden daha fazlaydı (p=0,018).
Sonuç: Dahili YBÜ'de ölen kritik hasta sayısı cerrahi YBÜ'de ölenlerden daha fazlaydı. Ölen kritik hastaların %40'ına sepsis teşhisi konuldu ve bunların 1/3'ünde XDR enfeksiyonu vardı. YBÜ'ye yatmadan önce antibiyotik kullanan hastalarda XDR enfeksiyonları daha sıktı.
Anahtar Kelimeler: Çoklu ilaç direnci, sepsis, ölen kritik hasta, yoğun bakım ünitesi

Introduction

Sepsis is a fatal syndrome that affects millions of people worldwide and life-threatening organ dysfunction due to a dysregulated host response to infection (1,2). The incidence of sepsis is increasing day by day and one of the most common causes of global mortality. Therefore, sepsis is an important public health problem with serious economic consequences. Its treatment is difficult and sepsis is one of the main causes of hospital and intensive care unit (ICU) deaths (3,4). Drug-resistant bacterial infections are one of the reasons that complicate the management of sepsis and increase mortality. There were many definitions of drug-resistant infections in the literature. Experts from the European Center for Disease and Control (ECDC) and the Centers for Disease Control and Prevention (CDC) have updated the definitions. Accordingly, multi-drug resistant defines the microorganism resistant to at least one of three or more antimicrobial agent categories; extensively drug-resistant (XDR); defines as nonsusceptibility to at least one agent in all but two or fewer antimicrobial categories. Pandrug resistant (PDR) defines as nonsusceptibility to all agents in all antimicrobial categories (5-7). Invasive procedures and usage of broad-spectrum antibiotics are associated with an increased incidence of sepsis and drug-resistant infections (6-8). The aim of this study was to determine the demographic and clinical characteristics of deceased critically ill patients, the prevalence of sepsis and XDR infectious-related deaths within 1 year in the ICU of Başkent University Medical Faculty Ankara Hospital.

Materials and Methods

The data of patients who died in the ICU of Başkent University Faculty of Medicine Ankara Hospital between January 1, 2019 and January 1, 2020 was retrospectively analyzed. Adult patients aged 18 years or more who died in ICU were included in the study. Patients younger than 18 years, who died within 24 hours of admission to ICU, who did not die in the ICU and whose data were not available were excluded. The following data were obtained from electronic medical and nursing records. The demographic characteristics and clinical characteristics (age, gender, comorbidities, transplantation, etc.), drugs used before ICU admission, reasons for ICU admission and severity scores [Acute Physiology and Chronic Health Evaluation (APACHE-II) score; Sequential Organ Failure Assessment (SOFA) score; Glasgow coma score (GCS)], incidence of infection, sepsis and XDR, focus of infection, septic shock, organ failures (change of consciousness, respiratory failure, cardiovascular failure and circulatory failure, acute kidney failure, acute liver failure), presence of vascular, urinary and drain catheters, intubation and mechanical ventilation characteristics, length of hospital and ICU stay of deceased critically ill patients were retrospectively analyzed. XDR strains were identified according to criteria defined by ECDC and CDC (5). Sepsis and septic shock were defined according to the 2020 surviving sepsis campaign (1). Acute kidney injury was identified on the basis to the Kidney Disease Improving Global Outcomes clinical practice guidelines (9).

Statistical Analysis

The statistical analysis was performed using The Statistical Package for Social Sciences 25.0 (version 25.0; SPSS Inc., Chicago, IL, USA). Frequencies were expressed as numbers (n) and percentages (%). Variables are expressed as mean values ± standard deviation. Categorical variables between the two groups were analyzed with the chi-square test. Values of $p<0.05$ were considered statistically significant. This study was approved by the Başkent University Institutional Review Board (project no: KA21/309).

Results

Of the 525 patients admitted to the ICU during the study period, of whom 269 died in the ICU. The mean age was 70.5±15.0 years (between 18 and 97 years) including 143 (53.2%) male and 126 (46.8%) female (Table 1). The mean APACHE-II score was 23.4±20.9, GCS was 9.8±4.4 and the SOFA score was 8.2±3.6 on ICU admission (Table 2). There were 151 patients (56.1%) in medical ICU and 118 patients (43.9%) in surgical ICU. Most of the patients were

admitted from other services (53.5%) within our hospital and emergency services (30.5%) (Table 1). Two hundred sixty (96.7%) of our patients had at least one comorbidity. Hypertension (130 patients, 48.3%) was the most common comorbidity and the others were malignancy (46.5%), cerebrovascular disease (35.7), immunosuppression (33.5%) and transplantation (2.6%). The reasons for ICU admission were respiratory failure (34.9%), neurologic dysfunction (19.0%), sepsis (17.8%), and cardiovascular failure (16.0%), respectively (Table 3). Two hundred forty two patients (90.0%) had central venous catheter, 55 patients (20.4%) had drain line, 238 patients (88.5%) had urinary catheterization. One hundred nine patients (40.5%) were followed up with a diagnosis of sepsis in the ICU. While 48 patients (44.0%) with sepsis were admitted to the ICU, 61 patients (55.9%) were diagnosed with sepsis during the follow-up in the ICU. Septic shock was seen in 170 patients (63.2%). The common focus of infection were the respiratory system (34.6%, n=93), genitourinary system (20.8%, n=56), blood stream infections (14.1%, n=38) and intraabdominal (10.0%, n=27), respectively. A total of 104 microorganisms were identified; 72 Gram-negative bacteria and 27 Gram-positive bacteria and 5 fungus. The infectious pathogens were *Klebsiella pneumoniae* (8.2%), *Enterococcus* spp. (5.6%), Extended-spectrum beta-lactamase *Escherichia coli* (5.2%), *Escherichia coli* (4.8%), *Pseudomonas aeruginosa* (4.5%), *Acinetobacter baumanii* (3.0%), respectively (Table 4). Nineteen percent of the patients had *Acinetobacter baumanii* colonization and 34.6% (n=93) had carbapenem resistance (XDR). Sixty-two (66.7%) patients with XDR infection used

Table 1. Demographic and clinical characteristics of patients

Variables	Total (n=269)
Age, years, mean ± SD, range, years	70.4±15.0 (18-97)
Sex	
Male	143 (53.2)
Female	126 (46.8)
Etiology	
Medical causes	151 (56.1)
Surgical causes	118 (43.9)
Admission from	
Emergency	82 (30.5)
Ward in hospital	144 (53.5)
From outer center	10 (3.8)
Others	33 (12.2)
Comorbidities	
Hypertension	130 (48.3)
Diabetes mellitus	87 (32.3)
Coronary artery disease	76 (28.3)
Obstructive pulmonary diseases	44 (16.4)
Malignancy	125 (46.5)
Cerebrovascular disease	96 (35.7)
Chronic kidney disease	48 (17.8)

SD: Standard deviation

Table 2. Severity scores on ICU admission of patients

Severtiy scores	Mean ± SD
APACHE-II score	23.4±20.9
SOFA score	8.2±3.6
GCS score	9.8±4.4

ICU: Intensive care unit, APACHE-II: Acute Physiology And Chronic Health Evaluation-II, SOFA: Sequential Organ Failure Assessment, GCS: Glasgow coma score, SD: Standard deviation

Table 3. The reasons to intensive care unit admission

Organ and system involvement	Number (%)
Respiratory system	94 (34.9)
Neurologic system	51 (19.0)
Cardiovascular system	43 (16.0)
Genitourinary system	10 (3.7)
Gastrointestinal system	6 (2.2)
Hematological system	3 (1.1)
Sepsis	48 (17.8)

Table 4. Types of infectious pathogens

Variables	Frequency (n)	Percent (%)
Patients with extensively drug resistant	93	34.6
Klebsiella pneumoniae	22	8.2
Pseudomonas aeruginosa	12	4.5
Acinetobacter baumanii	8	3.0
Proteus mirabilis	2	0.7
Extended-spectrum beta-lactamase-*Escherichia coli*	14	5.2
Escherichia coli	13	4.8
Enterococcus spp.	15	5.6
Staphylococcus aureus	11	4.1
Candida spp.	3	1.1
Aspergillus spp.	2	0.7

antibiotic before ICU admission. Presence of infection before ICU admission, central venous catheter, drain line and urinary catheter were associated with XDR infections (p=0.021, 0.001, 0.002, 0.044, respectively). While 37 (13.8 %) patients were isolated on ICU admission, 38 (14.1%) patients were isolated in the ICU. Fifty-one patients (19.0%) were not diagnosed with infection before ICU admission. There was an infection in 38.6% (n=104) of the patients while lying in the ward. Two hundred sixty four (98.1%) patients were intubated and 34 patients (12.6%) required tracheotomy. At the same time, mechanical ventilation were used in 226 patients (84.0%), and renal replacement therapy in 61 patients (22.7%) in the first 3 days.

The mean value of leukocyte, C-reactive protein and procalcitonin were 15.4±34.4 10^3/μL, 141.1±119.3 mg/dL and 9.1±15.7 ng/mL, respectively. There was no statistically significant difference between patients with and without XDR infection. The mean length of hospital stay was 12.3±21.6 days before ICU admission. The mean length of ICU and hospital stay were 10.1±12.7 and 22.0±25.8 days. Intubation was performed on the mean 2.2±3.8 day after ICU admission. The mean duration of intubation and mechanical ventilation were 4.8±4.2 and 7.1±10.0 days. The mean length of central venous catheter stay was 24.8±37.5 days. Patients with XDR infection had longer length of hospital stay before ICU admission, ICU-hospital stay. In this patient group, the number of days with intubation, mechanical ventilation and central venous catheter were higher than patients without XDR (p<0.05) (Table 5).

The 7 and 30 day mortality were 58.4% and 92.6%, respectively. The 30-day mortality rate of medical ICU (58.2%) was significantly higher than surgical ICU (41.8%) (p=0.018).

Discussion

In this study, we investigated the prevalence of sepsis and XDR infection in deceased critically ill patients for 1 year. Of the 525 patients admitted to the ICU during the study period, 269 deceased were evaluated. The deceased critically ill medical patients were higher than the surgical patients. Forty percent of deceased critically ill patients were diagnosed with sepsis and one third of them had XDR infection. XDR infections were more frequent among patients who used antibiotics, had infection and stayed in hospital before ICU admission, with central venous catheter, urinary catheter and drain line. The deceased patient with XDR infections had prolonged ICU-hospital stay and duration of intubation-mechanical ventilation. In our study, it was found that patients who died were mostly followed in the medical ICU. Orban et al. (10) presented that the mortality rate was higher in mixed (medical-surgical) ICU, most of the anticipited deaths were in the medical ICU. The number of organ failures was higher among anticipated death patients in Orban's study. This difference was thought to be related to the older age of our patients and the presence of more comorbidities in our study. At the same time, mortality rate was higher in medical ICU in the study of Ay et al. (11). Because, similar with our groups, they were older than 70 years and had more cardiopulmonary problems. Sepsis remain high-risk factor for mortality in critically ill patients. We presented that the the incidence of sepsis at ICU admission was 44%. Orban et al. (10) reported that the sepsis incidence was 28% and 63% of patients had central venous catheter. We thought that this high rate was related to the hospitalization, presence of infection and antibiotic usage of our patients before ICU admission. At the same time, our patients were older and had more comorbidities.

Table 5. Length of stay and outcomes of patients

	Mean ± SD			
	Total (n=269)	XDR (n=93)	Non-XDR (n=176)	p-value
Intubation time	4.8±4.2	5.2±0.5	3.2±0.2	<0.001
Duration of central venous catheter	24.8±37.5	37.5±2.8	36.2±3.7	0.006
Duration of MV	7.1±10.0	14.5±1.5	4.6±0.3	<0.001
LOS before ICU	12.3±21.6	27.5±2.8	17.5±1.3	0.038
LOS at ICU	10.1±12.7	17.6±1.8	6.1±0.4	<0.001
LOS at hospital	22.0±25.8	32.6±3.4	18.8±1.4	<0.001

SD: Standard deviation, XDR: extensively drug resistant, MV: mechanical ventilation, LOS: length of stay, ICU: intensive care unit

Invasive devices such as central venous or urinary catheters, or inadequate handwashing practices among healthcare workers, may cause the risk of infection in patients admitted to the hospital even for non-infectious reasons (4,10,12). A high number of our patients had central venous catheter and/or urinary catheterization. However, in our study, we did not investigate handwashing practices among healthcare workers. Further studies could meet this objective in the future. Antimicrobial resistance poses a major threat to patient's treatment as it leads to prolonged hospital-ICU stay, increased morbidity and mortality, and severe economic loss for patient and nation (13). We reported that 34.6% of deceased patients had XDR infection and infection before ICU admission, presence of central venous catheter, drain line and urinary catheter were associated with XDR infections. The patients with XDR infection had prolonged ICU and hospital stay. Longer duration of intubation and mechanical ventilation were required. Inappropriate and excessive usage of antibiotics and invasive procedures were common causes of drug-resistant infections have been presented (13,14). A clinical trial showed that receiving total parenteral nutrition, prior carbapenem use, and prior fluoroquinolone use were independently associated with XDR infections (8).

This study has some limitations. It was a retrospective study and had a small number of patients. It was conducted at a single center, which limits the generalizability of the results. Inclusion of only deceased patients is a limitation of the study for mortality rates. The data were collected from the digital patient records. There is a limitation for risk factors and a deficiency for identifying antibiotic types. Not all laboratory tests were done in all patients.

Conclusion

One of the most important causes of ICU death is sepsis and one of the causes of sepsis is drug-resistant infection. Forty percent of deceased critically ill patients were diagnosed with sepsis and one third of them had XDR infection. The deceased critically ill medical patients were higher than the surgical patients. XDR infections were associated antibiotic usage and hospital stay before ICU admission and invasive procedures (central venous catheter, drain line and urinary catheter, etc.). Preventing infections in ICU or hospital is most important than treatment. Determination and preventing risk factors for sepsis may reduce morbidity, mortality and economic losses.

Ethics

Ethics Committee Approval: This study was approved by the Başkent University Institutional Review Board (project no: KA21/309).

Informed Consent: Retrospective study.

Peer-review: Internally and externally peer-reviewed.

Authorship Contributions

Concept: H.Ş., P.Z., Design: H.Ş., P.Z., Data Collection and Process: F.İ.Y., Ç.Y., İ.U.O., T.Y.Y., Analysis or Interpretation: F.İ.Y., Ç.Y., İ.U.O., H.Ş., P.Z., Literature Search: F.İ.Y., Ç.Y., İ.U.O., T.Y.Y., Writing: F.İ.Y., H.Ş., T.Y.Y., P.Z.

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ORIGINAL RESEARCH / *ÖZGÜN ARAŞTIRMA*

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The Relationship Between Preoperative Prognostic Nutritional Index and Postoperative Mortality in Patients with Hip Fracture

İleri Yaş Kalça Kırığı Hastalarında Preoperatif Prognostik Beslenme İndeksinin Postoperatif Mortaliteyle İlişkisi

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ABSTRACT *Objective:* Hip fractures are an important health problem in geriatric patients. Preoperative estimation of mortality risk can be done by assessing malnutrition, establishing a perioperative treatment plan, determining the prognosis, and reducing morbidity and mortality. The prognostic nutritional index (PNI) is a simple, cost-effective, and easily applicable indicator of nutritional status in patients. This study aimed to determine the relationship between preoperative PNI and postoperative mortality in patients with hip fracture.
Materials and Methods: This prospective observational study included 183 patients aged 65-95 years who had I-IV American Society of Anesthesiologists physical status and were operated within the first 48 h after hip fracture. Patients were divided into two groups according to the 37.25 cutoff value of PNI. In total, 172 patients completed the study, of which 53 were in the low PNI group and 119 in the high PNI group.
Results: The length of hospital stay, postoperative delirium, and 3-month mortality were significantly higher in the low PNI group than in the high PNI group (p=0.035, p=0.001, p=0.0001, respectively).
Conclusion: Using PNI for diagnosing malnutrition in patients with hip fractures can help create an optimized treatment plan and reduce mortality. PNI is an easily calculated, objective, and inexpensive biomarker that can be used in routine screening.
Keywords: Prognostic nutritional index, hip fracture, mortality, delirium, malnutrition

ÖZ *Amaç:* Kalça kırıkları geriatrik hasta grubunda önemli bir sağlık sorunudur. Malnütrisyonun saptanması, perioperatif tedavi planının oluşturulması, prognozun belirlenmesi ve böylece morbidite ve mortalitenin azaltılması açısından önemlidir. Prognostik beslenme indeksi (Prognostic nutritional index, PNI), hastaların beslenme durumunun bir göstergesi olan basit, uygun maliyetli ve kolay uygulanabilir bir parametredir. Bu çalışmanın amacı, postoperatif kalça kırığı hastalarında preoperatif PNI ile mortalite arasındaki ilişkiyi incelemektir.
Gereç ve Yöntem: Bu prospektif gözlemsel çalışmaya, kalça kırığı sonrası ilk 48 saat içinde ameliyat edilen, Amerikan Anesteziyoloji Derneği skoru I-IV arası olan, 65-95 yaş arası 183 hasta dahil edildi. Hastalar PNI'nın 37,25 eşik değerine göre 2 gruba ayrıldı. Toplamda 172 hasta çalışmayı tamamladı: 53'ü grup düşük PNI'da ve 119'u grup yüksek PNI'da sınıflandı.
Bulgular: Hastanede kalış süresi grup düşük PNI'da anlamlı olarak daha yüksekti (p=0,035). Postoperatif deliryum grup düşük PNI'da anlamlı olarak daha yüksek bulundu (p=0,001). Üç aylık mortalite grup düşük PNI'da anlamlı olarak daha yüksekti (p=0,0001).
Sonuç: Rutin taramalarda kullanılabilecek kolay hesaplanabilen, objektif ve ucuz bir biyobelirteç olan PNI ile kalça kırıklarında malnütrisyon tanısı konarak optimize bir tedavi planı oluşturmak ve mortaliteyi azaltmak mümkün olabilir.
Anahtar Kelimeler: Prognostik beslenme indeksi, kalça kırığı, mortalite, deliryum, malnütrisyon

Introduction

The risk of osteoporosis increases with the decrease in bone mineral density with advancing age, and hip fractures occur as a result of low energy trauma (1). The incidence of hip fractures is an important health problem in the world with an aging population (2). Hip fractures with a 1-year mortality of 20-30% in the geriatric patient group fractures cause long intensive care unit and hospital stays (3). While the treatment and care process of hip fracture negatively affects the patient physically, psychologically and socially, it also creates a serious economic burden for the health system (4). Therefore malnutrition increases the postoperative complications shown in studies (5-7). Nutrition of the patient is important as it is a modifiable risk factor (8). Preoperative estimation of mortality risk by detecting malnutrition in hip fractures, establishing a perioperative treatment plan, determining the prognosis and reduce morbidity and mortality. The prognostic nutritional index (PNI) is calculated by serum albumin concentration and peripheral blood lymphocyte count. Its formula is 10 × serum albumin (g/dL) + 0.05 × total lymphocyte count (/mm^3) (9). The albumin concentration is an indicator of nutritional status associated with postoperative complications. Lymphocyte values may decrease with malnutrition, viral infections, autoimmune and inflammatory system activations. PNI is a simple, cost-effective and easily applicable parameter that has been frequently used in mortality, morbidity and prognosis studies in recent years to evaluate the immunological and nutritional status of patients in cancer surgery (9-12). To our knowledge, there are very few studies investigating the relationship of PNI in hip fracture patients (13,14). Therefore, the primary aim of this study was the relationship between preoperative PNI and 3-month mortality in postoperative hip fracture patients. Secondary aim of this study was the association of preoperative PNI and delirium.

Materials and Methods

This prospective observational study was conducted between January-March 2021, approved by the Institutional Board of İstanbul University, İstanbul Faculty of Medicine, Department of Orthopedics and Traumatology, with the number 21/01/2021-8. Patients were informed about the surgery, anesthesia, intensive care procedures, their participation to the study and the publication of the study, and their written consent was obtained. The study is reported according to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines (15). The study included hip fracture patients aged 65-95 years, with American Society of Anesthesiologists (ASA) physical status I-IV, operated within the first 48 hours after the fracture, without delirium and neurological disease in the preoperative period. Patients with hematological disease, liver pathologies, chronic kidney disease, patients who underwent general anesthesia, had insufficient follow-up data, and refused to participate in the study were excluded from the study. When the patients came to the operating room, routine monitoring (electrocardiogram, blood oxygen saturation, non-invasive blood pressure) was followed by radial artery cannulation so arterial blood pressure monitoring was performed. After mild/moderate sedation with 1.5 mcg/kg IV fentanyl under 4 lt/min mask O_2, hemispinal anesthesia was administered with 10 mg of hyperbaric bupivacaine through the L3-4 spinal space in the lateral position. The following variables were recorded on admission: demographic findings [age, gender, body mass index (BMI)], additional diseases before surgery; hypertension (HT), diabetes mellitus (DM), pulmonary pathologies (chronic obstructive pulmonary disease, asthma, interstitial pulmonary disease, atelectasis, obstructive sleep apnea syndrome), cardiac pathologies (coronary artery disease, congestive heart failure, atrial fibrillation, pacemaker/implantable cardioverter-defibrillator).

All patients were admitted and followed in the intensive care unit after surgery. No vasopressor/inotrope was used perioperatively. Postoperative mechanical ventilation or renal replacement therapy support was not required. Operation times, the amount of fluid given during the operation and blood transfusion, intensive care and hospital stays were recorded. Patients were followed up for 3-month mortality. The mental status of the patients at the preoperative and postoperative 48th hour was evaluated with the confusion assessment method (CAM) (16). The CAM method was validated in our country (17). Lymphocyte count and albumin values were recorded from the 1st day preoperative blood results and PNI was calculated with the formula 10 × serum albumin (g/dL) + 0.05 × total lymphocyte count (/mm^3) (9). Patients were divided into 2 groups according to the 37.25 cut-off value of PNI. C-reactive protein (CRP) and pro-BNP (B-type natriuretic peptide) values were recorded.

Statistical Analysis

Statistical analyses were performed with SPSS 21.0 (SPSS Inc, Chicago, IL, USA). All demographic data were analyzed using descriptive statistical methods (mean,

standard deviation, frequency). Comparisons between groups were performed using Student's t-test and chi-square test for normally distributed data and the Mann-Whitney U test for non-parametric data. A p-value of <0.05 was considered statistically significant. Receiver operating characteristic (ROC) curve analysis was executed to assess the predictive value of PNI for mortality, and the cutoff values were analyzed by Youden index.

If the true difference in the mean response of matched pairs is 3.94, a sample size of 164 patients achieved a power of 0.80 which allowed for the detection of a 10% PNI difference by using the Power Analysis Program (G-Power, P.S. version 3.1.2). Prior data indicate that the difference in the response of matched pairs is normally distributed with standard deviation 10.2. The type I error probability associated with this test of this null hypothesis is 0.05 (14).

Results

One hundred eighty threepatients with hip fractures who were operated under spinal anesthesia were eligible for the study and were divided into 2 groups, group low PNI and group high PNI, according to the PNI cut-off value. In total, 172 patients completed the study: 53 in group low PNI and 119 in group high PNI (Figure 1).

The mean PNI calculated from albumin and lymphocyte values was 40.12±6.32 and is shown in Table 1 as the demographic findings of the patients. There was no significant difference between the two groups in terms of age and gender (p>0.05). BMI was significantly lower in group low PNI (p=0.025). ASA scores were significantly higher in group low PNI (p=0.005) (Table 2). When the additional diseases of the patients are evaluated, there was no significant difference between the two groups in terms of preoperative HT, DM, pulmonary and cardiac

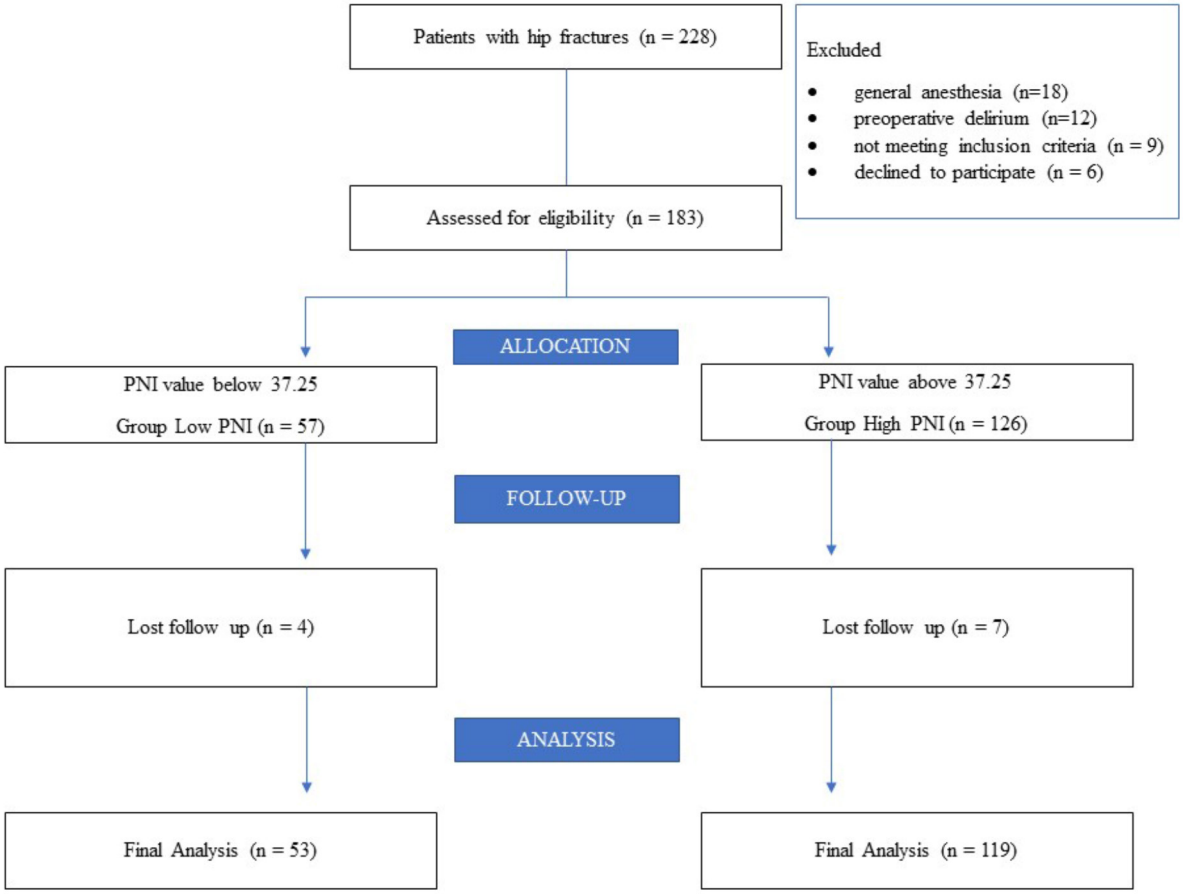

Figure 1. Flowchart of the hip fracture patients
PNI: Prognostic nutritional index

Table 1. Descriptive data of all patients			
			n=172
Age (years)			80.18±8.24
Sex	Male		55 (32.0%)
	Female		117 (68.0%)
BMI			26.02±4.97
ASA	1		5 (2.9%)
	2		62 (36.0%)
	3		88 (51.2%)
	4		17 (9.9%)
	5		0 (0%)
Preoperative hypertension	Yes		129 (75%)
	No		43 (25.0%)
Preoperative diabetes mellitus	Yes		117 (68.0%)
	No		55 (32.0%)
Preoperative pulmonary pathology	Yes		141 (82.0%)
	No		31 (18.0%)
Preoperative cardiac pathology	Yes		109 (63.4%)
	No		63 (36.6%)
CRP			64.88±59.53
PRo-BNP			3385.12±6433.01
Lymphocyte (/mm^3)			1157.61±549.41
Albumin (gr/dL)			3.40±0.66
Prognostic nutritional index			40.12±6.32
Perioperative fluid (mL)			1957.26±890.81
Perioperative blood transfusion (units)			0.2733±0.61
Operation time (hours)			1.83±0.64
Postoperative delirium	Yes		16 (9.3%)
	No		156 (90.7%)
Length of hospital stay (days)			13.41±5.34
Length of ICU stay (days)			2.33±1.36
3 months mortality		Yes	38 (22.1%)
		No	134 (77.9%)

BMI: Body mass index, ASA: American Society of Anesthesiologists, CRP: C-reactive protein, PRo-BNP: B-type natriuretic peptid, ICU: intensive care unit

pathologies (p>0.05). From the preoperative laboratory results, lymphocyte and albumin levels were significantly lower and CRP values were significantly higher in group low PNI (p=0.0001). pro-BNP was significantly higher in group low PNI (p=0.029) (Table 2).

There was no significant difference between the two groups in terms of operation times (p>0.05). The amount of fluid and blood transfusion given intraoperatively was similar in both groups (p>0.05). While there was no significant difference between the two groups in terms of intensive care unit length of stay (p>0.05), the length of hospital stay was significantly higher in group low PNI (p=0.035) (Table 2). Postoperative delirium was found to be significantly higher in group low PNI (p=0.001). 3-month mortality was significantly higher in group low PNI (p=0.0001) (Table 2). According to the ROC curve analysis, preoperative PNI level was a predictor for mortality with an area under the curve of 0.767 [95% confidence interval (CI)]=0.673-0.861,

Table 2. Comparison of group low-PNI and group high-PNI				
		Group low PNI n=53 (30.81%)	Group high PNI n=119 (69.28%)	p-value
Age (years)		81.67±8.81	79.51±7.92	0.112
Sex	Male	18 (34.0%)	37 (31.1%)	0.709
	Female	35 (66.0%)	82 (68.9%)	
BMI		24.74±6.25	26.59±4.19	0.025*
ASA	1	0 (%)	5 (4.2%)	0.005*
	2	11 (20.8%)	51 (42.9%)	
	3	33 (62.3%)	55 (46.2%)	
	4	9 (17.0%)	8 (9.9%)	
Preoperative hypertension	Yes	13 (24.5%)	30 (25.2%)	0.924
	No	40 (75.5%)	89 (74.8%)	
Preoperative diabetes mellitus	Yes	39 (73.6%)	78 (65.5%)	0.297
	No	14 (26.4%)	41 (34.5%)	
Preoperative pulmonary pathology	Yes	41 (77.4%)	100 (84.0%)	0.301
	No	12 (22.6%)	19 (16.0%)	
Preoperative cardiac pathology	Yes	37 (69.8%)	72 (60.5%)	0.242
	No	16 (30.2%)	47 (39.5%)	
CRP		92.48±59.86	52.95±55.52	0.0001*
Pro-BNP		5126.13±9087.01	2570.18±4547.35	0.029*
Lymphocyte (/mm^3)		859.62±363.65	1290.33±567.01	0.0001*
Albumin (gr/dL)		2.74±0.64	3.69±0.42	0.0001*
Perioperative fluid (mL)		1879.24±864.54	1992.01±903.68	0.445
Perioperative blood transfusion (units)		0.37 ±0.68	0.22±0.55	0.164
Operation time (hours)		1.88±59.60	1.80±50.66	0.0453
Postoperative delirium	Yes	11 (20.8%)	5 (4.2%)	0.001*
	No	42 (79.2%)	114 (95.8%)	
Length of hospital stay (days)		13.99±5.31	12.13±5.23	0.035*
Length of ICU stay (days)		2.15±1.06	2.41±1.48	0.393
3 months mortality	Yes	25 (47.2%)	13 (10.9%)	0.0001*
	No	28 (52.8%)	106 (89.1%)	

BMI: Body mass index, ASA: American Society of Anesthesiologists, ICU: intensive care unit, PNI: prognostic nutritional index, CRP: C-reactive protein, PRo-BNP: B-type natriuretic peptid, *p<0.05 is defined as statistically significant

p=0.0001) (Figure 2). The sensitivity and specificity were 0.791 and 0.342 respectively with the cut-off value of 37.25.

Discussion

In this prospective observational study, it was found that low PNI values calculated from preoperative laboratory results highly increased hospital stay length (p=0.035), postoperative delirium (p=0.001) and 3-month mortality (p=0.0001) in hip fracture patients operated under spinal anesthesia. The incidence of 3-month mortality ranges from 5-24% in hip fractures (18). This high mortality is related to the preoperative functional status and accompanying comorbidities of the patients as well as the trauma and surgical process (19). In this study, 3-month mortality was found to be 22.1% in all patient groups, consistent with the literature, but the low PNI group mortality was found to be as high as 47.2% (p=0.0001). Wilson et al. (20) by evaluating albumin and total lymphocyte counts separately, found that mortality in hip fractures with malnutrition was approximately

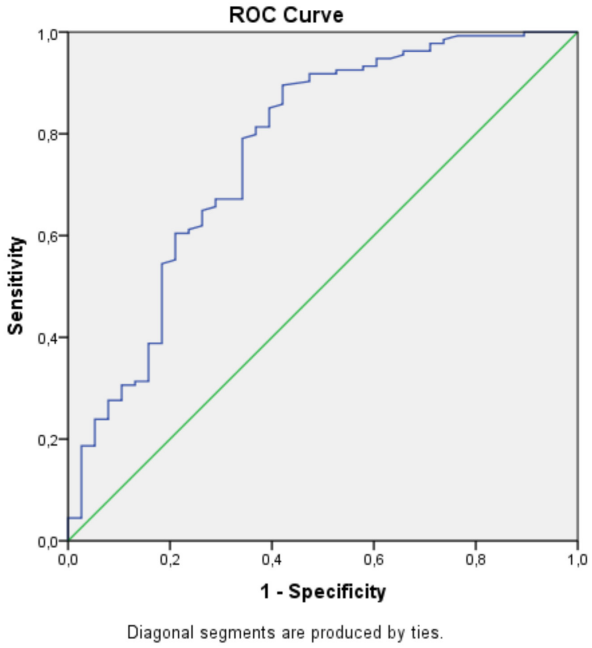

Figure 2. The ROC curve analysis
ROC: Receiver operating characteristic

25%. PNI calculated with the albumin lymphocyte formula reflects the balance between inflammation and nutrition. In this study, we concluded that PNI is more sensitive marker and can detect mortality more effectively than separately assessed albumin and total lymphocyte counts. Lu et al. (21) retrospectively demonstrated that low albumin and lymphocyte levels are prognostic factors in determining 1-year mortality in hip fractures with advanced age. Hypoalbuminemia may occur in synthesis disorders such as hepatocellular dysfunction and protein malnutrition, renal losses such as nephrotic syndrome, gastrointestinal losses such as protein-losing enteropathy, and increased catabolism such as sepsis (22). Lymphopenia can be seen in viral infections, autoimmune and inflammatory system activations and some types of gastrointestinal cancer, malnutrition and suppression of immunity. Although the exact mechanism is not understood, increased serum cortisol levels may cause a decrease in lymphocyte count (23). PNI biomarker, which we think can be used in routine screening of malnutrition in patients with hip fracture, has been shown to be an independent prognostic marker in various malignant tumors (9-12). In this paper, it was expected that BMIs would be low and ASA scores would be high in group low PNI as it indicated malnutrition (p=0.025, p=0.005, respectively). In accordance with the literature, albumin and lymphocytes were low, and CRP and pro-BNP were found to be significantly higher in group low PNI (p=0.0001, p=0.0001, p=0.0001, p=0.029, respectively) (24). Preoperative comorbidities, operation times, the amount of fluid and blood transfusion given intraoperatively was similar in both groups. Postoperative delirium and hospital stay length were also increased in group low PNI, that shown before in the study of Xing et al. (14) (p=0.001, p=0.035, respectively). The increase in post-fracture complications such as delirium, the deterioration of the general condition of the patients, prolongs the duration of care and increases the hospitalization period. The main limitation of this study is that it is based on data from a single center; therefore, prospective randomized controlled trials are required. The second limitation of our study is the small number of our sample group. Different results can be obtained in studies with larger patient groups.

Conclusion

In conclusion, malnutrition is an important factor increasing postoperative mortality in hip fractures. We think that it is possible to create an optimized treatment plan and reduce mortality by making the diagnosis of malnutrition in hip fractures with PNI, an easily calculated, objective and inexpensive biomarker that can be used in routine screening.

Ethics Committee Approval: The study was approved by the Institutional Board of İstanbul University, İstanbul Faculty of Medicine, Department of Orthopedics and Traumatology, with the number 21/01/2021-8.

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Authorship Contributions

Surgical and Medical Practices: İ.S., Y.S., H.D., Concept: N.C., D.B., D.A., M.I.B., Design: N.C., M.I.B., Data Collection and Process: D.B., İ.S., Analysis or Interpretation: N.C., Y.S., D.A., M.I.B., Literature Search: N.C., D.B., İ.S., Y.S., D.A., H.D., Writing: N.C., D.B., İ.S., Y.S., D.A., H.D., M.I.B.

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Results of 1,430 Patients Admitted to Intensive Care Unit with Suspicion of COVID-19 in Turkey's Capital-Ankara: A Single Center Study

Türkiye'nin Başkenti Ankara'da COVİD-19 Şüphesiyle Yoğun Bakıma Kabul Edilen 1,430 Hastanın Sonuçları: Tek Merkezli Çalışma

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ABSTRACT *Objective:* The patients admitted to coronavirus disease-2019 (COVID-19) intensive care units (ICUs) with the suspicion of COVID-19 in the first four months of the pandemic were evaluated both in diagnostics and according to periods of the pandemic.
Materials and Methods: The data of 1,430 patients admitted to the COVID-19 ICUs were recorded with the same algorithm in a single-center retrospectively. Patients were classified as COVID-19 and non-COVID-19 patients according to polymerase chain reaction results, radiological and clinical findings. Also, COVID-19 patients were compared as dying and surviving. Additionally, the data of patients admitted to COVID-19 ICUs during the onset of the pandemic and during the normalization period were also compared.
Results: Of 1,430 patients, 630 were included in the COVID-19 group and 800 in the non-COVID-19 group. While there was a significant difference in the mean age of the groups, there was no difference between the genders (p=0.001, p=0.262 respectively). The age in the COVID-19 and deceased group was higher than that in the survivors (p<0.001). The most common presenting symptom was dyspnea (51.2%), while hypertension's most common comorbidity (51.2%). During the normalization period, the rate of patients admitted to the ICU with the diagnosis of COVID-19 and the mortality rates in the ICU was higher.
Conclusion: The initial period of the pandemic was spent understanding COVID-19, which entered our lives as a mystery at the same time. It was a guiding period for us to treat patients more effectively while protecting the community and healthcare professionals.
Keywords: COVID-19, intensive care unit, mechanical ventilator, high flow nasal oxygen, mortality

ÖZ *Amaç:* Pandeminin ilk dört aylık döneminde koronavirüs hastalığı-2019 (COVİD-19) şüphesiyle, COVİD-19 YBÜ'lerine kabul edilen hastalar tanılarına ve dönemlere göre karşılaştırıldı.
Gereç ve Yöntem: Tek merkezde aynı algoritma ile COVİD-19 YBÜ'ye kabul edilen 1,430 hasta verisi retrospektif olarak kaydedildi. Hastalar polimeraz zincirleme reaksiyonu sonucu ile radyolojik ve klinik bulgulara göre COVİD-19 ve non-COVİD-19 hastalar olarak sınıflandırıldılar. Ayrıca COVİD-19 hastaları mortalite ve sağkalım açısından da karşılaştırıldı. Bunun yanında, pandeminin başlangıcı ve normalleşme döneminde COVİD-19 YBÜ'lerine kabul edilen hastaların verileri değerlendirildi.
Bulgular: Çalışmaya alınan 1,430 hastanın 630'u COVİD-19, 800'ü non-COVİD-19 gruptaydı. Yaş ortalamalarında anlamlı bir farklılık bulunurken, cinsiyetler arasında bir farklılık yoktu (p=0,001, p=0,262). COVİD-19 ölen grubun yaş ortalaması yaşayan gruptan daha yüksekti (p<0,001). En sık başvuru semptomu dispne (%51,2), en sık eşlik eden komorbidite hipertansiyon (%51,2) idi. Normalleşme döneminde "COVİD-19" tanısı ile yoğun bakıma kabul edilen hasta oranı ve yoğun bakımda mortalite oranı daha fazlaydı.
Sonuç: Pandemi başlangıç dönemi hayatımıza bir bilinmez olarak giren COVİD-19'u anlayabilmekle geçti ve aynı zamanda toplumu ve sağlık çalışanlarını koruyarak hastaları daha etkin bir şekilde tedavi etmemiz için yol gösterici bir periyod oldu.
Anahtar Kelimeler: COVİD-19, yoğun bakım ünitesi, mekanik ventilatör, yüksek akımlı nazal oksijen, mortalite

Introduction

A pandemic is defined as an epidemic occurring worldwide, or over a vast area, crossing international boundaries and usually affecting many people (1). The coronavirus disease-2019 (COVID-19) pandemic, which first appeared in China in December 2019 and is caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), has impacted all over the world. In Turkey, the first case was detected on March 11, 2020 (2).

The high rate of transmission of the disease caused an increase in the number of cases. Accordingly, the number of patients admitted to the hospital, the frequency of hospitalization, and the need for intensive care (3). COVID-19 can be asymptomatic or with symptoms similar to upper respiratory tract infection, and it can also cause symptoms that progress to respiratory failure and acute respiratory distress syndrome (ARDS) (4). Therefore, we now know that patients need supportive treatments that require nasal oxygen, high flow nasal oxygen (HFO), mechanical ventilators (MV), and even extracorporeal life support systems (5,6). One of the critical issues to be planned during the pandemic is determining areas such as the service and intensive care units where COVID-19 patients will be treated and the teams to work there. As recommended in the World Health Organization guide, in the COVID-19 pandemic, intensive care teams are established under the leadership of an experienced intensive care specialist in intensive care units. These teams consist of intensive care unit (ICU) specialists and other specialists and personnel, especially health workers who have previous intensive care experience or will specialize in this field (7). The hospital in which the study took place in a large hospital located in the capital city of Turkey, Ankara, with interconnected floors, six hospital buildings connected by the main mass in the middle, and each one of six hospitals has varying numbers of general and branch ICUs. During the pandemic, arrangements were made in inpatient services and intensive care units to treat patients diagnosed with COVID-19. Many patients from Ankara and surrounding provinces were hospitalized and admitted to the services and ICUs. In the literature, we could not find any study comparing the patients diagnosis with COVID-19 and non-COVID-19 patients admitted to a single-center and pandemic intensive care unit during the pandemic period. This study aims to evaluate and compare the demographic and clinical characteristics, intensive care and hospitalization times, intensive care support treatments, and mortality rates of patients admitted to COVID-19 ICUs with the suspicion of COVID-19 in the first four months of the pandemic, both according to diagnosis (COVID-19 and non-COVID-19), and in terms of pandemic periods (onset of pandemic and normalization period).

Materials and Methods

After the Ankara City Hospital Ethics Committee's approval (Ethics committee no: E1-20-527), all patients aged 18 years and older who were followed up in 14 COVID-19 ICUs between 19 March and 10 July 2020 were included in the study. Patient data were scanned and recorded retrospectively via the hospital ınformation management system.

The hospital where the study was conducted is a large health complex with many general and branch ICUs. All ICUs have 16 isolated and negative pressure rooms containing one bed each. On March 19th 2020, patients diagnosed with COVID-19 began to be admitted to the neurology-orthopedics hospital of the city hospital, which had the highest number of ICUs and beds (9 ICUs, 144 beds) the pandemic period. Then, in April 2020, COVID-19 patients were admitted to the general hospital with 80 beds and 5 ICUs. As of June 1st 2020, when the number of cases decreased and the normalization process began, only three general ICUs in the neurology-orthopedics hospital continued to accept COVID-19 patients while non-COVID-19 patients were hospitalized in the remaining 11 ICUs. Thus, patients with suspected or diagnosed COVID-19 were admitted to 14 ICUs with a total of 224 beds between March 19th, 2020 and May 31st, 2020, while they were admitted to 3 ICUs with 48 beds between June 1st, 2020 and July 10th, 2020. All ICUs had at least one intensive care specialist, and the nurse-patient ratio was 1:2. The presence of SARS-CoV-2 was confirmed by the polymerase chain reaction (PCR) method with oropharynx and nasopharynx swab or endotracheal aspiration samples. PCR results were classified as positive, negative, and patients with no PCR samples. The computed tomography (CT) findings of the thorax before admission to the ICU were classified as COVID-19 compatible, suspicious and incompatible. In the diagnostic classification, patients with positive PCR results and patients with negative PCR results but whose clinical and radiological findings were compatible with COVID-19 in the CT were considered as COVID-19. Other patients were accepted as non-COVID-19.

After all patients with suspected COVID-19 were admitted to the ICU, at least two PCR tests were taken from all patients at 24-hour intervals in the algorithm applied to decide which unit the patients would be transferred to during the transport phase. Patients with at least one positive PCR result who no longer needed intensive care were transferred to COVID-19 services. Patients with negative results for two consecutive PCRs were re-evaluated with the infectious diseases doctor. Those who had a continuing need for intensive care were transferred to the non-COVID-19 ICU. Those who no longer needed intensive care were transferred to the non-COVID-19 service. Patients who were accepted as COVID-19 were also divided into two groups: surviving (COVID-19 alive) and deceased (COVID-19 dead). Age, gender, symptom, comorbidity, Acute Physiology and Chronic Health Evaluation-II (APACHE-II) scores of the patients in the first 24 hours in the ICU were recorded. Nasal/mask oxygen, HFO, noninvasive mechanical ventilation (NIMV), invasive mechanical ventilation (IMV), hemodiafiltration or continuous renal replacement therapy (CRRT), extracorporeal membrane oxygenator (ECMO), vasopressor/inotrope requirements and the length of stay in the ICU were determined from the records. The unit where the patients were transferred to the ICU from (emergency department, COVID-19 service, non-COVID-19 service, another hospital), the length of stay in the service or intensive care unit before the intensive care unit, the length of stay in the COVID-19 ICU, where they are transferred from the ICU (COVID -19 service, non-COVID-19 service, non-COVID-19 ICU, home, external center, exitus), duration of hospitalization in the COVID-19 and non-COVID-19 service or non-COVID-19 ICU where they were transferred from the ICU, total length of ICU and hospital stay, ICU and hospital mortality rates were recorded. The number of patients hospitalized in ICUs was recorded daily. In addition, patients admitted to the ICU were classified according to 2 different periods: the onset of the pandemic (March 19th-May 31st, 2020) and the period when normalization began (June 1st, 2020-July 10th, 2020).

Statistical Analysis

Statistical analysis of the data obtained in the study was performed using the SPSS for windows 26.0 Statistical Package Program. Continuous variables were expressed as mean ± standard deviation. After evaluating the suitability of numerical data with normal distribution with Kolmogorov-Smirnov test, Student'st test was used to compare numerical data with normal distribution. The Mann-Whitney U test was used to compare the numerical data that did not fit the normal distribution. Categorical data were given as numbers and percentages. Chi-square test was used to compare categorical data. $P<0.05$ was considered significant.

Results

When the data of 1,430 patients who applied to 14 ICUs with the suspicion of COVID-19 between March 19th, 2020 and July 10th, 2020 were analyzed retrospectively, number of patients admitted to the ICU was highest on April 28th, 2020 (30 patients), while on June 2nd, 2020, no patient was admitted to the ICU (Figure 1). The mean age of all patients was 71.26, the number of males was 782 (54.7%), and the mean APACHE-II score was 17.42. Dyspnea (49.8%) was the most common symptom and hypertension (48.6%) was the most common comorbidity. Of all patients, 45.5% had mild clinical symptoms and 74.3% needed nasal/mask oxygen (Table 1). PCR results were positive in 308 (21.5%) of 1,430 patients. According to thoracic CT findings, 554 (38.8%) patients were compatible with COVID-19, 298 (20.8%) patients were incompatible with COVID-19, and 578 (40.4%) patients were suspected of COVID-19. Six hundred thirty patients constituted the COVID-19 group, with 308 patients with positive PCR results and 322 (22.5%) patients with negative PCR results but consistent with COVID-19 on thorax CT findings. A total of 800 patients with negative PCR tests and those with inconsistent or suspicious thoracic CT findings whose clinical findings were evaluated together with infectious diseases doctors were included in the non-COVID-19 group. The highest number of hospitalizations (203 patients) in the ICU with suspected COVID-19 were between 21st-30th April 2020, and the highest number of patients that were diagnosed with COVID-19 (81 patients) was between 11st-20th April, 2020 (Figure 2). The patients' intensive care and hospital mortality rates were 37.8% (n=541) and 38.1% (n=545), respectively. The gender distribution in hospital mortality was homogeneous, and the hospital mortality of all patients by gender in 10-day periods is shown in Figure 3.

When patients were divided into COVID-19 and non-COVID-19, the mean age and male sex ratios of the groups were 69.98 and 72.3 (p=0.001), 56.35%, and 53.38% (p=0.262), respectively. Fever, cough, and contact were significantly more frequent in the COVID-19 group (p=0.05, p=0.004, p=0.001, respectively). Other symptoms (edema, hemoptysis, hematemesis, vaginal bleeding, aspiration,

Table 1. Demographic and clinical characteristics of all patients, COVID-19, non-COVID-19, COVID-19 surviving and COVID-19 dying groups

Variables	All patients	COVID-19 n=630	Non-COVID-19 n=800	p	COVID-19 surviving n=365	COVID-19 dying n=265	p
Age*	71.26±15.3	69.98±15.3	72.3±15.3	0.001	67.44±16.4	73.40±12.8	<0.001
Female*	73.88±15	73.07±14.6	74.47±15.3	0.089	70.33±15.7	77.38±11.7	<0.001
Male*	69.09±15.3	67.59±15.3	70.33±15.1	0.006	64.98±16.6	70.83±13	0.001
Female (n), %	648 (45.3)	275 (43.65)	373 (46.62)	0.262	168 (46)	107 (40.4)	0.158
Male (n), %	782 (54.7)	355 (56.35)	427 (53.38)		197 (54)	158 (59.6)	
Symptoms	**n (%)**	**n (%)**	**n (%)**	**p**	**n (%)**	**n (%)**	**p**
Dyspnea	712 (49.8)	320 (51.2)	392 (48.7)	0.347	171 (46.8)	152 (57.4)	0.009
Fever	335 (23.4)	162 (25.9)	173 (21.5)	0.05	101 (27.7)	61 (23)	0.187
Chills/shivering	18 (1.3)	7 (1.1)	11 (1.4)	0.678	4 (1.1)	3 (1.1)	0.966
Cough	302 (21.1)	154 (24.6)	148 (18.4)	0.004	98 (26.8)	56 (21.1)	0.099
Sore throat	19 (1.3)	11 (1.8)	8 (1)	0.209	9 (2.5)	2 (0.8)	0.106
Myalgia/joint ache	30 (2.1)	13 (2.1)	17 (2.1)	0.967	10 (2.7)	3 (1.1)	0.161
Chest pain	46 (3.2)	15 (2.4)	31 (3.9)	0.123	9 (2.5)	6 (2.3)	0.870
Nausea	57 (4)	26 (4.2)	31 (3.9)	0.767	18 (4.9)	8 (3)	0.233
Vomiting	64 (4.5)	22 (3.5)	42 (5.2)	0.124	15 (4.1)	7 (2.6)	0.322
Stomach ache	37 (2.6)	12 (1.9)	25 (3.1)	0.161	9 (2.5)	3 (1.1)	0.227
Diarrhea	21 (1.5)	10 (1.6)	11 (1.4)	0.716	7 (1.9)	3 (1.1)	0.436
General disorder	209 (14.6)	87 (13.9)	122 (15.2)	0.512	48 (13.2)	41 (15.5)	0.409
Consciousness change	76 (5.3)	26 (4.2)	50 (6.2)	0.086	13 (3.6)	13 (4.9)	0.402
Headache	24 (1.7)	12 (1.9)	12 (1.5)	0.531	5 (1.4)	7 (2.6)	0.249
Loss of strength	60 (4.2)	26 (4.2)	34 (4.2)	0.953	17 (4.7)	9 (3.4)	0.432
Syncope	18 (1.3)	9 (1.4)	9 (1.1)	0.588	9 (2.5)	0	0.010
Speech disorder	21 (1.5)	5 (0.8)	16 (2)	0.064	4 (1.1)	1 (0.4)	0.316
Other neurological symptoms	12 (0.8)	4 (0.6)	8 (1)	0.467	4 (1.1)	0	0.087
Contact	21 (1.5)	17 (2.7)	4 (0.5)	0.001	11 (3)	6 (2.3)	0.567
Trauma	9 (0.6)	2 (0.3)	7 (0.9)	0.192	2 (0.5)	0	0.227
Asymptomatic	51 (3.6)	23 (3.7)	28 (3.5)	0.838	13 (3.6)	9 (3.4)	0.911
Other symptoms	74 (5.2)	19 (3)	55 (6.8)	0.001	13 (3.6)	6 (2.3)	0.347
Comorbidities	**n (%)**	**n (%)**	**n (%)**	**p**	**n (%)**	**n (%)**	**p**
HT	695 (48.6)	320 (51.2)	375 (46.6)	0.083	185 (50.7)	136 (51.3)	0.875
DM	447 (31.3)	206 (33)	241 (29.9)	0.221	114 (31.2)	93 (35.1)	0.308
CAD	356 (24.9)	161 (25.8)	195 (24.2)	0.505	90 (24.7)	71 (26.8)	0.544
CHF	154 (10.8)	38 (6.1)	116 (14.4)	<0.001	26 (7.1)	12 (4.5)	0.177
Arrhythmia	77 (5.4)	18 (2.4)	59 (7.3)	<0.001	9 (2.5)	9 (3.4)	0.489
COPD	205 (14.3)	83 (13.3)	122 (15.2)	0.315	43 (11.8)	40 (15.1)	0.225
Asthma	74 (5.2)	37 (5.9)	37 (4.6)	0.262	28 (7.7)	9 (3.4)	0.024
Kidney failure	178 (12.4)	69 (11)	109 (13.5)	0.155	39 (10.7)	31 (11.7)	0.690
Malignancies	215 (15)	76 (12.2)	139 (17.3)	0.007	40 (11)	36 (13.6)	0.318

Table 1. Continued

Variables	All patients	COVID-19 n=630	Non-COVID-19 n=800	p	COVID-19 surviving n=365	COVID-19 dying n=265	p
Past CVE	115 (8)	24 (3.8)	91 (11.3)	<0.001	12 (3.3)	12 (4.5)	0.422
Alzheimer's	79 (5.5)	25 (4)	54 (6.7)	0.026	12 (3.3)	13 (4.9)	0.304
Parkinson's	28 (2)	5 (0.8)	23 (2.9)	0.005	1 (0.3)	4 (1.5)	0.084
Dementia	43 (3)	17 (2.7)	26 (3.2)	0.576	11(3)	6 (2.3)	0.567
Other neurological disorders	36 (2.5)	8 (1.3)	28 (3.5)	0.008	6 (1.6)	2 (0.8)	0.325
Rheumatological diseases	16 (1.1)	3 (0.5)	13 (1.6)	0.043	3 (0.8)	0	0.139
Psychiatric diseases	24 (1.7)	10 (1.6)	14 (1.7)	0.839	8 (2.2)	2 (0.8)	0.154
Liver diseases	19 (1.3)	5 (0.8)	14 (1.7)	0.124	3 (0.8)	2 (0.8)	0.925
Thyroid disease	33 (2.3)	16 (2.6)	17 (2.1)	0.576	11 (3)	5 (1.9)	0.375
Other	132 (9.2)	42 (6.7)	90 (11.2)	0.004	21 (5.8)	21 (7.9)	0.281
Supportive treatments in the ICU	**n (%)**	**n (%)**	**n (%)**	**p**	**n (%)**	**n (%)**	**p**
Nasal/mask oxygen	1063 (74.3)	498 (79.5)	565 (70.2)	<0.001	320 (87.7)	178 (67.2)	<0.001
Nasal high flow	134 (9.4)	102 (16.3)	32 (4)	<0.001	48 (13.2)	54 (20.4)	0.015
NIMV	160 (11.2)	85 (13.6)	75 (9.3)	0.011	33 (9)	52 (19.6)	<0.001
MV	648 (45)	294 (46.6)	354 (44)	0.393	38 (10.4)	256 (96.6)	<0.001
Vasopressor/inotrope	547 (38)	249 (39.5)	298 (37)	0.434	34 (9,3)	215 (81.1)	<0.001
Hemodialysis	234 (16.3)	102 (16)	132 (16.4)	0.840	30 (8.2)	72 (27.2)	<0.001
CRRT	14 (1)	6 (1)	8 (1)	0.949	0	6 (2.3)	0.004
ECMO	2 (0.1)	2 (0.3)	0	0.108	0	2 (0.8)	0.096
Nursing care	475 (33.1)	140 (22.2)	335 (41.6)	<0.001	86 (23.6)	54 (20.4)	0.343
APACHE-II score*	17.42±10.7	17.49±10.8	17.36±10.6	0.977	11.74±6.2	25.42±10.8	<0.001
MV time (days)*,**	10.21±16.7	10.83±16.6	9.7±16.7	0.018	21.98±25.3	9.1±14.1	<0.001
Clinical course of the disease	**n (%)**	**n (%)**	**n (%)**	**p**	**n (%)**	**n (%)**	**p**
Mild	651 (45.5)	264 (42.2)	387 (48.1)	0.021	257 (70.4)	7 (2.6)	<0.001
Severe	136 (9.5)	72 (11.3)	64 (8)		70 (19.2)	2 (0.8)	
Critically severe	643 (45)	289 (46.2)	354 (44)		38 (10.4)	256 (96.6)	

*mean ± SD, **n=654, COVID-19: coronavirus disease-2019, HT: hypertension, DM: diabetes mellitus, CAD: coronary artery disease, CHF: congestive heart failure, COPD: chronic obstructive pulmonary disease, CVE: cardiovascular events, ICU: intensive care unit, NIMV: non-invasive mechanical ventilation, MV: mechanical ventilation, CRRT: continuous renal replacement therapy, ECMO: extracorporeal membrane oxygenator, APACHE-II: Acute Physiology and Chronic Health Evaluation-II

anaphylaxis, urinary incontinence, hypoglycemia, hematuria, constipation, positive result on screening, arrest, aggression, pericardial effusion, drug intoxication) were significantly higher in the non-COVID-19 group (p=0.001). The presence of congestive heart failure, arrhythmia, malignancy, previous cerebrovascular accident, and other neurological diseases, rheumatological and other diseases were significantly higher in the non-COVID-19 group. The need for nasal/mask oxygen, HFO, NIMV among the supportive treatments applied in the ICU was significantly higher in the COVID-19 group, and the patients in need of care were significantly higher in the non-COVID-19 group (p<0.001, p<0.001), p=0.011, p<0.001, respectively). While there was no significant difference between the two groups in terms of mean APACHE-II score, the duration of MV was longer in the COVID-19 group (p=0.977, p=0.018, respectively) (Table 1). Of the 630

Table 2. Hospitalization times of all patients in the COVID-19, non-COVID-19, COVID-19 surviving and COVID-19 dying group patients according to the hospitalization unit

Variables	All patients	n[1]	COVID-19	n[2]	Non-COVID -19	n[3]	p[1]	COVID-19 surviving	n[4]	COVID-19 dying	n[5]	p[2]
Total length of stay in hospital*	16.34±17	1430	16.81±16.3	630	15.97±17.5	800	0.013	18.18±15.3	365	14.94±17.3	265	<0.001
COVID-19 length of stay in the ICU*	10.14±10.5	1430	10.4±10.4	630	9.94±10.5	800	0.312	9.92±9.2	365	11.05±11.9	265	0.490
Total length of stay in ICU*	12.65±15.1	1430	12.76±14.6	630	12.57±15.5	800	0.039	12.18±12.6	365	13.56±17	265	0.299
COVID-19 ward length of stay before COVID-19 ICU*	4.08±4.1	257	3.99±3.3	146	4.2 ±4.96	111	0.182	4.04±3.1	97	3.88±3.6	49	0.711
Non-COVID-19 ward length of stay before COVID-19 ICU*	10.47±13.1	43	8.96±14	23	12.2 ±12.2	20	0.095	5±7.4	10	12±17.2	13	0.343
COVID-19 length of stay in the service after COVID-19 ICU*	9.64±12.5	363	9.03±12.4	188	10.31±12.5	175	0.414	8.97±12.4	187	19	1	0.096
Non-COVID-19 ward length of stay after COVID-19 ICU*	10.62±10.2	26	11.5±8.8	6	10.35±10.8	20	0.494	11.5±8.8	6	0	0	-
Length of stay in non COVID-19 ICU after COVID-19 ICU*	18.3±22	196	17.51±20.7	85	18.91±23.1	111	0.428	15.83±16.6	52	20.15±25.9	33	0.728
COVID-19 ICU admission from	**n (%)**	1430	**n (%)**	630	**n (%)**	800	**<0.001**	**n (%)**	365	**n (%)**	265	**0.069**
Emergency	989 (69.2)		386 (61.3)		60 (75.4)		<0.001	217 (59.5)		169 (63.8)		0.272
Pandemic ward	257 (18)		146 (23.2)		111 (13.9)		<0.001	97 (26.6)		49 (18.5)		0.018
Outer hospital	141 (9.9)		75 (11.9)		66 (8.3)		0.021	41 (11.2)		34 (12.8)		0.541
Non-COVID ward (n)%	43 (3)		23 (3.7)		20 (2.5)		0.206	1 (2.7)		13 (4.9)		0.152

Table 2. Continued

Variables	All patients	n[1]	COVID-19	n[2]	Non-COVID-19	n[3]	p[1]	COVID-19 surviving	n[4]	COVID-19 dying	n[5]	p[2]
Transfer location from COVID-19 ICU	**n (%)**		**n (%)**		**n (%)**		**<0.001**	**n (%)**		**n (%)**		**<0.001**
Pandemic ward	353 (24.7)		187 (29.7)		166 (20.8)		<0.001	187 (51.2)		0		<0.001
Non-COVID-19 ICU	201 (14.1)		85 (13.5)		116 (14.5)		0.586	52 (14.2)		33 (12.5)		0.515
Home	278 (19.4)	1,430	87 (13.8)	630	192 (24)	800	<0.001	87 (23.8)	365	0	265	<0.001
Outer hospital	109 (7.6)		33 (5.2)		76 (9.5)		0.003	33 (9)		0		<0.001
Exitus	461 (32.2)		231 (36.7)		229 (28.6)		0.001	0		231 (87.2)		<0.001
Non-COVID-19 ward	28 (2)		7 (1.1)		21 (2.6)		0.040	6 (1.6)		1 (0.4)		<0.001

*mean ± SD, days; n[1] number of all patients, n[2] number of patients in the COVID-19 group, n[3] Number of patients in the non-COVID-19 group; n[4] number of patients in the COVID-19 surviving group, n[5] number of patients in the COVID-19 dying group; p[1] comparison of COVID-19 and non-COVID-19 groups; p[2] comparison of COVID-19 surviving and COVID-19 dying groups, COVID-19: coronavirus disease-2019, ICU: intensive care unit, SD: standard deviation

patients in the COVID-19 group, 365 (58%) survived and 265 (42%) died. While a significant difference was found between the mean age of the patients diagnosed with COVID-19 in the surviving and dying groups, 67.44 and 73.40 (p<0.001), respectively (p=0.158), there was no difference between the groups according to gender. Of the 630 patients in the COVID-19 group, 365 (58%) survived and 265 (42%) died. While a significant difference was found between the mean age of the patients diagnosed with COVID-19 in the surviving and dying groups [67.44 and 73.40 (p<0.001), respectively], there was no difference between groups in terms of gender distribution (p=0.158). The mean APACHE-II score was significantly higher in the dying group (25.52) compared to the surviving group (11.74) (p<0.001). Among the symptoms, dyspnea was significantly more common in the dying group and syncope was significantly more common in the surviving group (p=0.009, p=0.010, respectively). Asthma was more common comorbidity in the surviving group than the dying group (p=0.024). The frequency of other symptoms and the types of comorbidities were similar in both groups. The need for supportive treatments in the ICU other than ECMO was significantly higher in the dying group. MV duration was significantly longer in the surviving group (p<0.001). The clinical course of the disease in the dying group was significantly more severe than in the surviving group (p<0.001) (Table 1). 69.2% of 1,430 patients were admitted to the ICU from the emergency department. The mean total hospitalizations of all patients in the hospital, in COVID-19 ICU and non-COVID-19 ICU, were 16.34, 10.14, 12.65 days, respectively. It was observed that in the COVID-19 and non-COVID-19 groups, patients were admitted to the ICU mainly from the emergency department. However, the acceptance of patients with COVID-19 from the pandemic services and outside medical institutions was higher than the non-COVID-19 group (p<0.001). The length of stay in hospital and ICU was significantly longer in the COVID-19 group than in the non-COVID-19 group (p=0.013, p=0.039, respectively). When the surviving and dying subgroups of COVID-19 patients were compared, it was found that most patients in both groups were admitted to the ICU from the emergency department. However, significantly more patients from the surviving group were admitted from the COVID-19 pandemic service (p=0.018). The mean total hospital stays in the COVID-19 surviving group was significantly longer than the dying group (p<0.001) (Table 2). When the patients were divided into two groups according to the date of admission

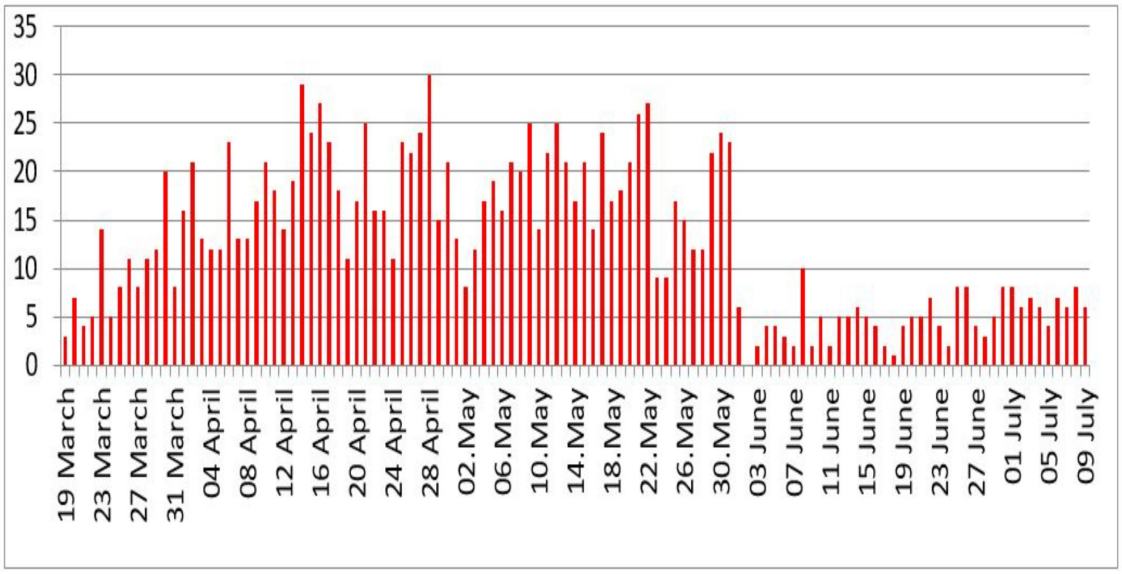

Figure 1. Number of patients admitted to the intensive care unit per day

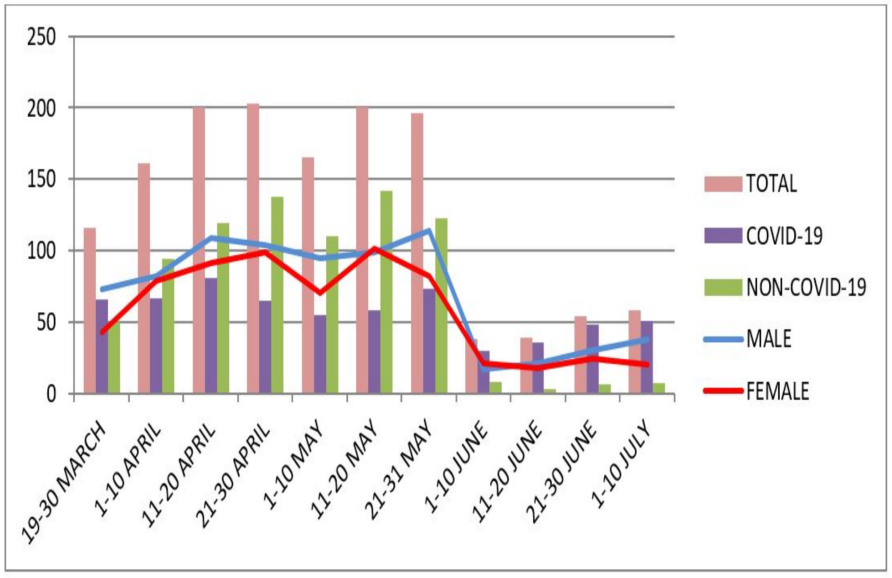

Figure 2. Distribution of patients over 10-day periods
COVID-19: Coronavirus disease-2019

to the ICU, as the onset of the pandemic (March 19th, 2020-May 31st, 2020) and the normalization period (June 1st, 2020 - July 10th, 2020), age, gender, and APACHE-II scores were similar. According to PCR positivity and thorax CT findings of the patients admitted to the ICU during the normalization period showed that the number of patients compatible with COVID-19 was significantly higher (p<0.001 for both). The ratio of patients admitted to COVID-19 to all patients was higher during the normalization period than at the onset of the pandemic (87.3%, 37.5%; respectively). Dyspnea and history of contact with a COVID-19 patient were detected more frequently in the normalization period, and vomiting, loss of strength and other symptoms were significantly more common at the onset of the pandemic (p=0.013, p<0.001, p=0.039, p=0.007, p<0.001, respectively). While congestive heart failure was the most common comorbidity at the onset

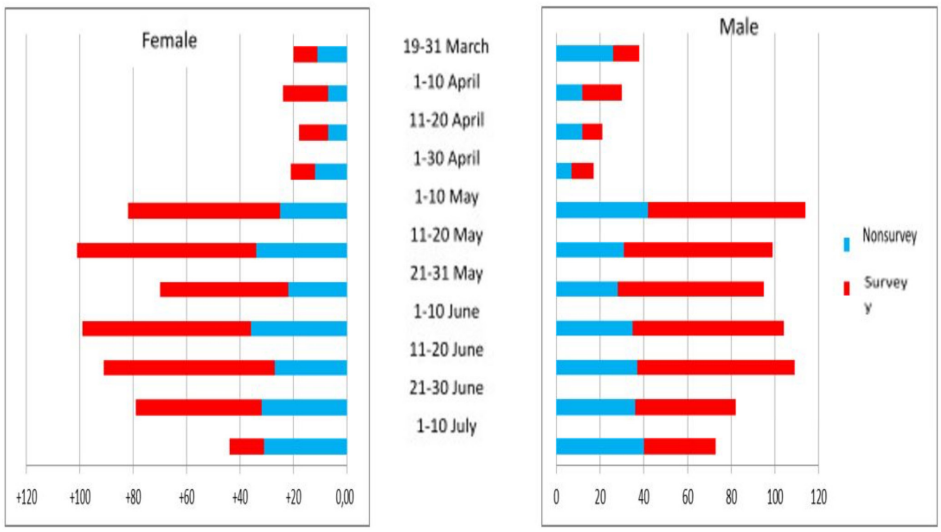

Figure 3. Hospital mortality of all patients by gender over 10-day periods

of the pandemic, asthma was the most common comorbidity in hospitalized patients during the normalization period, and there was statistical significance (p=0.035, p=0.028, respectively). Among the supportive treatments applied in the ICU, nasal high flow was applied significantly during the normalization period (p<0.001). The ratio of patients in need of care admitted to the ICU during the pandemic onset significantly higher (p=0.003) (Table 3). The length of stay in the COVID-19 ICU and the length of stay in the COVID-19 services after the COVID-19 ICU were significantly longer at the pandemic onset (p=0.045, p=0.025; respectively). The places where the patients were transferred from the COVID-19 ICU differed significantly between the two periods (p<0.001). During the normalization period, the ratio of patients who were transferred to the COVID-19 service and died was significantly higher (p=0.04, p=0.018, respectively). In the initial pandemic period, the rate of patients discharged home was found to be significantly higher (p<0.001). When intensive care and hospital mortality rates were compared, an increase was observed in both intensive care and hospital mortality during the normalization period. However, the increase in intensive care mortality was statistically significant (p=0.044). The gender distribution of the patients who died in the ICU and hospital was similar in both periods, and the mortality rate was higher in the male gender. ICU mortality rates were 37.3% and 44.3%, and hospital mortality rates were 37.6% and 44.3%, respectively, for the male gender during the pandemic onset and normalization period (Table 3).

Discussion

The hospital where the study was conducted is the largest in the region and country, with 3,810 beds and 696 intensive care beds, 500 of which are adults, and is therefore serving as a pandemic hospital since March 19th, 2020. Since the number of intensive care beds, mechanical ventilator and monitor systems in the hospital is sufficient, patients with a diagnosis of COVID-19, suspected of COVID-19, or those who need intensive care during the onset of the pandemic, who need care without intensive care, who may require routine dialysis and close contact or patients whose diagnosis could not be concluded were followed up in single rooms with negative pressure in the COVID-19 ICUs to minimize the risk of transmission until their diagnosis of COVID-19 was finalized. In the normalization period, unlike the initial period of the pandemic, all patients with a diagnosis of COVID-19, who did not need intensive care, or who might require routine dialysis and close contact, or whose diagnosis of COVID-19 could not be excluded, were followed up in the service with a companion whenever possible. In order to meet the increasing need for intensive care beds in China, where the pandemic first emerged, and then in Italy, which has become the center of the pandemic in Europe, new regulations have been made to increase the intensive care bed capacity (8-10). On the dates of this study, there was no need to create new intensive care areas in our hospital. The existing ICUs were sufficient to meet the need. However, branch ICUs such as neurology, neurosurgery, and general surgery also accepted COVID-19 patients, as did general

Table 3. Characteristics of patients admitted to the intensive care unit during the onset of the pandemic and normalization period			
Variables	**Pandemic onset period n=1241**	**Normalization period n=189**	**p**
Age (average)	71.39±15.4	70.38±14.7	0.196
Female age*	74.01±14.8	72.98±16.4	
Male age*	69.20±15.6	68.35±13	
Gender	**n (%)**	**n (%)**	0.678
Female	565 (45.5)	83 (43.9)	
Male	676 (54.5)	106 (56.1)	
APACHE score*	17.4±10.8	17.54±10.2	0.626
COVID-19 PCR result	**n (%)**	**n (%)**	<0.001
Positive	177 (14.3)	131 (69.3)	
Negative	1,043 (84)	58 (30.7)	
No test	21 (1.7)	0	
Thorax CT findings	**n (%)**	**n (%)**	<0.001
COVID-19 compatible	417 (33.6)	137 (72.5)	
COVID-19 suspicious	538 (43.4)	40 (21.2)	
COVID-19 incompatible	286 (23)	12 (6.3)	
COVID-19 patients	465 (37.5)	165 (87.3)	<0.001
PCR result positive	177 (14.3)	131 (69.3)	
PCR negative, clinical and radiologically compatible	288 (23.2)	34 (18)	
Non-COVID-19 patients	776 (62.5)	24 (12.7)	
Admission to COVID-19 ICU from	**n (%)**	**n (%)**	p
Emergency	892 (71.9)	97 (51.3)	<0.001
Pandemic ward	209 (16.8)	48 (25.4)	0.004
Outer hospital	102 (8.2)	39 (20.6)	<0.001
Non-COVID ward	38 (3.1)	5 (2.6)	0.755
Total length of stay in hospital*	16.49±17	15.35±17.1	0.103
COVID-19 length of stay in the ICU*	10.35±10.8	8.8±8.2	0.045
Total length of stay in ICU*	12.76±14.9	11.96±16.7	0.079
COVID-19 ward length of stay before COVID-19 ICU*	4.02±4.3	4.31±3.1	0.110
Non-COVID-19 ward length of stay before COVID-19 ICU*	11.42±13.7	3.2±3	0.128
COVID-19 length of stay in the ward after COVID-19 ICU*	10.16±13.3	6.91±6	0.025
Non-COVID-19 ward length of stay after COVID-19 ICU*	10.79±10.6	8.5±2.1	0.812
Length of stay in non-COVID-19 ICU after COVID-19 ICU*	17.69±20.6	22.11±30	0.988
MV time (days)	10.37±16.5**	9.28±17.4***	0.625
COVID-19 ICU admission from	**n (%)**	**n (%)**	**<0.001**
Pandemic ward	295 (23.8)	58 (30.7)	0.04
Non-COVID-19 ICU	174 (14)	27 (14.3)	0.922
Home (n), %	268 (21.6)	11 (5.8)	<0.001
Outer hospital (n), %	93 (7.5)	16 (8.5)	0.639
Exitus (n), %	385 (31)	75 (39.7)	0.018
Non-COVID-19 ward (n), %	26 (2.1)	2 (1.1)	0.338
Mortalite in the ICU (n), %	457 (36.8)	84 (44.4)	0.044

Table 3. Continued			
Variables	**Pandemic onset period n=1241**	**Normalization period n=189**	**p**
Female (n)%	205 (36.3)	37 (44.6)	0.145
Male (n)%	252 (37.3)	47 (44.3)	0.164
Hospital mortality (n), %	461 (37.1)	84 (44.4)	0.054
Female (n), %	207 (36.6)	37 (44.6)	0.163
Male (n), %	254 (37.6)	4 (44.3)	0.183
Symptoms	**n (%)**	**n (%)**	**p**
Dyspnea	602 (48.5)	110 (58.2)	0.013
Fever	284 (22.9)	51 (27)	0.215
Chills/shivering	16 (1.3)	2 (1.1)	0.711
Cough	254 (20.5)	48 (25.4)	0.122
Sore throat	15 (1.2)	4 (2.1)	0.310
Myalgia/joint ache	25 (2)	5 (2.6)	0.573
Chest pain	42 (3.4)	4 (2.1)	0.357
Nausea	51 (4.1)	6 (3.2)	0.540
Vomiting	61 (4.9)	3 (1.6)	0.039
Stomach ache	34 (2.7)	3 (1.6)	0.353
Diarrhea	29 (1.5)	2 (1.1)	0.615
General disorder	180 (14.5)	29 (15.3)	0.761
Consciousness change	71 (5.7)	5 (2.6)	0.079
Headache	19 (1.5)	5 (2.6)	0.267
Loss of strength	59 (4.8)	1 (0.5)	0.007
Syncope	18 (1.5)	0	0.096
Speech disorder	21 (1.7)	0	0.072
Other neurological symptoms	11 (0.9)	1 (0.5)	0.616
Contact	11 (0.9)	10 (5.3)	<0.001
Trauma	9 (0.7)	0	0.240
Asymptomatic	4 (3.7)	5 (2.6)	0.494
Other symptoms	72 (5.8)	2 (1.1)	0.006
Comorbidities	**n (%)**	**n (%)**	**p**
DM	381 (30.7)	66 (34.9)	0.244
HT	591 (47.6)	104 (55)	0.058
CAD	304 (24.5)	52 (27.5)	0.372
CHF	142 (11.4)	12 (6.3)	0.035
Arrhythmia	69 (5.6)	8 (4.2)	0.451
COPD	183 (14.7)	22 (11.6)	0.256
Asthma	58 (4.7)	16 (8.5)	0.028
Kidney failure	159 (12.8)	19 (10.1)	0.284
Malignancies	194 (15.6)	21 (11.1)	0.105
Past CVE	105 (8.5)	10 (5.3)	0.135
Alzheimer's	70 (5.6)	9 (4.8)	0.622

Table 3. Continued			
Variables	**Pandemic onset period n=1241**	**Normalization period n=189**	**p**
Parkinson's	24 (1.9)	4 (2.1)	0.866
Dementia	41 (3.3)	2 (1.1)	0.092
Other neurological disorders	35 (2.8)	1 (0.5)	0.061
Rheumatological diseases	16 (1.3)	0	0.116
Psychiatric diseases	24 (1.9)	0	0.054
Liver diseases	18 (1.5)	1 (0.5)	0.303
Thyroid disease	27 (2.2)	6 (3.2)	0.394
Other	113 (9.1)	19 (10.1)	0.675
Supportive treatments in intensive care	**n (%)**	**n (%)**	**p**
Nasal/mask oxygen requirement	920 (74.1)	143 (75.7)	0.638
Nasal high flow	82 (6.6)	52 (27.5)	<0.001
NIMV	131 (10.6)	29 (15.3)	0.52
MV	553 (44.5)	95 (50)	0.208
Vasopressor/inotrope need	473 (38)	72 (38)	0.792
Hemodialysis	191 (15.3)	35 (18.5)	0.480
CRRT	14 (1.1)	0	0.142
ECMO	2 (0.2)	0	0.581
Nursing care	420 (34.6)	45 (23.8)	0.003
Clinical course of the disease	**n (%)**	**n (%)**	**p**
Mild	585 (47.1)	66 (34.9)	<0.001
Severe	106 (8.5)	30 (15.9)	
Critically severe	550 (44.3)	93 (49.2)	

*Mean ± SD, **n=558, ***n=96, APACHE: Acute Physiology, and Chronic Health Evaluation, COVID-19: coronavirus disease-2019, PCR: polymerase chain reaction, CT: computed tomography, ICU: intensive care unit, MV: mechanical ventilation, DM: diabetes mellitus, HT: hypertension, CAD: coronary artery disease, CHF: congestive heart failure, COPD: chronic obstructive pulmonary disease, CVE: cardiovascular events, NIMV: noninvasive mechanical ventilation, CRRT: continuous renal replacement therapy, ECMO: extracorporeal membrane oxygenator, SD: standard deviation

ICUs under the leadership of the intensive care clinic. In the initial period of the pandemic, a maximum of 30 patients were admitted to ICU per day, and according to the second algorithm changed after the start of the normalization process, a maximum of 10 patients were admitted to ICUs per day. The difference may be the decrease in the number of newly diagnosed patients during the normalization period, the increased inexperience and the difference in the algorithms applied accordingly, namely the decrease in the acceptance of care patients and dialysis patients who do not need intensive care. In the literature, there are two studies reported from England and Brazil comparing COVID-19 and non-COVID-19 patient data (10,11). In both studies, the non-COVID-19 patient group was formed from patient data from the pre-pandemic period. In the study reported from England, the data was obtained from intensive care patients between 2017-2019, and in the study in Brazil, data of patients in the ICU in 2019. The present study, however, it differs from other studies in that all patient data belong to non-COVID-19 patients followed in the ICU during the pandemic period. In a study from Brazil, the mean age of non-COVID-19 patients (72.36) was higher than that of COVID-19 patients (65.19), similar to the data of our study (12). Although not statistically significant, in our study, the male gender was higher in both the COVID-19 and non-COVID-19 groups, similar to the results of the other two studies (10,11). It has been emphasized in other studies that the male gender is more frequent among COVID-19 patients admitted to the ICU (12-14). The first three most common symptoms in patients in the COVID-19 group were dyspnea, fever and cough, similar to previous studies (13-16). Considering that the disease is transmitted by airborne transmission, contact is an important factor in the spread of the disease, and accordingly, the contact rate was higher in the COVID-19 group (17). The

symptoms specified under the heading of other symptoms, which are not symptoms of COVID-19 but can also be seen in COVID-19 patients due to other comorbidities in the patients, were also higher in the non-COVID-19 group as expected. Hypertension and diabetes were the two most common comorbidities in all patients and the COVID-19 group, similar to the results of other studies (18-20). While there was no statistical difference in the frequency of hypertension and diabetes between the COVID-19 and non-COVID-19 groups, the comorbidity group with all malignancies, regardless of hematological or solid malignancy, was significantly more common in non-COVID-19 patients, and the results were similar in Brazil (11). In addition, it has been shown that comorbidities such as hematological malignancy, immunocompromised and metastatic disease are more common in the non-COVID-19 group (10). The ground-glass density appearance, one of the thoracic CT radiological findings of COVID-19, is not specific to COVID-19 and can also be seen on thorax CT of patients with loading findings due to heart failure or pulmonary edema (21). However, it should be kept in mind that signs of failure due to cardiac involvement may also develop in COVID-19 (22). Due to the similarity of COVID-19 with thoracic CT findings, patients who applied to the hospital with pulmonary edema or heart failure findings and needed intensive care during the pandemic period were followed in the ICU until COVID-19 was ruled out. Therefore, we believe that congestive heart failure is significantly higher in the non-COVID-19 group. Similarly, nursing care patients were admitted to intensive care until the diagnosis of COVID-19 was confirmed or ruled out. Since there may be comorbidities such as previous cerebrovascular disease, and other neurological diseases in patients who need nursing care. These comorbidities were significantly higher in the non-COVID-19 group. Rheumatological diseases were also significantly higher in the non-COVID-19 group. Although it is difficult to evaluate due to the low number of cases with rheumatological diseases, it may be because corticosteroids or other anti-inflammatory drugs, which are used in the treatment of rheumatological diseases are also included in the COVID-19 treatment guide, or people with the rheumatological disease who use these drugs need less intensive care when they get COVID-19. However, these assumptions are all separate research topics (23-25). HFO and NIMV applications in intensive care are among the treatment methods used in hypoxic respiratory failure. In the COVID-19 group, which revealed hypoxemia and progressed from respiratory failure to ARDS, the need for nasal/mask oxygen, HFO, and NIMV was higher since respiratory failure was prominent, similar to the results of the other study (11). In addition, the duration of MV was longer in the COVID-19 group, similar to the study in Brazil (10). The mean APACHE-II score (17.49) of the COVID-19 patient group was similar to the APACHE-II score (score 18) of the study reported from Canada (25). In a study in England, the APACHE-II score was similar between the COVID-19 and non-COVID-19 groups as in our study, and the most frequent admission to the ICU was from the wards (10). In this study, a large proportion of all COVID-19 and non-COVID-19 patients were admitted to the ICU primarily from the emergency department and the second most common from the COVID-19 services. The number of patients admitted to the ICU from the pandemic wards in the COVID-19 group is higher than the non-COVID-19 group. It can be explained by the fact that patients diagnosis with the COVID-19 are more stable on admission and are hospitalized inwards first. Then the respiratory failure progresses rapidly and they require intensive care. The rate of COVID-19 and non-COVID-19 patients admitted from other centers was higher than the UK data which can be explained by the fact that the hospital where our study was conducted was a pandemic hospital with higher intensive care bed capacity (10). Similar to other studies, the total hospital and total ICU length of stay were longer in the COVID-19 group than in the non-COVID-19 group which can be explained because COVID-19 is a complex disease with multisystem involvement as well as respiratory failure. (10,11). Advanced age and male gender are risk factors for mortality in COVID-19 (12,16,26,27). Consistent with the data from the literature, the mean age of the patient group who died from COVID-19 was higher and the male sex ratio was higher, although not significant. Although dyspnea, the main symptom of respiratory failure, was not significant, the need for supportive treatment methods in the ICU was higher as it was more common in the COVID-19 dying group. In patients who need IMV due to respiratory failure due to COVID-19 and ARDS, weaning from MV may be prolonged concerning the recovery time of other organ failures that may develop during the follow-up of ARDS. Consistent with a previous study, the duration of stay in MV was longer (14). The need for vasopressor/inotrope, hemodialysis, and CRRT, which show progression to shock and organ failure, and are the symptoms of the the disease's poor prognosis during

intensive care follow-up, was higher in the COVID-19 dying group, similar to previous studies (13,17). The APACHE-II score, an indicator of mortality and is the most important parameter related to mortality in intensive care studies, was significantly higher in the COVID-19 dying group than the COVID-19 surviving group (10). In the surviving COVID-19 group, the number of patients admitted from the wards was higher. In other words, the survival of patients admitted from the service was higher. Since treatments can be started in the ward before intensive care arises, the need for intensive care can be recognized early in the warding process, leading to faster intensive care support treatments. In our hospital, HFO and/or NIMV treatments are primarily applied in ICUs. Patients with deep hypoxemia and increased oxygen demand may be taken from the ward to the ICU and immediately initiating treatments such as HFO and/or NIMV in addition to their medical treatments may have increased survival. Similar to previous studies, the total hospital stay in the COVID-19 surviving group was extended than the COVID-19 dying group (10,11,14). The fact that the duration of stay in the MV in the COVID-19 surviving group is longer than in the dying group, consistent with other studies, may be related to the long and challenging recovery process of ARDS (14). When the characteristics of the patients admitted to the ICU during the onset of the pandemic and the normalization period in our hospital were compared, there was no significant difference between the demographic characteristics, APACHE-II score, and comorbidities other than asthma. However, during the normalization period more patients with a confirmed diagnosis of COVID-19 were admitted to the ICU due to the change in the hospital intensive care admission algorithm. In addition, the reasons why the contact history, which is one of the most important factors in the spread of the disease, is more frequent during the normalization period, can be due to the algorithm change, admission of the patients diagnosed with COVID-19, not the suspicious ones, to the ICU, or the society not complying with the rules like stretching the hygiene rules, mask and distance, depending on the wrong perception of normalization. The rate of symptoms such as other disease symptoms and signs of neurological diseases such as loss of strength was also higher in the initial period of the pandemic. The admission of nursing care patients to the ICU during the initial period of the pandemic, as required by the algorithm, may have led to the detection of symptoms such as loss of strength that are already present in these patients more frequently. About 2.5 months after the pandemic started in the world, we encountered COVID-19 for the first time. Even if we closely follow the countries's experiences before us, it was not as easy to implement in practice as in theory. The number of deaths announced from various parts of the world in the media and social media related to the highly contagious COVID-19 and increasing day by day has led everyone to approach the disease cautiously. At the beginning of the pandemic, the ministry of health tried to set goals for making correct diagnosis, preventing the spread of the disease, and using hospital resources effectively and correctly. In line with these goals, all suspected COVID-19 cases were tried to be followed and treated by the determined algorithm. Again in this period, in order to respond to the increasing number of patients, arrangements were required in services, laboratories, other units, and ICUs. For example, at the beginning of the pandemic, PCR tests were performed in the out-of-hospital public health center and mostly resulted in ≥48 hours. However, now PCR tests can also be studied in our hospital and can be concluded in a short time, such as 6-8 hours. Thus, the diagnosis of COVID-19 of patients was confirmed faster. We assume these arrangements worked out, taking the higher rate of PCR-positive patients in the normalization period into account. Although PCR is a valuable test for COVID-19, it may sometimes be insufficient to diagnose of the disease and may need confirmation by retesting clinical examination or radiological findings (28). Therefore, the diagnosis of COVID-19 cannot be definitively excluded in cases with negative PCR results (29).

Thoracic CT is important in diagnosing of patients with moderate to severe respiratory failure whose clinical and laboratory findings are compatible with COVID-19 but have a negative PCR test (29). We believe that as radiologists become more familiar with the thoracic CT findings of COVID-19 over time, they can provide clinicians with more precise information about the presence or absence of COVID-19. The fact that the experience of physicians increased on COVID-19 during the normalization period and their knowledge in the light of new studies in the literature can be the reason for the lower rate of patients diagnosed with COVID-19 with radiological findings during the normalization period. It should also be kept in mind that the total number of HFO devices in our hospital was lower than the normalization period in the first days of the pandemic. As the awareness of patients benefiting from HFO increased, new HFO devices

were procured (30). While the first reason for using more HFOs during the normalization period is more HFO devices, the second reason can be explained by the fact that more COVID-19 patients with respiratory failure were admitted to the ICU during this period the effectiveness of HFO treatment in COVID-19 was noticed. This hospital, which has the highest intensive care bed capacity in the region and the country, has enabled patients with suspected COVID-19 at the beginning of the pandemic period and need the care to be followed up and treated in the ICU until the diagnosis of COVID-19 is confirmed. During the normalization period, the diagnosis was accelerated with earlier PCR results, and patients in need of care were admitted to appropriate services according to test results and radiology findings. This way, the disease transmission from patients to their relatives or among other health workers was minimized. Thus, the use of COVID-19 ICU beds became more effective. In both periods, the most frequent admission to the ICU was from the emergency department, but this rate was higher in the first period than the normalization period. One of the reasons for this is that, as mentioned above, all patients, including COVID-19 suspected care patients and dialysis patients, were admitted to the ICU during the onset of the pandemic. Another reason for the high number of patients coming directly from the emergency department to the ICU in the early period may be the delay in admission to the hospital, and the increased need for intensive care due to the poor knowledge of the disease and its symptoms. Since such cases were higher in the initial period, admission to the emergency room increased rapidly. In order to reduce the patient load in the emergency room, critically ill patients were followed up in the COVID-19 ICUs until COVID-19 was excluded. The high admission rates of patients from pandemic services during the normalization period were no longer because of suspected patients with COVID-19 but rather the admission of patients who needed intensive care and were diagnosed with COVID-19 while being followed in the services to the ICU. Again, during the normalization period, patient admission from other centers to the ICU was more frequent. It may be because the hospital is the central pandemic hospital in the city, and patients diagnosed with COVID-19 are primarily directed here from other centers. The intensive care capacities of other hospitals were less. The reason why patients were hospitalized longer in the initial period of the pandemic in the COVID-19 ICU was that even if the PCR tests of the patients who needed care became negative, the patients could be sent to their homes or out-of-hospital care centers after the 14-day isolation period was completed in the ICU in line with the recommendation of the infectious diseases. Again, patients who were transferred from the ICU to the COVID-19 ward were discharged after completing their isolation period in the hospital. After the treatment of COVID-19 patients in the ICU was completed, the patients who did not need intensive care were either discharged home or transferred to the COVID-19 or non-COVID-19 services according to the discharge algorithm from the ICU. Those who continued to need intensive care were transferred to the non-COVID-19 ICU in or out of hospital. We believe that the high rate of discharge home from the ICU during the onset of the pandemic was because the patients were completing the hospitalization period in intensive care. Because in this period, as mentioned before, these patients completed their isolation period in the ICU and were discharged home from the ICU. On the other hand, the rate of patients transferred to the COVID-19 services during the normalization period was higher. In this normalization period, the clinical course of the patients more severe. The need for HFO, NIMV, MV was higher because they care and dialysis patients who do not need intensive care were not followed up in the ICU, and the rate of patients diagnosed with COVID-19 in the ICUs was higher. Patients who did not require these treatments were followed up in the ward for nasal oxygen or other treatments for a while. It may be that the mortality is higher during the normalization period, the rate of COVID-19 patients is higher in the normalization period compared to the onset of the pandemic, and the mortality rate in COVID-19 patients is higher than in non-COVID-19 patients. The limitation of our study is that it is retrospective.

Conclusion

As a result, the initial period of the pandemic was spent understanding COVID-19, which entered our lives as an unknown. At the same time, it was a guiding period for us to treat patients more effectively while protecting the community and healthcare professionals. Thanks to this knowledge and skill gained, systemic changes were made that could benefit patients during and after the normalization period. This hospital continues to be a pandemic hospital. The superiority of our study to other studies is that it is single-centered, the number of patients is higher, and

patients were admitted to 14 ICUs with the same algorithm. There are studies in the literature on COVID-19 patients followed in the intensive care unit, where the number of patients is higher than our study, but these are generally multicenter studies. Although ICU indication criteria have been determined in the literature, these criteria may change in favor of the general health policy in exceptional cases such as pandemics, depending on the intensive care bed capacity, the number of intensive care doctors, nurses, and auxiliary personnel, and the adequacy of other devices such as MV, monitor. We believe that intensive care is used safely and effectively for patients, healthcare professionals, and society with the algorithms applied. Another feature of this study that differs from other studies is that it compares COVID-19 and non-COVID-19 patients admitted to the ICU during the pandemic period.

Ethics

Ethics Committee Approval: The study protocol was approved by the Ankara City Hospital Ethics Committee (decision no: E1-20-527, date: 07.05.2020).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: B.D.K., G.M.K., N.M.M., I.Ö.T., Concept: B.D.K., N.M.M., I.Ö.T., Design: B.D.K., N.M.M., I.Ö.T., Data Collection and Process: B.D.K., G.M.K., Analysis or Interpretation: B.D.K., N.M.M., T.T.P., Ö.B.S., Literature Search: B.D.K., T.T.P., Writing: B.D.K., T.T.P., Ö.B.S.

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ORIGINAL RESEARCH / *ÖZGÜN ARAŞTIRMA*

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Assessment of Anxiety and Stress Levels of Health Care Workers Who Serve in Frontlines in Anesthesia and Intensive Care Units During the Pandemic

Pandemi Süresince Anestezi ve Yoğun Bakım Ünitelerinde Çalışanların Anksiyete ve Stres Düzeylerinin Değerlendirilmesi

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ABSTRACT *Objective:* The spread of coronavirus disease-2019 (COVID-19) worldwide has caused sudden and dramatic changes in our daily routines and work lives. Healthcare workers tried to adapt to the pandemic process, protecting patients, themselves, and their families from COVID-19 infection. Our study explains the early psychological effects of the COVID-19 pandemic on healthcare professionals working in the front line in intensive care units and operating rooms.
Materials and Methods: This cross-sectional type of study was conducted face-to-face with 125 medical personnel working on the front line in the COVID-19 intensive care unit (ICU) during the pandemic. The beck depression inventory and perceived stress scale were used in our study to measure the depression and stress levels of worker healthcare care.
Results: 73.6% of the participants were female, 52.8% were nurses, and 28% were working in a pandemic ICU. The mean age was 34.17±7.72. Compared to the low-stress group, the high-stress group consisted of females with a statistically significantly higher frequency.
Conclusion: Unfortunately, history indicates that pandemics are inevitable and that we must help each other in these difficult times. Understanding early signs of the stress factors of healthcare workers can be helpful in protecting them from posttraumatic disorder. During this period, social distancing was the key to slowing down the transmission of the virus, but it led to increased health sector employees' increased anxiety. Understanding the early signs of healthcare workers' signs of anxiety and depression can protect them from serious health problems such as burnout syndrome and posttraumatic stress disorder.
Keywords: COVID-19, health workers, stress, anxiety

ÖZ *Amaç:* Koronavirüs hastalığı 2019'un (COVID-19) dünya çapında yayılması, günlük rutinlerimizde ve iş hayatımızda ani ve dramatik değişikliklere neden oldu. Sağlık çalışanları pandemi sürecine uyum sağlamaya çalışarak hastaları, kendilerini ve ailelerini COVID-19 enfeksiyonundan korumaya çalıştılar. Çalışmamız, COVID-19 pandemisinin yoğun bakım ünitelerinde ve ameliyathanelerde ön saflarda görev yapan sağlık çalışanları üzerindeki erken dönem psikolojik etkilerini araştırmayı amaçlamaktadır.
Gereç ve Yöntem: Bu kesitsel tipteki çalışma, pandemi sırasında COVID-19 yoğun bakım ünitesinde ön saflarda görev yapan 125 sağlık personeli ile yüz yüze gerçekleştirildi. Çalışmamızda sağlık çalışanlarının depresyon ve stres düzeylerini ölçmek için beck depresyon envanteri ve algılanan stres ölçeği kullanıldı.
Bulgular: Katılımcıların %73,6'sı kadın, %52,8'i hemşire ve %28'i pandemi yoğun bakım ünitesinde çalışmaktaydı. Ortalama yaş 34,17±7,72 yıl idi. Düşük stresli grupla karşılaştırıldığında, yüksek stresli grup, istatistiksel olarak anlamlı derecede daha yüksek sıklıkta kadınlardan oluşuyordu.
Sonuç: Ne yazık ki tarih, pandemilerin kaçınılmaz olduğunu ve bu zor zamanlarda birbirimize yardım etmemiz gerektiğini göstermektedir. Sağlık çalışanlarının stres faktörlerinin erken belirtilerinin anlaşılması onları travma sonrası bozukluktan korumaya yardımcı olabilir. Bu dönemde sosyal mesafe virüsün bulaşmasını yavaşlatmanın anahtarıydı, ancak sağlık sektörü çalışanlarının artan kaygısına yol açtı. Sağlık çalışanlarında anksiyete ve depresyon erken belirtilerinin anlaşılması, onları tükenmişlik sendromu ve travma sonrası stres bozukluğu gibi ciddi sağlık sorunlarından koruyabilir.
Anahtar Kelimeler: COVID-19, sağlık çalışanları, stres, anksiyete

Introduction

The world faces an unprecedented health crisis caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Coronavirus disease-2019 (COVID-19) infection, also known as SARS-CoV-2, continues to cause concern worldwide, with a total number of 92,506,811 confirmed cases, including 2,001,773 deaths in more than 200 countries, as of January 16, 2021 (1). Among confirmed cases with COVID-19, the case mortality rate is estimated to be between 0.2% and 9.5% (2). In Turkey, the total number of patients as of January 16, 2021, is 2,380,665, while the number of patients who died is 23,882 (3). The COVID-19 disease is predominantly viral pneumonia and highly contagious (4) Approved viral infection routes mainly contact contaminated environmental surfaces and aerosolization (5). Procedures for COVID-19 patients in the intensive care unit (ICU) and operating room, especially air management, can produce aerosols that increase the risk of infection and are high-risk for medical personnel (6). Personnel involved in air management of COVID-19 patients and health employees treating the disease have a higher risk of infection by the disease (7). In a Washington Post article, anesthesiologist Cory Deburghgraeve described his work during the outbreak as "basically you are next to the nuclear reactor" (8). In addition to these causes, the world's unpreparedness for the Coronavirus outbreak has created a sense of fear and anxiety. As the number of cases has increased rapidly, these feelings have increased. COVID-19 has brought severe burdens to the health system worldwide, and doctors' and nurses' efforts to recognize and prevent anxiety and stress levels, which are among the short-and long-term harmful effects, have been significant. Because the main goal in health policy is to prevent disease, fight against infection, ensure the development of treatment and vaccines, and focus on saving lives, doctors' and nurses' anxiety is at risk of being ignored. In this process, if health employees' stress and anxiety are not treated sufficiently, we can observe adverse effects such as fatigue, depression, mood disorders, drug abuse, suicide, low quality of patient care, unexpected resignations, and early retirements (9). Our research aims to understand the mental health consequences of the COVID-19 pandemic on health employees working on the front line in our hospital's intensive care units and operating rooms and reveal the consequences of its psycho-physical impact.

Materials and Methods

This cross-sectional type of study was conducted face-to-face with 125 medical personnel working on the front line in the COVID ICU during the pandemic, with written permission from the Ministry of Health and the Ethics Board Dokuz Eylül University Faculty of Medicine (acceptance no: 2021/02-38). COVID-19 first case in Turkey was announced by the health ministry on 11 March 2020. The first death due to the virus in the country occurred on March 15, 2020. Our study was completed in February 2021. An informed consent form was obtained from the participants. Beck depression inventory (BDI) and perceived stress scale (PSS) were used in our study to measure the depression and stress levels of workers health. BDI was developed by Beck et al. (10) in 1961 to measure behavioral signs of depression in adolescents and adults. In 1978, the full scale was revised, and duplications defining violence were extracted, and patients were asked to mark their status for the last week, including today. With respect to severity scoring is interpreted as follows; 0-9=minimal, 10-16=light, 17-29=moderate, 30-63=severe. The scale was converted into Turkish as BDI and beck depression scale in two separate forms, and a validity and reliability study was conducted (11). A high level of correlation has been found between the original and revised versions. Cross-cultural validity and reliability were also found to be high. The internal reliability of BDE has been tested at different times with an average value of 0.86 between 0.73-0.92 (12).

PSS was developed by Ali et al. (13). PSS, consisting of 14 articles, is designed to measure how several situations in a person's life are perceived as stressful. PSS-14's scores range from 0 to 56, while PSS-10's scores range from 0 to 40, and PSS's scores range from 0 to 16. A high score indicates an excess of a person's perception of stress.

Statistical Analysis

All analyses were performed on SPSS v21 (SPSS Inc., Chicago, IL, USA). Data are given as mean ± standard deviation or median (minimum - maximum) for continuous variables according to normality of distribution and frequency (percentage) for categorical variables. Normally distributed variables (height, weight and blood glucose) were analyzed with independent samples t-test and ANOVA test. Non-normally distributed variables were analyzed with the Mann-Whitney U test. Categorical variables evaluated using the chi-square tests or Fisher's Exact tests. $P<0.05$ values accepted as statistically significant results.

Results

73.6% of the participants were female, 52.8% were nurses, and 28% were working in pandemic ICU. The mean age was 34.17±7.72. 67.8% of those with low stress levels and 88.6% of those with high stress levels were female. Compared to the low-stress group, the high-stress group consisted of females with a statistically significantly higher frequency (p=0.018) (Figure 1). 25.6% of the group with low-stress level and 48.6% of the group with high-stress level stated that they did sports. Compared with the group with high stress level, the group with low stress level was doing sports with a statistically significantly higher frequency (p=0.013). Summary of individuals characteristics with regard to stress level were shown in Table 1.

Among the groups determined according to the anxiety level, the frequency of insomnia and concentration disorder, forgetfulness and mental complaints was determined at a statistically significant level (p=0.026, 0.017, 0.015, respectively). 94.1% of the minimal anxiety group and 12.5% of the severe anxiety group stated that they felt stressed. The frequency of feeling stress was statistically significantly different among the groups determined according to the anxiety level (p<0.001). Summary of individuals characteristics with regard to anxiety level were shown in Table 2.

Discussion

Our research revealed the psychological effects of the COVID-19 pandemic on medical staff working on the front line in intensive care units and the operating rooms. 73.6% of participants were women, and 52.8% were nurses. Compared to the low-stress group, the high-stress group consisted statistically significantly of female health employees. The prevalence of insomnia and concentration disorder, forgetfulness, and mental reactions (easy irritability, depressive emotion, inability to enjoy life, feeling helpless, pessimism) were high among the groups determined by the anxiety level of health professionals who were directly involved in the care of patients infected by COVID-19. During the COVID-19 pandemic, anxiety was detected by 23.2% in a meta-analysis that included 13 studies with 33,062 participants to understand and analyze factors that had the potential to affect medical personnel's mental health in critical areas (14). In this meta-analysis, nurses and doctors were compared for anxiety, and mental symptoms were shown in nurses with a higher prevalence, unlike in our study. When gender and occupation analysis was performed, it was noted that female health employees and nurses showed higher levels of emotional symptoms than male health personnel. Our study also found that the vast majority of staff with high-stress levels were female health employees. Again, a study investigating the anxiety and stress levels of 1,830 health employees in Wuhan found that emotional burden was more significant in female employees and nurses (15). In another analysis made for health professionals, it was found that depression and anxiety symptoms for women employees were higher for those less prepared psychologically, self-competence, and those who lacked family support and who have a low quality of sleep (16). A web-based survey of 7,236 people in China, which was participated voluntarily, found that anxiety symptoms were significantly higher in health employees, for women and youth (age<35) (17). The high proportion of nurses participating in our survey and the fact that nurses were engaged in closer and longer working hours with COVID-19 patients may have increased the level of anxiety and stress (18). It was found that high anxiety levels of healthy employees can cause harmful cognitive interference in making task-related goals, negatively affecting their decision-making ability and performance (14). Higher anxiety may also increase burnout; it can invite depression and similar diseases (17). Since previous studies have shown that emotional distress is often associated with inadequate patient care and professional inefficiencies, and a long-term low effect on healthcare professionals' health status, these results require special attention (19). The COVID-19 pandemic is complicated due to infection caused by those infected but asymptomatic. It causes additional risk for people they live with and increases the emotional burden of medical personnel (20). A survey found that 48% of anesthesiologists said they were most likely to get COVID-19 at work but thought they would heal after the disease with mild symptoms (21). Among the causes of anxiety and stress of medical staff; in addition to the fear of being infected with COVID-19, the uncertainty of personal protective equipment or other essential equipment, difficulties with child care, witnessing critical illness or death of co-employees, irregular work hours, and high workload can be specified (22). Maintaining health employees' mental well-being is imperative for the health workforce's long-term capacity for caring for COVID-19 patients (21). On the other hand, health employees' satisfaction with their work and

Table 1. Summary of individuals characteristics with regard to stress level				
	Level of stress (PSS)			
	Low (n=90)	High (n=35)	Total (n=125)	p
Age	33.0 (29.0-38.0)	34.0 (29.0-43.0)	33.0 (29.0-40.0)	0.496*
Gender				
Female	61 (67.78%)	31 (88.57%)	92 (73.60%)	0.018[a]
Male	29 (32.22%)	4 (11.43%)	33 (26.40%)	
Duty				
Specialist physician	12 (13.33%)	3 (8.57%)	15 (12.00%)	0.763[b]
Nurse	47 (52.22%)	19 (54.29%)	66 (52.80%)	
Stuff	10 (11.11%)	3 (8.57%)	13 (10.40%)	
Assistant	13 (14.44%)	4 (11.43%)	17 (13.60%)	
Anesthesia technician	6 (6.67%)	5 (14.29%)	11 (8.80%)	
Secretary	1 (1.11%)	0 (0%)	1 (0.80%)	
Lecturer	1 (1.11%)	1 (2.86%)	2 (1.60%)	
Unit				
Pandemic ICU	27 (30.00%)	8 (22.86%)	35 (28.00%)	0.638[b]
CVS ICU	9 (10.00%)	1 (2.86%)	10 (8.00%)	
PACU	10 (11.11%)	6 (17.14%)	16 (12.80%)	
Operating room	19 (21.11%)	10 (28.57%)	29 (23.20%)	
Internal Medicine ICU	17 (18.89%)	7 (20.00%)	24 (19.20%)	
Other	8 (8.89%)	3 (8.57%)	11 (8.80%)	
Symptoms				
Tiredness	75 (83.33%)	32 (91.43%)	107 (85.60%)	0.247[b]
Insomnia and concentration disorder	55 (61.11%)	25 (71.43%)	80 (64.00%)	0.281[b]
Forgetfulnes	51 (56.67%)	18 (51.43%)	69 (55.20%)	0.597[b]
Somatic complaints	50 (55.56%)	17 (48.57%)	67 (53.60%)	0.482[b]
Mental complaints	57 (63.33%)	25 (71.43%)	82 (65.60%)	0.392[b]
Sleep	69 (76.67%)	26 (74.29%)	95 (76.00%)	0.780[b]
Spor	23 (25.56%)	17 (48.57%)	40 (32.00%)	0.013[b]
Psychological support	12 (13.33%)	1 (2.86%)	13 (10.40%)	0.085[a]
Eating				
Decreased	25 (27.78%)	13 (37.14%)	38 (30.40%)	0.540[b]
Same	26 (28.89%)	10 (28.57%)	36 (28.80%)	
Increased	39 (43.33%)	12 (34.29%)	51 (40.80%)	
Separation from familiy	45 (50%)	16 (45.71%)	61 (48.80%)	0.667[b]
Smoking				
Never smoked	44 (48.89%)	19 (54.29%)	63 (50.40%)	0.234[b]
Still smoking	38 (42.22%)	10 (28.57%)	48 (38.40%)	
Quit smoking	8 (8.89%)	6 (17.14%)	14 (11.20%)	
Stress				
No	29 (32.22%)	16 (45.71%)	45 (36.00%)	0.158[b]
Yes	61 (67.78%)	19 (54.29%)	80 (64.00%)	

Table 1. Continued				
	Level of stress (PSS)			
	Low (n=90)	High (n=35)	Total (n=125)	p
Media				
More than ever	58 (64.44%)	24 (68.57%)	82 (65.60%)	0.846[b]
Less than usual	25 (27.78%)	8 (22.86%)	33 (26.40%)	
More than ever	4 (4.44%)	1 (2.86%)	5 (4.00%)	
Less than usual	3 (3.33%)	2 (5.71%)	5 (4.00%)	
Level of anxiety (BAI)	15.91±9.21	18.60±8.34	16.66±9.02	0.135[c]
Minimal	15 (16.67%)	2 (5.71%)	17 (13.60%)	0.107[b]
Mild	35 (38.89%)	13 (37.14%)	48 (38.40%)	
Moderate	32 (35.56%)	12 (34.29%)	44 (35.20%)	
Severe	8 (8.89%)	8 (22.86%)	16 (12.80%)	

BAI: Beck anxiety inventory, CVS: cardiovascular surgery, ICU: intensive care unit, PACU: post-anesthesia care unit, PSS: perceived stress scale, data are given as mean ± standard deviation or median (1st quartile-3rd quartile) for continuous variables according to normality of distribution and as frequency (percentage) for categorical variables, *Mann-Whitney U test, [a]Fischer's Exact test, [b]Pearson chi-square test [c]independent t-test

personal satisfaction can be considered a protective factor against anxiety (21,22). It is possible to define personal satisfaction as a sense of professional recognition and self-sufficiency (21). In particular, providing psychological support to front-line employees seems to retain its importance over the coming weeks and months (19). Besides, in our study, insomnia and concentration disorders were detected by 75% in the severe anxiety group. In a study conducted during the pandemic, health employees' anxiety was reported between 13% and 46.4%, and insomnia was reported between 20% and 89.7% (23). Another study conducted on health employees in Wuhan found a high prevalence of anxiety (44.6%) (along with high depression, insomnia, and general distress) (24). In another study, the prevalence of insomnia was 32-34% (25). Surveys conducted during the COVID-19 outbreak found a significant relationship between anxiety and depression and sleep quality (26). In the study, which investigated the findings of Novitiate syndrome for health professionals in Italy, 45% of participants reported experiencing at least one physical symptom, including increased irritability, changes in eating habits, difficulty falling asleep, and muscle tension (19). In our study, somatic symptoms such as chest constriction sensation, palpitations, novelties, and gastrointestinal tenderness were observed in 81% of the severe anxiety group employees. Besides, all participants answered the open-ended questions of our survey in writing. It suggested that this reflected the desire of medical staff to express and share their feelings and concerns. Our study found that compared to the group with high-stress levels, the group with low-stress levels regularly exercised at a statistically significantly higher rate. It has been known for many years that regular physical activity benefits individuals with depressive and anxiety symptoms (27). Studies have shown that individuals without psychiatric symptoms who exercise regularly experience better moods than those who do not (28). Also, it is believed that regular exercise can protect against the development of depression due to its healing effects, such as self-esteem, fitness, general well-being, and satisfaction with physical appearance (27). During the COVID-19 pandemic, it is suggested to spend as much time as possible with the family, regular exercise and good nutrition, methods such as therapy and meditation in order to help reduce the stress of health employees and reducing the use of social media can be considered to avoid stimuli that arouse anxiety (23). In order to avoid the undesirable social, psychological, and economic burden like working factors (excessive workloads, irregular working hours, the uncertainty of personal protection equipment), personal characteristics (work-life imbalance, insufficient social support, sleep deprivation), and organizational factors (workload, expectations, rewards, and peer communication are insufficient, managers negative feedback) it is essential to determine the cause of the outbreak (19). Our work has some limitations. First, the data from self-reported surveys were not compared with clinical data on healthcare professionals' health. Second, health workers were not asked if any of their relatives had COVID-19.

Table 2. Summary of individuals characteristics with regard to anxiety level					
	Level of anxiety (BAI)				
	Minimal (n=17)	Mild (n=48)	Moderate (n=44)	Severe (n=16)	p
Age	32.18±6.37	33.54±7.51	34.73±8.01	36.63±8.75	0.429[c]
Gender					
Female	9 (52.94%)	38 (79.17%)	34 (77.27%)	11 (68.75%)	0.172[b]
Male	8 (47.06%)	10 (20.83%)	10 (22.73%)	5 (31.25%)	
Duty					
Specialist	2 (11.76%)	7 (14.58%)	4 (9.09%)	2 (12.50%)	0.596[b]
Nurse	7 (41.18%)	27 (56.25%)	24 (54.55%)	8 (50.00%)	
Stuff	1 (5.88%)	3 (6.25%)	5 (11.36%)	4 (25.00%)	
Assistant doctor	4 (23.53%)	6 (12.5%)	6 (13.64%)	1 (6.25%)	
Technician	3 (17.65%)	3 (6.25%)	5 (11.36%)	0 (0%)	
Secretary	0 (0%)	1 (2.08%)	0 (0%)	0 (0%)	
Lecturer	0 (0%)	1 (2.08%)	0 (0%)	1 (6.25%)	
Unit					
Pandemic ICU	4 (23.53%)	15 (31.25%)	13 (29.55%)	3 (18.75%)	0.495[b]
CVS ICU	0 (0%)	3 (6.25%)	5 (11.36%)	2 (12.50%)	
PACU	2 (11.76%)	6 (12.50%)	6 (13.64%)	2 (12.50%)	
Operating room	2 (11.76%)	10 (20.83%)	13 (29.55%)	4 (25.00%)	
IM ICU	6 (35.29%)	9 (18.75%)	4 (9.09%)	5 (31.25%)	
Other	3 (17.65%)	5 (10.42%)	3 (6.82%)	0 (0%)	
Symptoms					
Tiredness	13 (76.47%)	42 (87.50%)	38 (86.36%)	14 (87.50%)	0.715[b]
Insomnia and concentration disorder	6 (35.29%)	34 (70.83%)	27 (61.36%)	13 (81.25%)	0.026[b]
Forgetfulnes	5 (29.41%)	23 (47.92%)	29 (65.91%)	12 (75.00%)	0.017[b]
Somatic complaints	7 (41.18%)	23 (47.92%)	24 (54.55%)	13 (81.25%)	0.085[b]
Mental complaints	6 (35.29%)	30 (62.5%)	34 (77.27%)	12 (75.00%)	0.015[b]
Sleep	9 (52.94%)	39 (81.25%)	33 (75.00%)	14 (87.50%)	0.076[b]
Spor	7 (41.18%)	19 (39.58%)	10 (22.73%)	4 (25.00%)	0.259[b]
Psychological support	0 (0%)	7 (14.58%)	5 (11.36%)	1 (6.25%)	0.360[b]
Eating					
Decreased	4 (23.53%)	14 (29.17%)	16 (36.36%)	4 (25.00%)	0.924[b]
Same	6 (35.29%)	15 (31.25%)	10 (22.73%)	5 (31.25%)	
Increased	7 (41.18%)	19 (39.58%)	18 (40.91%)	7 (43.75%)	
Separation from family	7 (41.18%)	23 (47.92%)	23 (52.27%)	8 (50.00%)	0.889[b]
Smoking					
Never smoked	8 (47.06%)	29 (60.42%)	20 (45.45%)	6 (37.50%)	0.358[b]
Still smoking	5 (29.41%)	16 (33.33%)	19 (43.18%)	8 (50.00%)	
Quit smoking	4 (23.53%)	3 (6.25%)	5 (11.36%)	2 (12.50%)	
Stress					
No	1 (5.88%)	9 (18.75%)	21 (47.73%)	14 (87.50%)	<0.001[b]
Yes	16 (94.12%)	39 (81.25%)	23 (52.27%)	2 (12.50%)	

Table 2. Continued					
	Level of anxiety (BAI)				
	Minimal (n=17)	Mild (n=48)	Moderate (n=44)	Severe (n=16)	p
Media					
More than ever	13 (76.47%)	30 (62.50%)	29 (65.91%)	10 (62.50%)	0.955[b]
Less than usual	4 (23.53%)	13 (27.08%)	12 (27.27%)	4 (25.00%)	
More than ever	0 (0%)	2 (4.17%)	2 (4.55%)	1 (6.25%)	
Less than usual	0 (0%)	3 (6.25%)	1 (2.27%)	1 (6.25%)	
PSS score	31.88±3.72	33.48±4.85	32.25±6.80	34.31±5.28	0.349[c]

BAI: Beck anxiety inventory, CVS: cardiovascular surgery, ICU: intensive care unit, IM: ınternal medicine, PACU: post-anesthesia care unit, PSS: perceived stress scale, data are given as mean ± standard deviation or median (1st quartile-3rd quartile) for continuous variables according to normality of distribution and as frequency (percentage) for categorical variables, [b]Pearson chi-square test, [c]ANOVA test

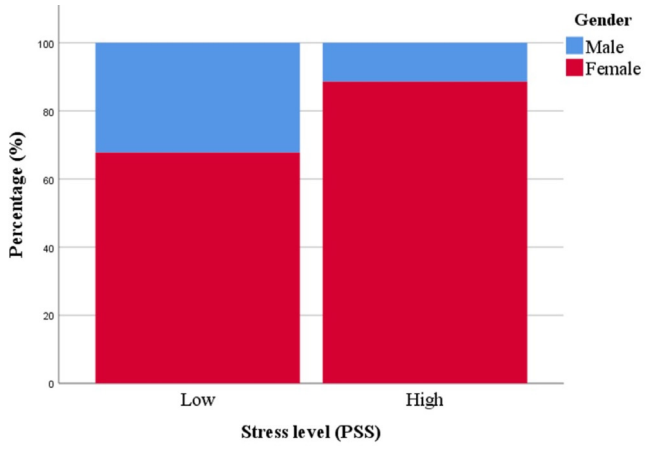

Figure 1. Gender distribution with regard to stress level
PSS: Perceived stress scale

Conclusion

Because intensive care and operating room employees are healthy employees on the front lines responding to the COVID-19 outbreak, health care professionals' investment should be made to avoid short-and long-term distress caused by anxiety and stress. Essential measures should be taken to identify and manage employee anxiety and its consequences, especially in the early stages of COVID-19. Instead of reacting later when stress deepens, it is more beneficial to start moving in advance in terms of employee health. Even though our study revealed the state of anxiety and stress, especially for staff working in the operating room and intensive care units, we think it might reflect front-line workers in hospitals.

Ethics

Ethics Committee Approval: The study was approved by the Ministry of Health and the Ethics Board on 18 January 2021 (decision no: 2021/02-38) from the Dokuz Eylül University.

Informed Consent: An informed consent form was obtained from the participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: Ö.Ö., S.B., N.G., Design: Ö.Ö., S.B., N.G., Data Collection and Process: Ö.Ö., S.B., N.G., Analysis or Interpretation: Ö.Ö., S.B., N.G., Literature Search: Ö.Ö., S.B., N.G., Writing: Ö.Ö., S.B., N.G.

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ORIGINAL RESEARCH / *ÖZGÜN ARAŞTIRMA*

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Özlem Terzi

CT Measured Cardiovascular and Metabolic Risk Factors in Patients with COVID-19 Infections

COVİD-19 Olgularında BT ile Değerlendirilen Kardiyovasküler ve Metabolik Risk Faktörleri

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ABSTRACT *Objective:* The aim of this study was to document some measurable thoracic computed tomography (CT) parameters investigated as a risk factors for prognosis in patients with coronavirus disease-2019 (COVID-19).
Materials and Methods: We retrospectively analysed the patients with COVID-19 infection in three groups. Group 1 patients were the patients who were treated in the inpatient clinic or at home for COVID-19 pneumonia, group 2 patients consisted of patients who survived after treatment for COVID-19 pneumonia in intensive care unit (ICU), group 3 patients consisted of patients who died during treatment for COVID-19 pneumonia in the ICU. We evaluated the diameter of the aorta (A) and pulmonary artery (PA), PA/A ratio, cardiothoracic ratio (CTR), the fat to muscle ratio, and paraspinal muscle density as CT parameters evaluated as risk factors for COVID-19 infection.
Results: The median age of all patients was 67 (Q1: 58-Q3: 75) and 60,6 % (n=143) of the patients were male. CTR was the only parameter for admission to ICU found statistically significant in multivariate analysis for both men and women. Additionally, it was the only significant risk factor for death in patients with COVID-19 infection. Although not statistically significant, the diameter of PA was found to be high in all groups. The other parameters evaluated did not provide statistically significant results between the groups.
Conclusion: CTR may be taken into consideration as a potential risk factor in the evaluation of the patients with COVID-19 infections The diameter of PA was found to be higher in all groups so it might be an indicator of inflammation of the lungs.
Keywords: CT, COVID-19, metabolic

ÖZ *Amaç:* Bu çalışmanın amacı koronavirüs hastalığı-2019 (COVİD-19) olgularında risk faktörü olabilecek toraks bilgisayarlı tomografi (BT) tetkiki ile değerlendirilen bazı ölçülebilen parametrelerin dökümente edilmesidir.
Gereç ve Yöntem: Çalışmada COVİD-19 olguları retrospektif olarak incelendi ve 3 grup oluşturuldu. Grup 1 COVİD-19 pnömonisi nedeni ile normal servislerde veya evde tedavi olan olgular, grup 2 COVİD-19 pnömonisi olan ve yoğun bakım ünitesine (YBÜ) alınan ve yaşayan olgular, grup 3 ise COVİD-19 pnömonisi sonrası eks olan olgulardan oluştu. BT tetkikinde aorta (A) ve pulmoner arter (PA) çapı, PA/A oranı, kardiyotorasik oran (KTO), yağ kas oranı, paraspinal kas densitesi gibi COVİD-19 enfeksiyonu için risk olarak kabul edilen parametreler değerlendirildi.
Bulgular: Olguların ortanca yaşı 67 yıl idi (Q1: 58-Q3: 75). Olguların %60,6'sı (n=143) erkek hastalardı. Multivariate analizde KTO, erkek ve bayan olgular için YBÜ'ye başvuruda tespit edilen tek risk faktörü idi. Ek olarak COVİD-19'lu erkek olgularda KTÖ ölüm riski ile ilişkili olarak bulunan tek parametre idi. Tüm olgularda PA çapı normalden daha yüksek bulundu. Diğer incelenen parametrelerde gruplar arasında istatistiksel olarak anlamlı bir fark saptanmadı.
Sonuç: KTO, COVİD-19 olgularının değerlendirilmesinde potansiyel bir risk faktörüdür. PA çapı tüm olgularda yüksek olup akciğer enflamasyonunun bir bulgusu olabilir.
Anahtar Kelimeler: BT, COVİD-19, metabolik

Introduction

Coronavirus disease-2019 (COVID-19) is a complicated infectious disease with different organ involvements affecting the lung predominantly. It spread all over the world and became a burden to healthcare systems. The real time reverse transcription polymerase chain reaction (RT-PCR) test is considered the gold standard for the diagnosis of coronavirus. Moreover, the computed tomography (CT) examination is performed with high sensitivity in diagnosis with short acquisition times. It is almost routine in emergency settings in many hospitals in patients evaluation for coronavirus infection. It provides early diagnosis of the disease with great sensitivity and detects its complications that is an advantage for disease management and prognosis (1). It is known that the older age, male sex and additional comorbid diseases such as hypertension and diabetes are associated with bad prognosis and decreased survival in patients with COVID-19 (2,3). Therefore, it is important to detect the possible risk factors affecting disease's prognosis in the first evaluation of the patient for early intervention. It has been demonstrated that imaging-based cardiac indices can predict increased risk of morbidity and mortality in a number of acute and chronic illnesses. In individuals with respiratory disorders, an elevated cardiothoracic ratio (CTR) or increased pulmonary artery-to-aorta (PA/A) ratio is associated with an unfavorable prognosis (4,5); these indices might also be indicative of increased risk of cardiovascular diseases (6,7). In Eslami et al.'s (8) study, the elevated CTR and increased PA/A ratio associated with bad prognosis in patients with COVID-19 pulmonary diseases. Body composition was also evaluated in different CT studies in patients with COVID-19 for detecting muscle mass or visceral obesity [high visceral to subcutaneous adipose tissue (SAT) area ratio] (9-11). They found that increased visceral accumulation of fat is linked to worse COVID-19 severity.

The aim of this study is to document some measurable CT parameters investigated as a risk factors for prognosis in patients treated in intensive care units (ICU) for COVID-19 and to compare the data with patients treated in inpatient clinic, or at home.

Materials and Methods

We retrospectively analysed the patients with COVID-19 infection who had treatments in our ICU founded for COVID-19 pandemic between March 2020 and May 2021. All of the participants in the study had thorax CT scans and real-time reverse transcriptase polymerase chain reaction (RT-PCR) results that were positive. Totally 151 patients were treated. Of all 79 patients were treated successfully, in contrast, 72 patients succumbed because of the disease itself or its complications. The patients with acute coronary syndrome, pulmonary emboli and oxygen dependent chronic obstructive pulmonary disease were excluded from the study. In addition, suboptimal image quality due to motion artefacts and narrow field of view were not included. We also grouped 85 patients with COVID-19 for comparison that had pneumonia of COVID-19 infection and given medical and supportive treatments inpatient unit of our hospital or at home. These patients were chosen randomly from patients that applied our hospital for COVID-19 infection, had positive nasopharyngeal swab for RT-PCR and thorax CT examination. These patients were at the same age and sex. We made three groups of patients; group 1 patients were the patients that were treated in inpatient clinic or at home for COVID-19 pneumonia, group 2 patients consisted of patients that survived after treatment for COVID-19 pneumonia in ICU, group 3 patients consisted of patients that expired during treatment for COVID-19 pneumonia in ICU. We did not note the CT severity scores of the patients because we don't know the exact stage of the disease and different stages may cause faulty evaluation.

All thorax CT examinations were evaluated by one general radiologist with 18 years experience. If the patient had more than one CT only the initial CT was evaluated. CT images were obtained from 128 slice CT scanner (Philips Ingenuity CT scanner, Germany) in supine position, in end inspiration stage. CT exams were performed with low dose protocol and IV contrast material were not given. The scanning parameters were tube voltage: 120 kVp; tube current: 50-90 mAs with automatic exposure control, slice thickness: 1 mm. The fat to muscle ratio (FMR) was calculated from axial CT images at T11-T12 level by dividing the waist circumference to mean muscle circumference. We calculated the waist circumference manually by drawing the abdominal circumference and both paravertebral muscle circumferences at the level of T11-T12th vertebra (Figure 1). The CTR was calculated by dividing the greatest transverse diameter of the heart to the greatest transverse diameter of the inner to inner thoracic cavity (Figure 2). In addition, the diameter of ascending A and main PA were calculated at the level of pulmonary bifurcation (Figure 3). Then PA/A ratio was

noted. In addition we calculated the right paraspinal muscle density (PMD) at the level of T11-T12th vertebra. The 1.5 cm^2 sized region of interest was drawn manually and the mean Hounsfield unit (HU) and standard deviation was collected (Figure 4).

Statistical Analysis

We used SPSS (Version 22 for Windows, SPSS Inc, Chicago, IL, USA) programme for analysis of data. The continuous variables were presented as mean ± standard deviation if they are parametric values and presented as median (first quarter-Q1 and third quarter-Q3) if they are nonparametric values. The suitability of variables for normal distribution were evaluated by "Shapiro-Wilk test". The variables that were not normally distributed were evaluated by "Kruskal-Wallis test". Then the variables that were statistically significant were analysed by "Bonferroni corrected Mann-Whitney U test" for detect the group forming statistical difference. The logistic regression analysis were used for evaluation of factors affecting ICU admission and death according to the sex in univariate and multivariate analysis. Statistically significant difference accepted as $p<0.05$ for Kruskal-Wallis test and logistic regression analysis and $p<0.016$ for Bonferroni corrected Mann-Whitney U test.

The protocol for this retrospective study received permission from the Ondokuz Mayıs University Clinical Research Ethics Committee (decision no: 2021/393, date: 23.09.2021).

Results

The median age of the all patients was 67 (Q1: 58-Q3: 75) and 60.6% (n=143) of the patients were male. Fifty seven (39.9%) of male patients were treated in service and survived (group 1-m), 45 (31.5%) of them were treated in ICU and survived (group 2-m) and 41 (28.7%) were treated in ICU and died (group 3-m).

The study parameters of male patients were shown in Table 1. There was statistically significant difference in the median values of age, FMR and CTR between three groups (p=0.001, p=0.033 and p=0.001 respectively).

Of 93 woman 28 (30.1%) were treated in service and survived (group 1-f), 34 (36.6%) were treated in ICU and survived (group 2-f), 31 (33.3%) were treated in ICU and

Table 1. The study parameters of male patients [median (Q1-Q3)]

	Group 1-m (n=57)	Group 2-m (n=45)	Group 3-m (n=41)	p*
Age (year)	66 (57-74)	61 (49-71)	69 (60-76)	0.001 1-2:0.056 1-3:0.36 2-3:0.006
Abdominal cicumference	1026 (977-1072)	1030 (93-1108)	1040 (95-1110)	0.11
Muscle circumference	191 (169-199)	186 (170-192)	183 (161-192)	0.26
Fat to muscle ratio	5.5 (5.0-6.1)	5.6 (5.3-6.0)	5.8 (5.3-6.2)	0.033 1-2:0.013 1-3:0.041 2-3:0.82
Cardiotoracic ratio	0.46 (0.40-0.51)	0.51 (0.46-0.54)	0.52 (0.48-0.55)	0.001 1-2:0.008 1-3<0.001 2-3:0.21
The diameter of pulmonary artery	29 (26-31)	29 (27-33.5)	30 (26.5-32)	0.15
The diameter of aorta	38 (35-41)	36 (33-39)	38 (35.5-40.0)	0.77
Pulmonary artery to aorta ratio	0.75 (0.71-0.81)	0.81 (0.74-0.90)	0.78 (0.71-0.84)	0.17
Paraspinal muscle density	46.9 (35.5-53.0)	49.0 (32.7-57.7)	44.2 (33.7-56.6)	0.48
Standard deviation of paraspinal muscle density	25.4 (19.3-34.0)	27.0 (22.2-32.3)	29.9 (21.6-36.1)	0.06

*The statistical significance was accepted as p<0.05 for Kruskal-Wallis tests and p<0.016 for Bonferroni corrected Mann-Whitney U test

Table 2. The study parameters of female patients [median (Q1-Q3)]				
	Group 1-f (n=28)	**Group 2-f (n=34)**	**Group 3-f (n=31)**	**p***
Age (year)	63.5 (60-70)	65 (60-75)	81 (66-83)	0.021 1-2:0.53 1-3:<0.001 2-3:0.002
Abdominal cicumference	995.5 (938-1118)	1072 (977-1145)	985 (897-1121)	0.96
Muscle circumference	167 (147-179)	164 (147-176)	157 (136-178)	0.31
Fat to muscle ratio	5.9 (5.5-6.5)	6.4 (5.9-7.0)	6.4 (5.9-7.1)	0.30
Cardiotoracic ratio	0.48 (0.46-0.54)	0.54 (0.50-0.56)	0.56 (0.52-0.61)	<0.001 1-2:0.001 1-3:<0.001 2-3:0.102
The diameter of pulmonary artery	27.5 (25.2-30.7)	30.0 (27.7-32.2)	30.0 (27.0-33.0)	0.41
The diameter of aorta	37.0 (34.0-39.0)	36.0 (35.0-40.0)	37.0 (34.0-40.0)	0.019 1-2:0.012 1-3:0.72 2-3:0.019
Pulmonary artery to aorta ratio	0.77 (0.71-0.81)	0.82 (0.75-0.87)	0.79 (0.72-0.88)	0.020 1-2:0.008 1-3:0.55 2-3:0.044
Paraspinal muscle density	38.5 (8.9-45.4)	33.9 (15.4-48.7)	25.1 (4.3-39.1)	0.34
Standard deviation of paraspinal muscle density	36.7 (30.4-44.1)	32.2 (27.8-42.4)	32.1 (29.5-45.4)	0.52
*The statistical significance was accepted as p<0.05 for Kruskal-Wallis tests and p<0.016 for Bonferroni corrected Mann-Whitney U test				

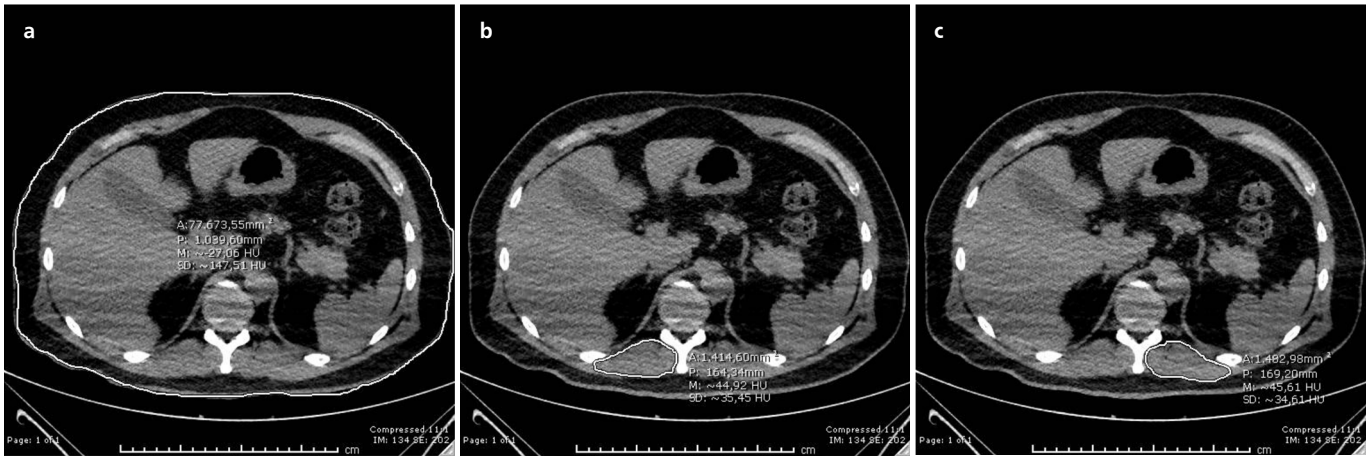

Figure 1. (a-c) The waist circumference were calculated manually by drawing the abdominal circumference and both paravertebral muscle circumferences at the level of T11-T12th vertebra

died (group 3-f). The study parameters of female patients were shown in Table 2. There was statistically significant difference in the median values of age, CTR, diameter of A and the P/A ratio between three groups (p=0.021, p<0.001, p=0.019 and p=0.020 respectively).

We classified the factors according to the sex separately to analyse their impaction on the death in both population. In male population, age and CTR had impaction on the death in univariate analysis. In multivariate analysis, it was seen that the effect of age was disappeared and only CTR [odds

ratio (OR)= 11.45 (confidence interval (CI) 95%=2.65-122.2), p=0.002] was detected as risk factor for death. In contrast, it was found that age was only risk factor in woman in both univariate and multivariate analysis (Table 3).

We also classified the risk factors for admission to ICU according to sex separately. We noticed that age and CTR are risk factors for death in male patients in univariate analysis, but the CTR is only risk factor for admission to ICU in male patient in multivariate analysis [OR=17.50 (CI 95%=3.95-182.72), p<0.001] (Table 4). In woman the age was the only risk factor for admission to ICU in univariate analysis [OR=1.09 (CI 95%=1.043-1.146) , p<0,001] in contrast CTR was only risk factor in multivariate analysis [OR=11.7 (CI 95%=8.1-18.39), p=0.017 (Table 4).

Discussion

Normal values of CTR range between 0.42 and 0.50 and a value above 0.50 is accepted as abnormal and may show cardiomegaly. In our study, the CTR was the only parameter for admission to ICU found statistically significant in multivariate analysis for both men and woman. Additionally, it was an only significant risk factor in death for man with COVID-19 infection. In all group median value of CTR was in normal range in patients that not admitted to ICU as expected. In literature, in Eslami et al.'s (8) study he studied cardiac indices in 87 patients with a diagnosis of COVID-19 infection and discovered that in these patients, CTR is a highly effective predictor of mortality. Additionally, they

Table 3. The comparison of risc factors for death in COVID-19 patients in different sexes

	Male		Female
Univariate			
	OR (CI 95%)	**p***	**OR (CI 95%)**
Age (year)	1.03 (1.004-1.069)	0.028	1.09 (1.043-1.146)
Fat to muscle ratio	1.45 (0.83-2.54)	0.185	1.44 (0.88-2.36)
Cardiotoracic ratio	12.41 (3.40-48.64)	0.001	0.86 (0.34-2.18)
Pulmonary artery to aorta ratio	0.24 (0.11-5.23)	0.36	4.66 (0.06-34.61)
Multivariate			
Age (year)	1.02 (0.98-1.06)	0.19	1.09 (1.04-1.15)
Fat to muscle ratio	0.89(0.46-1.72)	0.73	1.44 (0.76-2.73)
Cardiotoracic ratio	**11.45 (2.65-122.2)**	**0.002**	**0.66 (0.19-2.30)**
Pulmonary artery to aorta ratio	**0.16 (0.005-5.03)**	**0.30**	**4.68 (0.03-652.31)**

OR: Odds ratio, CI: confidence interval, COVID-19: coronavirus disease-2019, *The statistical significance was accepted as p<0.05 for Kruskall-Wallis tests and p<0.016 for Bonferronni corrected Mann-Whitney U test

Table 4. The comparison of risk factors for admission to ICU in COVID-19 patients in different sexes

	Male		Female
Univariate			
	OR (CI 95%)	**p**	**OR (CI 95%)**
Age (year)	1.03 (1.004-1.069)	0.028	1.09 (1.043-1.146)
Fat to muscle ratio	1.45 (0.83-2.54)	0.185	1.44 (0.88-2.36)
Cardiotoracic ratio	12.41 (3.40-48.64)	0.001	0.86 (0.34-2.18)
Pulmonary artery to aorta ratio	0.24 (0.11-5.23)	0.36	4.66 (0.06-34.61)
Multivariate			
Age (year)	0.96 (0.92-0.99)	0.040	1.03 (0.98-1.08)
Fat to muscle ratio	1.35 (0.69-2.62)	0.36	1.88 (0.92-3.87)
Cardiotoracic ratio	17.50 (3.95-182.72)	<0.001	**11.7 (8.1-18.39)**
Pulmonary artery to aorta ratio	**8.39 (0.25-265.43)**	**0.28**	**47.5 (0.18-1214)**

OR: Odds ratio, CI: confidence interval, COVID-19: coronavirus disease-2019

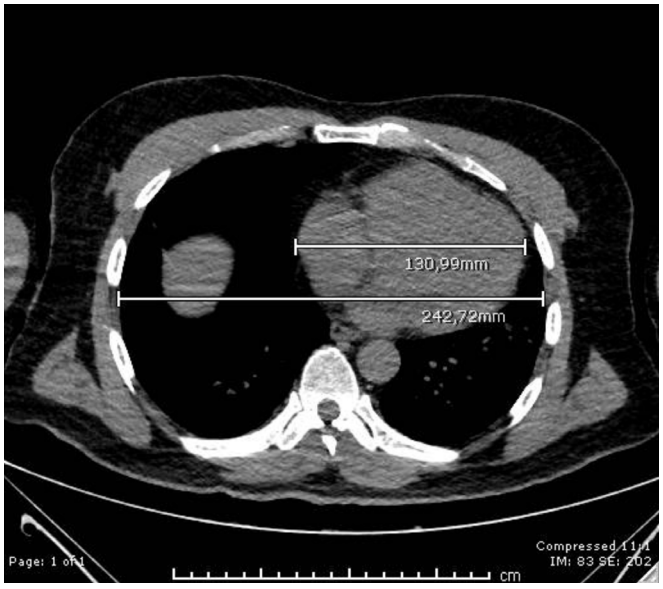

Figure 2. The cardiothoracic ratio was calculated by dividing the greatest transverse diameter of the heart to the greatest transverse diameter of the inner to inner thoracic cavity

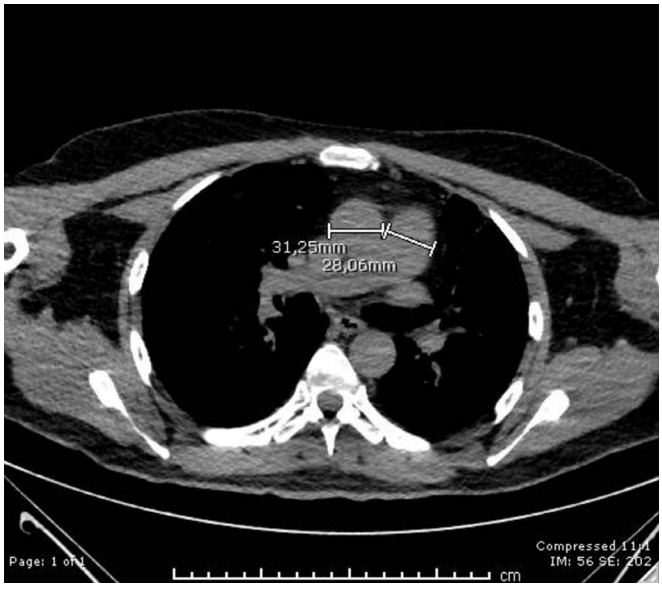

Figure 3. The diameter of ascending aorta and main pulmonary artery were calculated at the level of pulmonary bifurcation

observed a strong correlation between elevated CTR, which was found in 76% of patients who ultimately died and more than 50% of patients who were hospitalized, and poor illness outcomes (8). Our result supported the importance of CTR in prognosis of COVID-19 patients.

In routine radiology practice, chest X-ray is used for measurement of CTR. Miller showed that thorax CT is also can be used for the measurement of CTR and the results showed no statistically significant difference between CT and chest radiography in the evaluation of CTR (12). However, this study did not investigate the correlation between CTR and with other measures of cardiac function or structure at echocardiography (ECHO) or nuclear scintigraphy. The other study by Gollub et al. (13) supported this study by finding that these ratios are equivalent. They showed that there was moderate ability of CT CTR to identify left ventricular hypertrophy [area under the receiver operating characteristic curve (AUC)= 0.70; 95% CI, 0.51Y0.90]. The CT left ventricular short diameter showed a moderate correlation with the ECHO left ventricular internal diameter (r=0.49) and left ventricular mass (r=0.37). But their study was in cancer patients and their prevalence of cardiac disease was very low in the group. Mean age of the patients was 58 years and mean CTR measured at CT was 0.46±0.05. So larger studies were needed for older ages with a high prevalence of cardiac disease.

In our study, except for female patients that didn't need ICU, measurement of PA was ≥29 mm in all groups. A cut-off value of 29 mm for PA diameter is accepted as highly indicative of pulmonary hypertension, while a PA/A ratio >0.9 has been found to be progressively correlated with pulmonary vascular impairment. But in Truong et al.'s (14) study, they

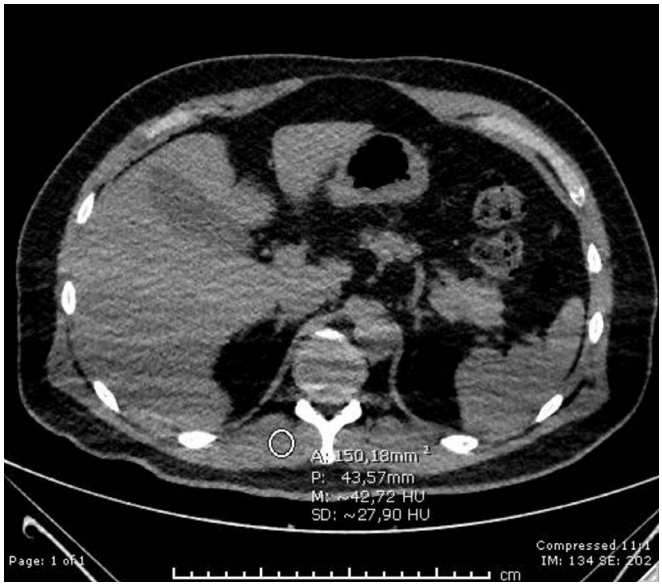

Figure 4. PA to A ratio was noted. The right paraspinal muscle density were noted at the level of T11-T12th vertebra. The 1.5 cm^2 sized ROI was drawn manually and the mean Hounsfield unit and standard deviation was collected
ROI: Region of interest

established sex-specific normative reference values for mPA of 29 mm in males and 27 mm in women, and 0.9 for ratio PA. Therefore, the median of PA was higher in all groups in our study. We don't know it was because of disease itself or was present before. As we consider the PA/A ratio, we found the statistically significant difference between the female patients treated in inpatient clinics or at home and the female patients lived in ICU. When compared to findings obtained from earlier chest CTs that were conducted for any reason other than cardiovascular illnesses, Spagnolo discovered that COVID-19 patients had greater median PA maximal diameter and median PA/A ratio values (median 36 months) (15). They hypothesized that the inflammatory state brought on by the severe acute respiratory syndrome coronavirus-2 infection may be connected to an increase in pulmonary vascular pressure. Patients with good and adverse outcomes differed significantly in terms of PA maximum diameter. In their study, median age was 75 years old and was older compared to our study. In Eslami et al.'s (8) study, they noted a nonsignificant increase in the odd of the death in patients with PA/A>1 that is a possible marker of pulmonary hypertension. These results combined with ours may show that diameter of PA is a finding deserving further investigation as a potential effect of COVID-19 inflammation on it.

It was known that age is an important known prognostic factor in COVID-19 infection. Our study supported this finding yet we found it as a significant risc factor in both admission to ICU and death in male and female patients with COVID-19 infection in univariate analysis. Moreover it was also a risc factor for death in woman with COVID-19 infection in multivariate analysis.

In addition to several cardiac indices, we assessed FMR to comprehend its role in COVID-19 infection prognosis. After studying FMR, Kottlors et al. (16) discovered that it might be used to predict whether a patient would require ICU treatment after being admitted. They suggested it is an important factor next to age and gender within a logistic regression analysis. Examining the logistic regression graphics, the possibility of a potential ICU treatment decrease below 50% at a FMR of 5.5 and is going down in the range of less than 10% at a FMR of under 5. However, the possibility of the requirement for an ICU treatment increases to about 80% at a FMR of 7 and higher. In our study, although FMR was lower in patients in group 1 in both genders which were not admitted to ICU, there were no difference between three groups in terms of FMR in female. Although it was statistically different in male patients between group 1 and 2 and between group 1 and 3, it was not noted as a risk factor in statistical analysis. The paravertebral skeletal muscle mass on both sides of the spine, which includes the skeletal muscle mass of the erector spinae muscle, longissimus thoracis muscle, spinalis thoracis muscle, and iliocostalis lumborum muscle, was found to be independently associated with ICU admission and in-hospital mortality by Schiaffino et al. (17). Ufuk discovered that in adult COVID-19 patients, pectoralis muscle area (PMA) and pectoralis muscle index [= PMA/patient's height square (m^2)] are strongly related with a number of unfavorable outcomes (18). Giraudo et al. (19) looked at whether low muscle mass-defined as HU values below 30-was a reliable indicator of ICU admission and/or unfavorable results. They emphasized that the severity and progression of the disease may be significantly impacted by the early symptoms of muscle loss (19). We found no significant difference in PMD in all groups. Although we noted the HU values <30 (mean: 25.1) in female patients that expired during treatment for COVID-19 pneumonia in ICU, it was not statistically significant. The age of woman was older in that group and the reason may be related to it. At the level of the T7-T8 vertebrae, Besutti investigated the density of the pectoralis muscles and the total, visceral (VAT), and intermuscular adipose tissue (20). They discovered that in COVID-19, VAT was specifically linked to an inflammatory response, whereas all other indices, including pectoral muscle density, were linked to parenchymal involvement. Low muscle quality appears to be one mechanism for the powerful effect of age on COVID-19 mortality.

Obesity is recognized as a risk factor for hospitalization as well as the need for mechanical ventilation in patients with COVID-19. (21). Additionally, it is regarded as a low-grade inflammatory state, with various inflammatory products secreted by adipose tissue (22). VAT, which secretes inflammatory cytokines, is metabolically more active than SAT, which is more passive. The metabolic syndrome, heart disease, and an elevated risk of infection and septic shock are all associated with VAT. Bioelectrical impedance analysis is a method used for assessing skeletal muscle mass. They are used for defining the patients with sarcopenia and cachexia. But in clinical practice, it is difficult to use this technique, especially in emergency conditions in patients with COVID-19. Therefore, it is logical to use a method routinely used for evaluating COVID-19 patients for investigating obesity. CT is used in some studies for

measuring the visceral fat. Chandarana et al.'s (11) studied visceral and subcutaneous fat tissue in patients with COVID-19 patient. In contrast to outpatients, hospitalized COVID-19 patients had higher levels of VATL3, and Chandarana et al.'s (11) study with 51 patients found that adding VATL3 to the clinical model increased AUC in separating hospitalized from outpatients. Body mass index (BMI) differences between the two groups of patients were not statistically significant. Other risk factors for hospitalization and severe illness have also been found, including diabetes mellitus, hypertension, a history of cardiac disease, and an immunocompromised state. In our study there were no difference between CT measured abdominal crcumference between groups that include subcutanous and visceral fat. But we don't know the BMI of the patients.

Our study has some limitations. First there was a statistically significant difference between the age of the woman with COVID-19 infection died in ICU was compared to other groups. But we could not find the patients of the same age and sex for woman that not admitted to ICU for COVID-19 treatment in our hospital. The second limitation is the BMI of the patient, which is important in body composition and was not known. The third, as a part of national CT guidelines, non-contrast and non-gated chest CT was used in all patients, decreasing accuracy in measurements of vessels and ratios, especially in obese patients. Further studies with larger study groups with BMI values available and with additional cardiac studies such as ECHO were needed to evaluate CT parameters.

Conclusion

In summary, the evaluation of some CT parameters in our study showed the CTR may be taken into consideration as a potential risk factor in the evaluation of the patients with COVID-19 infection. High CTR values increase the risk of ICU admission and also death of the patient with COVID-19 infection. It supports the other studies in the literature. The diameter of PA is found higher in all groups so it might be an indicator of inflammation of lungs. But if the previous CT values were known, it would be more concise decision. FMR and PMD are not found as a risk factor in admission to ICU or death of the patient in our study, which differed from other studies. The reason is not known. The further studies with larger groups with known BMI indexes may be more accurate.

Ethics

Ethics Committee Approval: The protocol for this retrospective study received permission from the Ondokuz Mayıs University Clinical Research Ethics Committee (decision no: 2021/393, date: 23.09.2021).

Informed Consent: Retrospective study.

Peer-review: Internally and externally peer-reviewed.

Authorship Contributions

Concept: E.M.K.U., Design: E.M.K.U., Data Collection and Process: E.M.K.U., Ö.T., Analysis or Interpretation: Ö.T., Literature Search: E.M.K.U., Ö.T., Writing: E.M.K.U., Ö.T.

Conflict of Interest: No conflict of interest was declared by the authors.

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ÖZGÜN ARAŞTIRMA / *ORIGINAL RESEARCH*

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COVİD-19 Pnömonili Hastalarda, Eritrosit Dağılım Genişliği Değerinin, Mortalite ile İlişkisi

The Relationship of Erythrocyte Distribution Width Value with Mortality in Patients with COVID-19 Pneumonia

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ÖZ *Amaç:* Koronavirüs hastalığı-2019 (COVİD-19) pnömonili hastalarda hastaneye yatış, yoğun bakım ünitesi (YBÜ) ihtiyacı ve mortalite oranları yüksektir. Bu çalışmada COVİD-19 pnömonili hastaların yoğun bakım ihtiyacı ve mortalite oranlarını, ucuz ve erişilebilir olması nedeniyle, kırmızı kan hücresi dağılım genişliği (RDW) değeri ile takip etmeyi amaçladık.
Gereç ve Yöntem: Çalışmaya, YBÜ'de yatan şiddetli COVİD-19 pnömonili hastalar (n=162), serviste yatan hafif COVİD-19 pnömonili hastalar (n=163) ve sağlıklı bireyler (COVİD-19 pnömoni öyküsü olmayan sağlık çalışanları) (n=162) dahil edildi. Hastaların hastaneye başvuru sırasında alınan ilk hemogramlarından hemoglobin (HGB), beyaz kan hücresi (WBC), kırmızı kan hücresi (RBC) ve RDW değerleri tespit edilerek, mortalite üzerindeki etkileri retrospektif olarak değerlendirildi.
Bulgular: Mortaliteye göre gruplar karşılaştırıldığında, COVİD-19 hastalığından ölen hastaların yaş ortalaması daha yüksek tespit edildi. Yaş bakımından düzeltilmiş model sonuçlarına göre mortaliteye etkili risk faktörlerinin araştırıldığı çalışmamızda, RDW değerinin mortalite üzerinde etkili olmadığı görüldü. Ayrıca yaş, HGB, WBC ve COVİD-19 pozitifliğinin mortalite üzerindeki etkisi istatistiksel olarak anlamlı bulundu.
Sonuç: Mortalitesi yüksek olan şiddetli COVİD-19 pnömonili hastaların YBÜ'de takiplerini azaltmak için hızlı ve kolay erişilebilen belirteçlere ihtiyaç vardır. Çalışmamızda WBC, HGB gibi hematolojik parametrelerin mortalite üzerindeki etkisi anlamlı iken RDW değerinin mortalite üzerinde etkili olmadığı görülmüştür. Bu konuda yapılacak prospektif randomize çalışmalara ihtiyaç vardır.
Anahtar Kelimeler: COVID-19 pnömonisi, eritrosit dağılım genişliği, yoğun bakım, mortalite

ABSTRACT *Objective:* Patients with coronavirus disease-2019 (COVID-19) pneumonia have high hospitalization, intensive care unit (ICU) need and mortality rates. In this study, we aimed to follow-up the need of intensive care and mortality rates in patients with COVID-19 pneumonia with red blood cell distribution width (RDW) value because it is a cheap and easyl accesible marker.
Materials and Methods: Patients with severe COVID-19 pneumonia hospitalized in the ICU (n=162), patients with mild COVID-19 pneumonia hospitalized in the ward (n=163), and healthy individuals (healthcare workers without a history of COVID-19 pneumonia) (n=162) were included in the study. Hemoglobin (HGB), white blood cell (WBC), red blood cell and RDW values were determined from the first admission hemogram and their effect on mortality was evaluated retrospectively.
Results: When the groups were compared according to mortality, the average age of the patients who died of COVID-19 was found to be higher. According to the age-adjusted model analysis, in our study, in which the risk factors affecting mortality were investigated, RDW value was not found to be effective on mortality. Also age, HGB, WBC and COVID-19 positivity were found to be statistically significant parameters on mortality.
Conclusion: Rapid and easily accessible markers are needed to reduce the follow-up of patients with severe COVID-19 pneumonia with high mortality in the ICU. In our study, while the effect of hematological parameters such as WBC and HGB on mortality was significant, it was observed that the RDW value did not affect mortality. Prospective randomized studies are needed in this regard.
Keywords: COVID-19 pneumonia, erythrocyte distribution width, intensive care unit, mortality

Giriş

Koronavirüs hastalığı-2019 (COVİD-19), şiddetli akut solunum yetmezliği sendromu koronavirüs-2 (SARS-CoV-2) etkenine bağlı gelişen (1), asemptomatik, hafif üst solunum yolu enfeksiyonu gibi hafif tablolarla başlayıp, solunum yetmezliğinin eşlik ettiği ağır viral pnömonilere varan, geniş spektrumlu bir hastalıktır (2). COVİD-19, Mart 2020'de Dünya Sağlık Örgütü (DSÖ) tarafından pandemi olarak ilan edildiği günden beri dünyada ölüm ve hastalığa neden olmaktadır ve hızla yayılmaya devam etmektedir (3). COVİD-19 hastalarının hastaneye yatış oranı, yoğun bakım ihtiyacı ve mortalitesi yüksektir (4). Son epidemiyolojik veriler, şiddetli COVİD-19 hastalarının ölüm oranının, şiddetli olmayan COVİD-19 hastalarından daha yüksek olduğunu göstermektedir (5). Şiddetli COVİD-19'a ilerleme riski yüksek olan hastaların erken tespiti, uygun destekleyici tedavi ile ölüm oranının azalmasına, gereksiz ve uygunsuz sağlık hizmeti kullanımını azaltacaktır. Ne yazık ki hastalığın tanısında hızlı, kolay ve güvenilir bir test bulunamamıştır.

COVİD-19 hastalığına, çoğunlukla lökopeni, lenfopeni ve bazen trombositopeni eşlik eder (6). Artan D-dimer ve azalan lenfosit sayısı kliniğin kötüleşmesi, yoğun bakım ihtiyacı ve mortalite artışıyla ilişkilidir (7). Bu belirteçler bizim için önemli olmakla birlikte daha fazla prognostik belirtece ihtiyacımız vardır.

Tam kan sayımının bir bileşeni olan ve hücresel hacim varyasyonunu yansıtan kırmızı kan hücresi dağılım genişliğinin (RDW), çeşitli hastalıklarda artmış morbidite ve mortalite riski ile ilişkili olduğu gösterilmiştir (8). RDW, eritrosit kan hücresi (RBC) boyut ve hacim değişkenliğini gösteren, anizositozu (9) işaret eden, basit ve ucuz bir parametredir (10). Klinikte sıklıkla aneminin tanısı, tipi ve derinliğinin belirlenmesinde kullanılmaktadır (11).

Yüksek RDW; kalp hastalığı, akciğer hastalığı, sepsis, grip, kanser ve tüm nedenlere bağlı mortalite için artan risk ile ilişkilidir (12). Yüksek RDW; kalp yetmezliği, koroner arter hastalığının şiddeti, viral hepatit, birçok ileri evre kanser, diyabet, kronik obstrüktif akciğer hastalığı, inme, anemi ve diğer birçok durumun gelişimi için artan morbidite ile ilişkilidir (13). RDW, yeni ve bilinmeyen bir hastalık için yararlı olabilecek genel kantitatif risk sınıflandırması sağlama potansiyeline sahip, spesifik olmayan hastalık belirteci gibi görünmektedir.

RDW-katsayı değişimi, eritrosit hacim dağılımının standart sapmasının (RBC-SS), ortalama eritrosit hacmine (MCV) bölünmesi ve yüzde elde etmek için 100 ile çarpılmasıyla hesaplanır (14). (RBC-SS) / (MCV) × 100

COVİD-19 ilişkili RDW değişikliği için spesifik mekanizma veya mekanizmalar belirsizliğini korumaktadır (15). Retikülositlerin dolaşıma salınmasıyla sonuçlanan herhangi bir işlem RDW'de artışa neden olmaktadır. COVİD-19 hastalarında RDW yüksekliği, proenflamatuvar faktörlerle yakından ilişkilidir. Proenflamatuvar sitokinler, kırmızı kan hücrelerinin yarı ömrünü azaltabilir ve kırmızı kan hücrelerinin morfolojisini değiştirebilir. Enflamasyon, kırmızı kan hücrelerinin olgunlaşmasını geciktirebilir, retikülositozun up-regülasyonu ve çok sayıda retikülositin periferik dolaşıma salınmasına neden olarak RDW'nin artmasına yol açmaktadır (16). Oksidatif stres, RDW mortalite ilişkisine katkıda bulunan faktör olabilir (17). Mekanik ventilasyon ve akut akciğer hasarı olan hastalarda oksidatif stres, kırmızı kan hücrelerinin ömrünü kısaltabilen reaktif aktif oksijen serbest radikallerine neden olmaktadır ve böylece genç hücrelerin dolaşıma salınmasını teşvik etmektedir (18).

Bu çalışmada COVİD-19 pnömonili hastaların yoğun bakım ihtiyacı ve mortalite oranlarını, ucuz ve erişilebilir olması nedeniyle; RDW değeri ile takip etmeyi amaçladık.

Gereç ve Yöntem

Çalışmamıza, Gaziosmanpaşa Eğitim ve Araştırma Hastanesi Etik Kurul onayı ile (karar no: 75, tarih: 01.06.2020) 1 Nisan ve 31 Mayıs 2020 tarihleri arasında, yoğun bakım ünitesinde yatan ağır COVİD-19 pnömonili ters transkriptaz-polimeraz zincir reaksiyonu (RT-PZR) (+) hastalar (n=162) ve serviste yatan hafif COVİD-19 pnömonili RT-PZR (+) hastalar (n=163) ile sağlıklı bireyler (COVİD-19 hastalık öyküsü olmayan, sağlık çalışanları) (n=162) dahil edildi. Dosya taraması yapılarak, hastaların hastaneye başvuru sırasında alınan ilk hemogramlarından, hemoglobin (HGB; g/dL), beyaz kan hücresi (WBC; x10^3/μL), RBC (x10^3/μL), ortalama hücresel hacim MCV (fL) ve RDW (%) değerleri, retrospektif olarak değerlendirildi, üç grup karşılaştırılarak, mortalite üzerine etkisi belirlendi.

COVİD-19 Enfeksiyonunun Tanı ve Tedavisi Kılavuzu'na göre (27 Mayıs 2021 COVİD-19 Rehberi), T.C. Sağlık Bakanlığı Bilimsel Danışma Kurulu tarafından yayınlanan (19):

Hafif olgular: Hastaların hafif klinik semptomları olduğu ve pnömoninin görüntüleme bulgularının olmadığı olgular olarak sınıflandırıldı.

Orta olgular: Hastalarda ateş, solunum yolu semptomları ve pnömoninin görüntüleme bulguları olan olgular olarak sınıflandırıldı.

Ağır olgular: Ateş ve solunum yolu enfeksiyon bulguları olan hastada; 1- solunum sayısı >30/dk, 2- ağır solunum sıkıntısı (dispne, ekstra solunum kaslarının kullanımı), 3- oda havasında oksijen satürasyonu <90 (oksijen alan hastada PaO_2/FiO_2 <300) 4- COVİD-19 pnömonisinin karakteristik göğüs bilgisayarlı tomografi bulgusu olan (bilateral lobüler tarzda, periferik yerleşimli, yaygın yamalı buzlu cam opasiteler), 5- mekanik ventilasyon ihtiyacı, 6- şok, 7- akciğer yetmezliği dışındaki organ yetmezliği nedeniyle yoğun bakım ünitesinde takibi gerekli olan olgular olarak sınıflandırıldı.

İstatistiksel Analiz

Çalışmanın istatistiksel hesaplamasında SPSS Statistics for Windows, version 17.0 kullanılmıştır. Çalışma öncesinde bağımsız 3 grubun RDW ölçümleri arasındaki farkın orta etki büyüklüğünde (d=0,30) Tek-Yönlü Varyans analizi çift taraflı hipotez kontrolü için örneklem büyüklüğü hesaplanmıştır ve her bir gruba 146 kişinin alınmasının uygun olacağı bulunmuştur. Sürekli ölçüm biçiminde elde edilen değişkenlerin dağılımlarının incelenmesi için Shapiro-Wilk normallik testinden faydalanıldı. Dağılım varsayımının sağlanması durumuna göre bağımsız iki grubun kıyaslanmasında Student's t-testi ve Mann-Whitney U testi kullanılırken, ikiden fazla grubun karşılaştırılması için ise Tek-Yönlü Varyans analizi ve Kruskal-Wallis testleri uygulandı. Tek-Yönlü varyans analizi ve Kruskal-Wallis testleri için gruplar arasındaki farkın anlamlı bulunması durumunda, farklılığı yaratan grupların tespiti için çoklu karşılaştırma testlerinden (sırasıyla Bonferroni ve Dunn) yararlanıldı. Kategorik değişkenlerin dağılımları ki-kare ve Fisher'ın Exact testi ile değerlendirildi ve elde edilen sonuçlar sürekli değişkenler için ortalama ± standart sapma - medyan (minimum-maksimum), kategorik değişkenler için ise frekans dağılımları ve yüzdelikler kullanılarak özetlendi. Mortaliteye etkili risk faktörlerini belirlemek için tek değişkenli analiz sonuçlarına göre anlamlı bulunan değişkenler çoklu lojistik regresyon analizi başlangıç modeline dahil edildi ve Bacward LR metoduyla gerçekleştirilen analiz sonucunda, modelde kalan değişkenler olasılık oranları, %95 güven aralıkları ve ilgili p değerleri ifade edildi. Çalışmamızda istatistiksel anlamlılık sınırı p<0,05 olarak alındı.

Bulgular

Çalışmaya yoğun bakım ünitesinde yatan ağır COVİD-19 pnömonili, serviste yatan hafif COVİD-19 pnömonili ve sağlıklı bireyler (COVİD-19 pnömoni öyküsü olmayan, sağlık çalışanları) olmak üzere 487 hasta dahil edildi. Ağır pnömonili, hafif pnömonili ve sağlıklı bireylerin medyan yaş değerleri arasında fark gözlendi (64/58/32; p<0,001) (Tablo 1). Ağır pnömonili ve hafif pnömonili hastaların medyan yaş değerleri benzer iken, kontrol grubu medyan yaş değeri daha düşük idi (Tablo 1). Cinsiyet dağılımına bakıldığında; her üç grup benzer bulundu (p=0,062). Ağır pnömonili hastaların, hafif pnömonili hastaların ve sağlıklı bireylerin hematolojik parametrelerine bakıldığında HGB medyan değerleri arasında anlamlı bir fark saptandı (p<0,001) (Tablo 1). Hafif pnömonili ve sağlıklı bireyler de RBC ortalama değerleri benzer iken ağır pnömonilerde RBC değeri diğer iki gruptan düşük bulundu (p<0,001) (Tablo 1). Bu da, hastalığın eritrositlerin yarılanma ömrünü kısalttığını veya üretimlerini baskıladığını göstermektedir. Ağır pnömonili hastaların, hafif pnömonili hastaların ve sağlıklı bireylerin WBC ve RDW medyan değerleri karşılaştırıldığında gruplar arasında anlamlı fark saptandı (p<0,001) (Tablo 1).

Mortaliteye göre gruplar karşılaştırılığında COVİD-19 hastalığından ölen ve sağ kalan hastaların yaş ortalamaları arasında anlamlı fark saptandı (66,23±13,30/47,73±18,95; p<0,001) (Tablo 2). COVİD-19 hastalığından ölen hastaların yaş ortalaması daha yüksek idi. COVİD-19 hastalığından ölen ve sağ kalan hastaların hematolojik parametreleri karşılaştırıldığında HGB, RBC, WBC, RDW değerleri arasında anlamlı bir fark saptandı (p<0,001) (Tablo 2).

Mortaliteye etkili risk faktörlerinin araştırıldığı çoklu lojistik regresyon analizi sonuçları incelendiğinde yaş bakımından düzeltilmiş bir modelle Backward LR opsiyonu kullanılarak elde edilen sonuçlara göre RDW değerinin mortalite üzerine etkili olmadığı görülmüştür (Tablo 3). Ayrıca yaş, HGB, WBC ve COVİD-19 pozitifliğinin mortalite üzerine etkisi istatistiksel olarak anlamlı bulunmuştur (p<0,001) (Tablo 3).

Tartışma

Çalışmada, RDW değerinin; COVİD-19 hastalığı nedeniyle yoğun bakım ihtiyacı olan ağır pnömonili hastaların tespiti ve mortaliteyi belirlemedeki yeri değerlendirilmiştir. Çalışmanın sonucunda, RDW ile mortalite arasında ilişki bulunmamıştır.

Devam eden COVİD-19 pandemisi, solunum desteği ve yoğun bakım gerektiren ciddiyet düzeyine ilerlemesi nedeniyle, hastane yatakları için önemli talebe yol açarak dünya çapında birçok sağlık hizmeti sistemi aşmıştır (20). Sınırlı sağlık hizmeti kaynakları ile hasta yönetimini iyileştirmek için doğru ve zamanında prognostik bilgiye ihtiyaç duyulmaktadır

Tablo 1. Çalışma grupları arasında demografik ve hematolojik parametreleri arasında yapılan karşılaştırma

	Ağır pnömoni COVİD-19 n=162		Hafif pnömoni COVİD-19 n=163		Kontrol grubu		p
	Ortalama ± standart sapma	Medyan (min-maks)	Ortalama ± standart sapma	Medyan (min-maks)	n=162	Medyan (min-maks)	
Yaş	63,52±14,65	64 (18-98)[a]	58,13±17,14	58 (18-107)[a]	33,02±9,73	32 (18-72)[b]	<0,001
HGB (g/dL)	11,8±2,04	11,8 (7,1-16,4)[a]	13,47±1,43	13,5 (8,316,2)[c]	14,02±1,69	14,2 (8,8-17,3)[b]	<0,001
RBC (x10^3/µL)*	4,17±0,75[a]	4,16 (2,35-6,2)	4,63±0,48[b]	4,66 (3,06-5,63)	4,75±0,56[b]	4,73 (3,42-6,63)	<0,001
MCV (fL)	91,36±66,12	88,45 (10,12-916)[a]	87,07±5,67	87,2 (65,6-110,8)[b]	87,95±5,25	88,10 (64-102)[a]	0,013
RDW (%)	14,62±1,97	14 (11,5-21,2)[a]	13,48±1,15	13,3 (11,4-18,2)[c]	13±1,38	12,9 (4,21-17)[b]	<0,001
WBC (x10^3/µL)	11,38±6,16	10,17 (1,28-50,55)[a]	6,33±2,95	5,42 (2,13-20,78)[c]	8,08±5,37	7,36 (3,62-71)[b]	<0,001

*ANOVA testi p-değeri, tüm diğerleri için Kruskal-Wallis testi sonucudur. [a,b] ve [c] indisler için, aynı harf indisi ile ifade edilen ortalama ya da ortancalar birbirleriyle aynıyken, farklı harflerle gösterilen ortalama ve ortancalar birbirinden istatistiksel olarak farklıdır (p<0,05). COVİD-19: Koronavirüs hastalığı-2019, min-maks: minimum-maksimum, HGB: hemoglobin, RBC: kırmızı kan hücresi, MCV: ortalama eritrosit hacmi, RDW: kırmızı kan hücresi dağılım genişliği, WBC: beyaz kan hücresi

Tablo 2. COVID-19 ölenler ve sağ kalanlar arasında demografik ve hematolojik parametreleri ile yapılan karşılaştırma

	COVİD-19 sağ kalanlar		COVİD-19 ölenler		p
	Ortalama ± standart sapma (min-maks)	Medyan (min-maks)	Ortalama ± standart sapma (min-maks)	Medyan (min-maks)	
Yaş	47,73±18,95	45 (18-107)	66,23±13,3	68 (26-98)	<0,001
HGB (g/dL)	13,53±1,69	13,7 (8,3-17,3)	11,43±2,08	11,5 (7,1-16,4)	<0,001
RBC (x10^3/µL)*	4,64±0,56	4,65 (3,04-6,63)	4,04±0,78	4,05 (2,35-6,2)	<0,001*
MCV (fL)	87,33±6,22	87,7 (32,7-110,8)	94,37±83,45	88,8 (10,12-916)	0,521
RDW (%)	13,42±1,46	13,2 (4,21-21,1)	14,78±2	14,2 (11,9-21,2)	<0,001
WBC (x10^3/µL)	7,67±4,55	7,06 (2,13-71)	12,11±6,89	10,69 (1,28-50,55)	<0,001

*Student's t-test p-değeri, tüm diğerleri Mann-Whitney U testi sonucudur. COVİD-19: Koronavirüs hastalığı-2019, min-maks: minimum-maksimum, HGB: hemoglobin, RBC: kırmızı kan hücresi, MCV: ortalama eritrosit hacmi, RDW: kırmızı kan hücresi dağılım genişliği

(1). Bu nedenle, düşük invazivlik, yüksek verim ve hızlı geri dönüş ile karakterize edilen prognostik laboratuvar testlerinin varlığı, diğer tanısal araştırmalarla karşılaştırıldığında, risk sınıflandırması için oldukça değerli araçlar olabilir (21). Hastanede yatan hastalarda rutin olarak bakılan tam kan sayımı analizlerindeki RDW değeri bu nedenle klinisyenler için ek maliyet olmadan kullanılabilir.

Gong ve ark. (5) yaptıkları çalışmada, şiddetli COVİD-19'a ilerleme riski yüksek olan olguların erken tespiti için etkili bir model oluşturmayı amaçlamışlar ve RDW'nin şiddetli COVİD-

Tablo 3. Çoklu lojistik regresyon analizi

	B	Standart hata	p	Olasılık oranı	%95 güven aralıkları	
					Üst sınır	Alt sınır
Sabit	0,045	1,532	0,977	1,046		
Cinsiyet (Kadın)	-0,594	0,304	0,051	0,552	0,305	1,001
Yaş	0,028	0,009	0,003	1,028	1,009	1,047
HGB (g/dL)	-0,489	0,083	0,001	0,613	0,521	0,722
WBC (x10^3/µL)	0,123	0,025	0,001	1,131	1,078	1,187
COVİD-19 pozitif	2,593	0,944	0,006	13,375	2,102	85,100

Mortaliteye etkili risk faktörlerinin araştırıldığı çoklu lojistik regresyon sonuçlarına göre, yaş bakımından düzeltilmiş bir modelle Backward LR opsiyonu kullanılarak sonuçlar elde edilmiştir. Buna göre; yaştaki 1 br artış mortalite riskini 1,009 kat artırmaktayken, HGB'deki artış mortaliteye olumlu yansımış, WBC'deki kendi birimi cinsinden bir birimlik artış ise mortalite riskini 1,13 kat artırmıştır. Daha önemlisi COVİD pozitifliği ise mortalite riskini 13,37 kat artırmaktadır ve bu değişkenlerin hepsi istatistiksel olarak anlamlı bulunmuştur. COVİD-19: Koronavirüs hastalığı-2019, HGB: hemoglobin, WBC: beyaz kan hücresi

19 için önemli bir prognostik belirteç olduğunu bulmuşlardır. Sharma ve ark. (22) RDW ve mortalite arasında anlamlı bir ilişki olmadığı sonucuna varmışlardır. Bizim çalışmamızda bu sonucu doğrulamaktadır. RDW'nin COVİD-19 enfeksiyon şiddeti ve mortalitesini tahmin etmedeki duyarlılığı ve özgüllüğü, çalışmalar arasında farklılık göstermektedir. Hastaların klinik veya demografik özellikleri çalışma sonuçlarındaki farklılıklara sebep olabilmektedir. RDW'nin COVİD-19'da prognostik biyobelirteç olarak değerlendirilmesi için mevcut protokollerin standardizasyonunun fayda sağlayabileceğini düşünüyoruz.

SARS-CoV-2 ağırlıklı olarak solunum yolu patojeni olmasına rağmen, çok fazlı ve çok faktörlü bir bozukluk olarak ilerler ve akciğer tutulumuna daha sonra sistemik bir immünoenflamatuvar reaksiyon, immünotromboz durum eşlik eder, akciğer ve çoklu organ hasarı oluşur. Yoğun bakım kabul oranındaki farklılıklar toplumların demografik özellikleri, yoğun bakıma kabul kriterleri gibi faktörler ile ilişkilidir. 11 Şubat 2022 tarihi itibariyla resmi olarak DSÖ tarafından kayıt altına alınmış 404.910.528 COVİD-19 olgusu ve 5.783.776 üzerinde mortalite bildirilmiştir (23). Bazick ve ark. (17), 51.785 kritik hasta üzerinde yaptıkları çalışmada RDW artışının, yoğun bakımda takip edilen hastaların 30, 90, 365 günlük mortalitesinin, hastane içi mortalitesinin ve kan dolaşımı enfeksiyonunun önemli bir belirteci olduğunu bulmuşlardır.

Kritik hastalıklarla ilgili ilk çalışma, 2010 yılında Çin'de 602 hastadan oluşan bir kohort çalışmasında gerçekleştirildi ve RDW'nin yoğun bakım ünitesinde mortalite ile ilişkili olduğu bulundu (24). Artan RDW, proenflamatuvar sitokinlerin, kemokinlerin, oksidatif stres kombinasyonunun varlığını yansıtır.

Yüksek RDW, viral hastalığın şiddeti için bir belirteç olarak önerilmiştir (25). Bununla birlikte, viral enfeksiyonların yüksek RDW'yi indüklediği kesin mekanizma belirsizliğini korumaktadır. Viral enfeksiyon NF-κB'i ve daha sonra enflamasyonu başlatan ve kronik enflamasyona ilerleyen diğer immün faktörleri aktive eder. Viral kaynaklı kronik enflamasyon, eritrosit olgunlaşmasını bozar ve eritropoezde değişikliklere ve eritropoietin hormonunun yetersiz üretilmesine yol açar, bu nedenle RDW seviyeleri ile viral enfeksiyonların şiddeti arasındaki pozitif korelasyondan sorumlu olması muhtemeldir. Viral hastalıklarda RDW'nin prognostik değerinin altında yatan mekanizmaları bulmak için daha ayrıntılı çalışmalara ihtiyaç vardır.

Foy ve ark.'nın (1) COVİD-19 nedeniyle hastaneye yatırılan 1.641 yetişkin hastayı içeren kohort çalışmasında, hastaneye yatış sırasında ve hastanede kalış sırasında ölçülen RDW'nin, mortalitede istatistiksel olarak anlamlı artışla ilişkilendirmişlerdir. RDW'nin, hastanede yatan COVİD-19 hastalarının risk sınıflandırmasında faydalı olabilecek rutin bir laboratuvar testi olduğunu düşünmüşlerdir.

COVİD-19 hastalarında, düşük HGB seviyeleri ve patolojik olarak artmış ferritin seviyeleri aneminin varlığını göstermektedir (26). HGB konsantrasyonu, kanın oksijen taşıma kapasitesinin en önemli belirleyicilerinden biridir. COVİD-19 hastalarında, özellikle komplikasyon ve ölüm riski taşıyan popülasyonlarda düşük HGB, hastaların enfeksiyon sırasında hipermetabolik durumlar nedeniyle oksijen için artan periferik doku taleplerini desteklemek için azalmış HGB kapasitesini gösterebilir (27). Bizim çalışmamızda da yoğun bakım yatışı yapılan şiddetli COVİD-19 hastalarında düşük HGB seviyeleri gözlenmiştir. Taneri ve ark. (27) yaptıkları meta-analizde orta dereceli olgularla karşılaştırıldığında, şiddetli COVİD-19 olgularında daha düşük HGB, MCV ve daha yüksek ferritin ve RDW elde etmişlerdir.

Solunum yetmezliği, COVİD-19 hastalarında ölümlerin önde gelen nedenidir (28). İleri yaş ve erkek cinsiyetin ölümle ilişkili olduğu bulunmuştur (29). Bizim çalışmamızda da, ileri yaş ve erkek cinsiyetin kötü prognoz göstergesi olduğu bulunmuştur.

Sonuç

Yoğun bakım üniteleri, şiddetli COVİD-19'a ilerleme riski olan hastaların yakından izlenmek üzere takip edildiği yerlerdir. Yoğun bakım yataklarına talep oldukça fazladır. COVİD-19 hastalığının teşhisi ve prognozu; hızlı ve doğru bir şekilde gerçekleştirilebilirse, hastalığın morbiditesi ve mortalitesi azaltılabilir. Hemogram gibi ucuz ve kolay testlerin COVİD-19'da kullanılabilmesi hastalığın takibi açısından fayda sağlayabilecektir. Sonuç olarak çalışmamızda hemogram değerlerinden HGB, RBC, WBC ile mortalite ilişkisi gösterilmiş, RDW değerininin mortalite üzerine etkisi saptanmamıştır. Ancak bu konu üzerinde yapılacak prospektif randomize kontrollü çalışmalara ihtiyaç vardır.

Çalışmamızın bazı sınırlamaları vardır; çalışmamız retrospektif bir çalışma ve yaş dağılımının gruplar arasında standardizasyonu sağlanamadığından, RDW'nin mortalite üzerine etkisi çoklu lojistik regresyon analizi ile değerlendirilmiştir. Çalışmada RDW'nin COVİD-19 hastalarının mortalitesi üzerine etkisi anlamlı bulunmamıştır ancak bu konuda yapılacak randomize kontrollü çalışmalara ihtiyaç vardır.

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Yoğun Bakımda Çalışan Hekimlerin Teletıp ve Tele-yoğun Bakım Hakkındaki Düşünceleri

Opinions of Physicians Working in Intensive Care on Telemedicine and Tele-intensive Care

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ÖZ *Amaç:* Tele-tıp uygulamalarının bir parçası olan tele-yoğun bakım ünitesinin (YBÜ) Sağlık Bakanlığı tarafından ülkemizde kullanımı önerilmektedir. Bu çalışmada yoğun bakımda çalışan hekimlerin teletıp ve teleYBÜ hakkındaki düşünce ve bilgi seviyelerinin incelenmesi ve kullanılmasının önündeki engeller hakkında bilgi edinilmesi amaçlanmıştır.
Gereç ve Yöntem: Etik kurul izni alındıktan sonra çalışmacılar tarafından Google Forms ile oluşturulmuş 3 bölüm ve 44 sorudan oluşan anket sosyal mesajlaşma uygulaması üzerinden gönderildi.
Bulgular: Yoğun bakımda çalışan 147 hekim tarafından ankete katılım sağlandı. Katılımcıların yarısı YBÜ'de teletıp kullanmadığını belirtti. Katılımcıların sadece %5'i teletıbbın hukuksal zemini olduğuna katıldıklarını ve %83,7'si kullanımı için eğitim verilmesi gerektiğini belirtti.
Sonuç: Hukuksal zeminin hazırlanması ve yeterli eğitim desteği ile YBÜ'de teletıp kullanımında artış olması beklenebilir.
Anahtar Kelimeler: Tele-tıp, tele-YBÜ, hukuk, uzaktan erişim, yoğun bakım

ABSTRACT *Objective:* The use of tele-intensive care unit (ICU), which is a part of telemedicine, is recommended by the Republic of Turkey Ministry of Health in our country. In this study, we obtained information about the opinion, the level of knowledge and obstacles to the use of telemedicine and tele-ICU by physicians working in the ICU.
Materials and Methods: After getting the approval of the ethics committee, the questionnaire consisting of 3 sections and 44 questions created with Google Forms was sent via the social messaging platform.
Results: One hundred forty seven physicians working in the intensive care unit participated in the survey. Half of the them stated that they do not use telemedicine in the ICU. Only 5% of the participants stated that they agreed that telemedicine has a legal basis, and 83.7% stated that training should be provided for its use.
Conclusion: With the preparation of the legal grounds and adequate training support, an increase in the use of telemedicine in the ICU can be expected.
Keywords: Tele-medicine, tele-ICU, legal issues, remote access, intensive care

Giriş

Tele-yoğun bakım ünitesi (tele-YBÜ), tele-tıp uygulamalarının yoğun bakım ayağıdır (1). Tele-YBÜ uygulaması kritik hastanın değerlendirilmesi ve uzaktan sürekli gözlenmesi, tanı konması, standart tıbbi müdahale/tedavilerin uygulanmasına olanak vererek kritik hasta bakımına odaklanan görme ve işitmeye yönelik bir ağdır. Tele-tıp akıllı telefonlar, görüntülü haberleşme, e-posta, kablosuz araçlar ve diğer güncel iletişim araçları ile giderek artan çeşitli teknolojik uygulamaları ve hizmetleri içerir (2).

Tele-YBÜ kullanımıyla klinisyenlerin mesafe ve zaman kısıtlaması olmaksızın ülkedeki bütün yoğun bakımlara ulaşabileceği, hasta verilerinin elektronik ortamda inceleyebileceği ve optimal tedavilerin önerilebileceği düşünülmektedir (2). Ayrıca klinik karar destek sistemlerinin dahil edildiği Tele-YBÜ uygulamalarının yoğun bakımda iyi klinik uygulamalar oranlarını yükselttiği ortaya koyulmuştur (2).

Türkiye'de Temmuz 2020'de TC Sağlık Bakanlığı, Sağlık Bilgi Sistemleri Genel Müdürlüğü'nce yayınlanan "yoğun bakım bilgi yönetim sistemi kılavuzu" uyarınca tele-YBÜ kullanılması mecburi yazılım programları arasına girmiştir (3).

Tele-YBÜ'nün kullanımında karşılaşılabilecek altyapı eksiklikleri, hekim-hasta ve hasta yakını iletişiminde ortaya çıkabilecek sorunlar, hastalara ait verilerin depolanma ve muhafazasında yaşanacak zorluklar, yasal düzenlemelerin ve görev tanımlarının yetersizliği tele-YBÜ uygulamalarının beklenilen faydalarını olumsuz yönde etkileyebilir.

Koronavirüs hastalığı-2019 pandemisi dünyada ve ülkemizde yoğun bakımlarda hizmet verebilecek eğitilmiş yetkin uzman hekim ve hemşire gerekliliğinin ciddiyetini belirgin hale getirmiştir. Pandemi süreci boyunca dünyada ve ülkemizde sağlık hizmeti veren kurumlar yoğun bakım hizmeti sağlayabilecekleri bölümlerinin sayılarını yükseltmişlerdir. Fakat yetkin yoğun bakım personeli sayısı aynı hızda yükseltilememiştir.

Araştırmalar, yoğun bakımlarda devamlı ve branşında uzman kişilerin çalışmasının mortalitede düşme ve hasta bakım kalitesinde artışla ilişkisini ortaya koymaktadır (2). Eğitimli ve yetişmiş çalışanlara gereksinimin aniden yükseldiği, doğal afet ve salgın hallerinde yüksek nitelikli, devam edebilen hizmet sunumu sağlayabilmek için tele-YBÜ uygulamalarının ve bu uygulamaların kullanımı için standart kılavuzlar oluşturulması ile daha kolay olacaktır (2).

T.C. Sağlık Bakanlığı tarafından kullanılması önerilmekte ve yönlendirilmekle birlikte tele-tıp ve tele-YBÜ'nün ülkemizde ne oranda ve hangi şartlarda kullanıldığına dair veriler yetersizdir. Bu çalışmada tele-tıp uygulamalarının bir parçası olan tele-YBÜ'nün ülkemizde kullanımı hakkında düşünceleri, bu konudaki bilgi seviyesi ve kullanılma tercih ile oranları hakkında bilgi toplamak ve bu yöndeki çalışmalar için bir başlangıç oluşturması amaçlanmıştır. Ayrıca kullanımının önündeki engeller hakkında bilgi edinilmesi amaçlanmıştır.

Gereç ve Yöntem

Etik kurul onayı (Çankırı Karatekin Üniversitesi Girişimsel olmayan Araştırmalar Etik Kurulu; no: 23, tarih: 09.11.2021) alındıktan sonra çalışmaya başlandı. Katılımcılardan anketi cevaplamadan önce onamları alındı.

Anketin hazırlanması için literatürdeki çalışmalar incelendi. Sorular oluşturulduktan sonra farklı alanlardan hekim, hemşire ve öğretmelere okutularak sorulardaki anlam bozuklukları giderilmeye çalışıldı. Demografik, tele-tıp ve tele-YBÜ başlıkları olmak üzere toplam 3 bölümden oluşan 44 soruluk anket hazırlandı.

Google Forms ile hazırlanan anket formu sosyal mesajlaşma platformları üzerinden 1 Kasım 2021 ile 1 Aralık 2021 tarihi arasında paylaşıldı.

Veriler Google Tablolar ile değerlendirildi ve sonuçlar yüzde olarak verildi.

Bulgular

Google Forms üstünden gönderilen ankete 147 kişi katılmıştır. Anket soruları ve katılımcıların verdiği cevaplar yüzde olarak Tablo 1'de verilmiştir.

Tartışma

The American Telemedicine Association, hastalara standartları belirlenmiş, kaliteli bir tele-YBÜ hizmeti sunmak için kılavuzlar oluşturmuştur. Böylelikle tele-YBÜ organizasyon, sağlık çalışanları, lisanslandırma, hasta hekim ilişkileri, hasta hakları, kalite ve mali yönetim ile ilgili bilgiler rehberlerde yer almıştır (1). Bu kılavuzlara göre tele-YBÜ doktoru kullanılan programa göre 100-250 arası hastayı izleyebilir şeklinde önerme yapılmıştır (1).

Ülkemizden 2020 yılının başında yazılmış olan bir derlemede bu konu ile ilgili Dünya Tabipler Birliği tarafından hangi hastaların tele-tıp ile izleneceği, hangi durumlarda hastaneye başvuru önerileceği, yeni bir tedaviye uzaktan nasıl başlanılacağı, aydınlatılmış onamın nasıl alınacağı konularının

Tablo 1. Sorular ve katılımcıların verdiği cevaplar (% olarak verilmiştir)				
Genel bilgiler				
Cinsiyet	Erkek		Kadın	
	33,3		66,7	
Yaş	<30	30-35	36-45	>45
	2,7	17,7	52,4	27,2
Yoğun bakım deneyimi	<1	1-3	4-10	>10
	3,4	14,3	41,5	40,8
Branş	AR U	YB U	Diğer	
	48,3	31,3	20,4	
Çalıştığınız kurumun yer aldığı şehir	Bursa	İstanbul	Eskişehir	Diğer
	21,7	14,9	12,2	51,2
Çalıştığınız hastanenin türü	Üniversite	EAH	Kamu	Özel
	27,9	40,1	25,2	4,1
Çalıştığınız yoğun bakım türü	Karışık	Cerrahi	Dahili	Çocuk
	77,6	13,6	6,8	2
Çalıştığınız yoğun bakımın basamağı	3		2	
	91,2		8,8	
Çalıştığınız yoğun bakımın yatak sayısı	<10		11-20	>20
	6,8		31,3	61,9
Yoğun bakımda çalışan uzman hekim sayısı	1		1-3	>3
	24,5		45,6	29,9
Yoğun bakımda çalışan araştırma görevlisi hekim sayısı	Yok		1-3	>3
	48,3		29,9	21,8
Tele-tıp ile ilgili düşünceler				
	Katılıyorum	**Fikrim yok**	**Katılmıyorum**	
Tele-tıp uygulamaları daha hızlı tıbbi bakım hizmeti sunulmasını sağlar.	77,6	18,4	4,1	
Tele-tıp uygulamaları uzak bölgelere hizmet verilmesinde yardımcıdır.	82,3	15	2,7	
Tele-tıp uygulamaları hasta tedavi maliyetlerini azaltır.	54,4	35,4	10,2	
Tele-tıp uygulamaları hastaların, hastaneler arası gereksiz sevklerinin önüne geçilmesinde yardımcıdır.	68,7	22,4	8,8	
Tele-tıp uygulamaları hasta nakil maliyetlerini azaltır.	63,9	27,9	8,2	
Tele tıp uygulamaları hastaların kurumlar arası nakil sırasındaki risklerini azaltır.	70,1	24,5	5,4	
Tele-tıp uygulamaları hastaların YBÜ'ler arası nakil bekleme listelerini azaltır.	65,3	42,5	10,2	
Tele-tıp uygulamaları tıbbi hataların artmasına neden olur.	17,7	32	50,3	
Tele-tıp uygulamaları için eğitim gereklidir.	83,7	11,6	4,8	
Tele-tıp uygulamaları YBÜ'lerde yetişmiş uzman hekim eksikliğinin giderilmesine yardımcıdır.	41,5	27,9	30,6	
Tele-tıp uygulamaları hasta bakımında kaliteyi artırır.	66	25,9	8,2	
Tele-tıp uygulamaları hasta bakımında güvenliği artırır.	51	34,7	14,3	
Tele-tıp uygulamaları çalışmakta olan hekimler için mesleki tatmini artırır.	41,5	38,1	20,4	

Tablo 1. Devamı				
Tele-tıp uygulamaları çalışmakta olan hekimler için mesleki güveni artırır.	53,7	32	14,3	
Tele tıp uygulamaları hasta yakınları tarafından kabul edilebilir bir uygulamadır.	32	42,9	25,2	
Tele-tıp uygulamaları hata yakınları için tatmin edici bir uygulamadır.	21,1	48,3	30,6	
Tele-tıp uygulamaları çalışan hekimler ve hasta yakınları arasında güveni artırır.	25,2	47,6	27,2	
Tele-tıp uygulamaları hasta haklarını ve kişisel bilgi güvenliğini tehlikeye atar.	32,7	32,7	34,7	
Tele-tıp uygulamaları hemşireler için güven vericidir.	44,9	35,4	19,7	
Tele-tıp uygulamaları malpraktis davalarının artmasına neden olur.	40,8	43,5	15,6	
Tele-tıp uygulamalarının ülkemizde hukuki alt yapısı vardır.	2	46,3	51,7	
Tele YBÜ ile ilgili düşünceler				
	Evet		**Hayır**	
YBÜ'nüzde tele tıp kullanılıyor mu?	50,3		49,7	
Ünitenizde uzaktan monitorizasyon/hasta takip sistemi var mı?	36,1		63,9	
Hastane bilgi yönetim sisteminde klinik karar destek sistemi var mı?	7,5		92,5	
Klinik karar destek sitemi aktif olarak kullanılıyor mu?	5,5		94,5	
Çalıştığınız yoğun bakımda hasta başlarında/odalarında uzaktan erişimli kamera ve/veya ses kayıt cihazı var mı?	31,3		68,7	
Çalıştığınız yoğun bakımda SARS-CoV-2 sonrası tele tıp kullanımında artış oldu mu?	36,7		63,3	
Çalıştığınız yoğun bakımda entegre/bütünleşik tele yoğun bakım sistemi kullanılmasını ister misiniz?	88,4		11,6	
Tele tıp kullanılıyor ise hangi yöntemleri kullanılıyor? (birden fazla cevap içinde en sık olanlar)	T-Rad	T-Kons	T-Eği	Tel
	72,7	35,1	31,2	61
Telemonitörizasyon varsa hangi cihazlar bağlıdır? (birden fazla cevap içinde en sık olanlar)	HBM	MV	HBYS	HTF
	88,7	14,5	35,5	9,7
E-nabız ile ilgili düşünceler				
	Evet		**Hayır**	
E-nabız hakkında bilgi sahibi misiniz?	94,6		5,4	
E-nabız sisteminde kendi kişisel bilgilerinizin erişimine izin verdiniz mi?	62,6		37,4	
E-nabız sistemini hastalarınızın bilgilerine erişmek için aktif olarak kullanıyor musunuz?	68		32	

T-Rad: Teleradyoloji, T-Kons: telekonsültasyon, T-Eği: teleeğitim, Tel: telefon görüşmesi, HBM: hasta başı monitörü, MV: mekanik ventilatör, HBYS: hastane bilgi yönetim sistemi, HTF: hasta takip formu; AR U: anesteziyoloji ve reanimasyon uzmanı, YB U: yoğun bakım uzmanı, EAH: eğitim-araştırma hastanesi, YBÜ: yoğun bakım ünitesi, SARS-CoV-2: şiddetli akut solunum yolu sendromu koronavirüsü-2

düzenlenmesi gerekliliği ortaya konulmuştur (4). Ayrıca hasta hekim haklarının ve hasta-hekim ilişkisinin bilimsel standartlarının belirlenmesi ve uygulama kılavuzlarının oluşturulması gerekliliği vurgulanmıştır (4). Ek olarak farklı bir çalışmada klinik karar destek sistemleri kullanımının uygulamaya uyumu artırdığı gösterilmiştir (5). Ancak yasalar ve görev tanımlamalarının eksikliği bu yeni stratejinin yararının önüne geçebileceğine dikkat çekilmiştir (2).

Çalışmamızda anketlerimize cevap veren katılımcıların %33,3 kadın ve %52,4 35-45 yaş aralığında olup ve %31,3 yoğun bakım yan dal uzmanı %48,3 anesteziyoloji uzmanıydı. Buna göre katılımcılarımızın çoğunluğu konusunda deneyimli ve uzman olan hekimlerden oluştuğu söylenebilir. Katılımcıların %40,1 eğitim ve araştırma hastanesinden ve % 77,6 erişkin karışık tip yoğun bakımda çalışmaktaydı. Bu sonuçlardan çalışmamıza katılan hekimlerin büyük kısmının

T.C. Sağlık Bakanlığı'nın yoğun bakımlar için zorunlu tuttuğu tele-tıp programlarını kullanmaya başlamış veya başlayacakları sonucuna varılmıştır. Fakat bu konuda eğitim ve hukuksal zemin halen hazırlanmamış olup katılımcılarımızdan da bu konudaki kaygılarını ortaya koymuş olduğu düşünülmüştür.

Çalışmamıza katılan hekimler %68,7 oranında tele-tıp uygulamalarının hastaneler arası gereksiz sevklerin önüne geçilmesine yardımcı olduğu ifadesine "katılıyorum" demiştir. Bu sonucumuz ülkemizden yapılan derlemeye göre tele-YBÜ ile yatış ve çıkış için ortak algoritma geliştirerek hem gereksiz YBÜ yatışlarının önüne geçilebilir hem de uygunsuz hasta sevklerinin engellenebileceğine ve ayrıca boş yoğun bakım yatağına ulaşım kolaylaşacak ve gelişebilecek hukuki sorunların da önüne geçilebileceği yorumunu desteklemektedir (2). Diğer önemli bir konu olan verimlilik düzeyinin, tele-YBÜ programları ile hasta sayısının yükseltilebileceği, daha kısa YBÜ kalış süreleri ile maliyetlerin azaltılabileceğini bildiren çalışmanın sonucu ile benzer olduğu düşünülmüştür (6).

Çalışmamızda katılımcılarımızın %41,5'ine göre ise tele-tıp uygulamaları hekimlerin mesleki tatminini artıracağını belirtmiştir. Benzer şekilde Shahpori ve ark. (7) çalışmasında ise katılımcılarının %36'sı tele-YBÜ'nün ekip memnuniyetini artırdığını belirtmiştir. Tele-tıp uygulamaları ile konsültasyonların daha hızlı çözümlenmesi ve hasta verilerine daha hızlı ulaşım, hekimlerin hastaların ihtiyaçlarını daha hızlı çözümlemesini sağlayarak iş yükünü azaltıp mesleki tatmini artırabilir. Bu nedenle artan tele-tıp uygulamalarının kullanımı hekimlerimizi daha iyimser hale getirerek hekimlik mesleğindeki tatminlerini artırabilir.Ancak Shahpori ve ark. (7) çalışmasında yoğun bakım klinisyenlerinin insan kaynaklarının etkili kullanımı ve kaliteli hizmet sürecinde tele-YBÜ'nün yeri konusunda kararsız kalmışlardır.

Çalışmamıza katılan hekimler %54,4 oranında tele-tıp uygulamalarının tedavi maliyetlerini azalttığına katıldıklarını ifade etmiştir. Ayrıca %82,3'ü tele-tıp uygulamalarının uzak bölgelere hizmet verilmesinde yardımcı olduğu ifadesine katılmaktadır. %41,5 katılımcıya göre ise yetişmiş uzman personel ihtiyacının giderilmesine yardımcı olabileceğini belirtmektedir. Tele-YBÜ'nün ekonomik yönünü değerlendiren çalışmalara göre bu uygulamaların maliyet etkin ve tasarruf sağlayıcı olduğu sonucu ortaya konulmuştur (6). Tele-YBÜ yetişmiş nitelikli personel olan yoğun bakım uzmanlarının etkili kullanımına yardımcı olarak personel giderlerinin azalmasına da yardımcı olabilir. Birçok çalışmaya göre tele-YBÜ yaklaşımları YBÜ kalite ölçütlerinden olan mortalite, yoğun bakımda kalış süresini, mekanik ventilatöre kalış süresini azaltmıştır (8,9). Çalışmamıza katılan hekimlerin %66'sına göre ise tele-tıp uygulamaları hasta bakımında kaliteyi artırabileceğini belirtmişlerdir fakat %78,9 katılımcı tele-tıp uygulamalarının hasta yakınları tarafından tatmin edici olamayacağı şeklindeki endişelerini de belirtmişlerdir. Ülkemizde sağlık çalışanlarına karşı artan şiddet ve baskı nedeniyle hekimlerin çekinceleri ve tele-tıp hakkındaki bilgi eksikliğinden kaynaklanabiliyor olabilir. Sosyokültürel olarak ülkemizi tam yansıtmasa da Mısır'da halk ile yapılan bir çalışmada bu düşüncenin tam aksine bir düşünce ortaya konmuş ve hastaların da tele-tıp uygulamalarından tatmin olabileceği ortaya konmuştur (10).

Yasalarımızda hekimin hastasını fiziksel olarak görüp teşhis tedavi uygulaması gerekir ancak hekimin kendisinin muayene sorumluluğunu tele-tıp uygulamaları ile uzaktan yapamayacağına dair bir uygunsuzluk olmadığı yönünde hukukçuların değerlendirmeleri mevcuttur (11). Klinisyenlerde genel endişe tele-YBÜ'nün malpraktis davalarına etkisinin belirsizliği olsa da çalışmalara göre bu uygulamalar malpraktis iddialarını azaltmıştır (5,6). Bizim çalışmamızda "tele-tıp uygulamaları malpraktis davalarının artmasına neden olur" ifadesine katılımcılarımızın %43,5'i "fikrim yok" derken %40,8'i "katılıyorum" yanıtı vermiştir. Bu durum maalesef üstte bahsedilen hekim-hasta yakını iletişim sürecinde yaşanan olumsuzlukların hekimlerimizi daha temkinli ve karamsar bir yaklaşıma yöneltmiş olmasıyla açıklanabilir.

Mısır halkının tele-tıp uygulamalarına yaklaşımını değerlendiren çok yakın tarihli bir çalışmaya göre katılımcıların %49,4'ü tele-tıp uygulaması kullanmış. Katılımcıların %60,8'i tele-tıp uygulamalarını klasik uygulamalara tercih ettiğini belirtmiş ancak katılımcıların yarısı tele-tıp uygulamalarının medikal hataları artıracağını düşünmekte ve %13,7'si tele-tıp uygulamada zorluklarının olduğunu düşünmektedir. Fakat bu yönde görüş bildiren grubun ileri yaşlı, az eğitimli ve sosyoekonomik olarak geri kalmış bölgelerde yaşayan insanlardan oluştuğu belirtilmiştir. Katılımcıların %21,9'u tele-tıp uygulamalarının hasta mahremiyetini tehlikeye soktuğunu düşündüğünü belirtmiş (10). Katılımcıların hekim olduğu bizim çalışmamızda ise tele-tıp uygulamalarının hasta haklarını ve kişisel bilgi güvenliğini tehlikeye atar ifadesine %34,7 oranında katılmadıklarını belirtmişlerdir. Bunun nedeni olarak kişisel verilerin kullanımı kanunun henüz aktif olarak uygulanmaması veya bilişim teknolojilerinin güvenliğine olan inançlarının düşük olmasından kaynaklanabilir.

Bu çalışmamıza göre %94,6 katılımcı hekim tele-tıp uygulaması olan e-nabız hakkında bilgi sahibi olmasına rağmen %37,4'ü kişisel verilerini bu sistem üzerinde paylaşılmasına izin vermediğini belirtti. Bakanlığın yasal tele-tıp uygulaması olmasına rağmen hekimlerce bile yeterli kullanım oranına ulaşamamasının üstte bahsedilen nedenler kaynaklı olabileceği düşünülmüştür. Buna rağmen katılımcıların %68'i hastaların verilerine ulaşmak için e-nabız sistemine başvurduğunu da belirtmiştir. Ülkemizde halkın ne oranda e-nabız uygulaması kullanımına ait net bir veriye ulaşılamamıştır. Yine de eğitim seviyesi yüksek olan hekimler için e-nabız kullanımı düşük olarak değerlendirilebilir. Bu durumun katılımcıların "tele tıp uygulamalarının ülkemizde hukuki alt yapısı vardır" sorusuna %5 oranında verdikleri "katılıyorum" cevabının altında yatıyor olabileceğini düşündük.

Yeni bir teknolojiye uyum sağlamak için kullanıcıların yeni konsepti anlaması, gerekli becerilere sahip olmaları ve uygun çalışma ortamına sahip olmaları gerekir. Yeni sağlık uygulamalarının kullanımı için yeterli bilgi sahibi olmak cesaretlendirici olacaktır (12). Becker ve ark. (13) tele-YBÜ programları hastane ve yoğun bakımın ihtiyaçlarına özel hazırlanırsa, tele-YBÜ ekibi ve yatak başı ekibinin ortak katılımıyla karar almaya yönlendirirse daha faydalı olacağını belirtmişlerdir. Ayrıca merkezi tele-YBÜ'lerin tersiyer hastanelerin YBÜ bakım kalitesini artırmaya yardımcı olacağı belirtilmiştir (14). Anketimize katılan hekimler %83,7 oranında tele-tıp uygulamaları için eğitim gerektiği düşüncesi ile bu bakış açısını desteklemektedir.

Bu ankette sorulan soruların çalışmacılar tarafından hazırlanması bu çalışmanın başlıca sınırlılığıdır. Fakat hem Türkiye Cumhuriyeti hem de dünyada bu konuda uygulanan geçerli ve güvenli bir anket olmaması nedeniyle yoğun bakımlarda çalışan hekimlerin farkındalıklarını ve çekincelerini öğrenmek için çalışmacılar tarafından hazırlanan soruların yine de yol gösterici olacağını düşünüyoruz. Anket ülkemizde yoğun bakımda çalışan tüm hekimlere gönderilmeye çalışmış olsa da ancak 147 hekim tarafından cevaplanmıştır. Ülkemizin farklı şehirlerinden katılımcı olmasına rağmen ülkenin farklı bölgelerinde ve farklı şartlarda çalışan tüm yoğun bakım hekimlerinin düşüncelerini yansıtamayacağı da bir diğer önemli kısıtlılığımızdır.

Sonuç

Ülkemizde tele-YBÜ uygulamalarının yoğun bakımda kullanımı teşvik edilip zorunlu hale getirilmeye çalışılsa da yoğun bakımlarda çalışan hekimlerin çoğunluğu tele-tıp uygulamalarının hukuki süreçlerine olan güven eksikliğinden dolayı kullanımdan emin değildir/çekinmektedir. Tele-YBÜ uygulamalarının sınırlarının ve yasal zeminin netleştirildikten ve verilecek eğitimden sonra bu sürecin başlatılması, tele-tıbbın kullanımının artmasına yardımcı olabilir.

Etik

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ORIGINAL RESEARCH / *ÖZGÜN ARAŞTIRMA*

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The Effect of Secondary Infections on Mortality in Patients with COVID-19 Associated Severe ARDS

COVİD-19 ile İlişkili Şiddetli ARDS Hastalarında Sekonder Enfeksiyonların Mortalite Üzerine Etkisi

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ABSTRACT *Objective:* In the beginning of the coronavirus disease-2019 (COVID-19) pandemic, secondary bacterial, fungal and viral infections have been reported in the intensive care unit (ICU), but there is limited experience with infections in critically ill patients over time. The aim this study was to evaluate the characteristics of secondary infections related to ICU and their effects on mortality in COVID-19 patients.
Materials and Methods: Our study was planned as a retrospective single-center case-control study involving 145 patients with severe severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) pneumonia hospitalized in the ICU between March and June 2020. The epidemiological, clinical and microbiological characteristics and results of ICU-related infections were evaluated.
Results: The mean age of the patients was 61.2 years and mean body mass index was 28 kg/m^2. At least one comorbidity was found in 140 patients (96.6%). Seventy seven of (53.1%) the patients diagnosed with COVID-19 included in the study died. In addition to SARS-CoV-2, the isolation of different pathogens was observed in 62 (42.75%) patients' samples. In the group with secondary infections, a significant increase in lymphocyte and lactate levels was observed between the time of admission and time of sampling culture (p<0.001). There was statistical significance in lymphocyte (p<0.026) and lactate (p<0.020) levels between the groups with and without infection. There was a significant increase in C-reactive protein, ferritin, procalcitonin levels and Acute Physiology and Chronic Health Evaluation-II scores in the group with secondary infection compared to the group without secondary infection (p<0.041, p<0.009 p<0.001, and p=0.028, respectively). In the group without secondary infection, the D-dimer levels patients were significantly lower (p<0.014).
Conclusion: In conclusion, bacterial and fungal secondary infections are a common complication in patients with COVID-19 admitted to the ICU. It usually occurs as a severe form of infection accompanying comorbidity and is associated with high mortality and prolonged ICU stay.
Keywords: COVID-19, intensive care unit, co-infection, mortality

ÖZ *Amaç:* Koronavirüs hastalığı-2019 (COVİD-19) pandemisinin ilk dönemlerinde yoğun bakım ünitesinde (YBÜ) takip edilen hastalarda bakteriyel, fungal ve viral kaynaklı daha az sekonder enfeksiyonlar olduğu bildirilmiştir. COVİD-19'lu kritik hastalarda bakteriyel enfeksiyon deneyimi sınırlıdır. Bu çalışmanın amacı, COVİD-19 hastalarında YBÜ kaynaklı sekonder enfeksiyonların özelliklerini ve mortalite üzerine olan etkilerini değerlendirmektir.
Gereç ve Yöntem: Çalışmamız, Mart ve Haziran 2020 tarihleri arasında YBÜ'de yatan ve şiddetli akut solunum yolu yetersizliği sendromu (SARS-CoV-2) pnömonisi olan 145 hastayı içeren tek merkezli retrospektif bir olgu-kontrol çalışması olarak planlandı. YBÜ kaynaklı enfeksiyonların epidemiyolojik, klinik ve mikrobiyolojik özellikleri ve sonuçları değerlendirildi.
Bulgular: Hastaların ortalama yaşı 61,2 yıl ve vücut kitle indeksleri 28 kg/m^2 olarak saptandı. Yüz kırk (%96,6) hastada en az bir komorbidite olduğu belirlendi. Çalışmadaki tüm COVİD-19 tanılı hastalardan 77'sinde (%53,1) ölüm gerçekleşti. Altmış iki (%42,75) hastada SARS-CoV-2'ye ek olarak farklı patojen üremesi saptandı. Kültürde ek mikroorganizma üreyen grupta ilk ölçülen lenfosit ve laktat düzeyleri ile kültür alındıktan sonra yapılan ölçümler arasında anlamlı bir artış belirlendi (p<0,001). Üreme olan ve olmayan gruplar arasında ölçülen lenfosit (p<0,026) ve laktat (p<0,020) düzeylerinde de istatistiksel anlamlılık görüldü. Üreme olan grupta üreme olmayan gruba göre C-reaktif protein, ferritin, prokalsitonin düzeylerinde ve de Akut Fizyoloji ve Kronik Sağlık Değerlendirmesi-II skorlarında anlamlı bir artış olduğu görüldü (sırasıyla; p<0,041, p<0,009, p<0,001 ve p=0,028). Üreme olmayan grupta ise hayatta kalan hastalar ile ölen hastaların D-dimer düzeyleri önemli ölçüde düşük saptandı (p<0,014).

Sonuç: Sonuç olarak bakteriyel ve fungal sekonder enfeksiyonlar, YBÜ'ye yatan COVİD-19'lu hastalarda yaygın bir komplikasyondur. Genellikle şiddetli bir enfeksiyon şekli olarak ortaya çıkar ve eşlik eden komorbidite ile birlikte yüksek mortalite ve uzamış YBÜ yatış süresi ile ilişkilidir.
Anahtar Kelimeler: COVİD-19, yoğun bakım ünitesi, ko-enfeksiyon, mortalite

Introduction

Coronavirus disease-2019 (COVID-19) pandemic is spread over the world starting from Wuhan in December 2019 (1). The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), an enveloped RNA betacoronavirus, is responsible for the infection. Fever, cough and respiratory failure are known as its most common symptoms (2). Advanced age and the presence of chronic diseases have been associated with a worse prognosis and higher mortality in patients diagnosed with COVID-19 (3). In addition to the disease, different levels of bacterial or fungal co-infection have been observed in other respiratory viruses such as influenza, Middle East respiratory syndrome, and SARS-CoV-1; it is thought that this situation may result in more serious problems in infectious diseases (4). Infections are among the most important causes of mortality, especially in patients followed up in the intensive care unit (ICU). Comorbidities, age of the patients and invasive procedures applied in ICUs cause an increase in development of infection in these patients. After the acute inflammatory reaction and pulmonary tissue damage caused by viral infections, a repair phase occurs in the lung tissue. Therefore, bacterial co-infection may develop following viral infection and this may cause an increase in mortality rate (5). Recognition of the SARS-CoV-2 infection is important to ensure implementation of appropriate infection control procedures and administration of appropriate antiviral therapy (6-8).

In this study it is aimed to determine the secondary infection rate, distribution of causative agents of these infections, selection of antibiotics for treatment and resistance patterns of microorganisms in patients with acute respiratory distress syndrome (ARDS) secondary to SARS-CoV-2 viral pneumonia who followed-up in ICU and analyze the effects of secondary infection on mortality and morbidity retrospectively.

Materials and Methods

Our study was initiated by obtaining the approval of the clinical local ethical committee of University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital dated 08/06/2020, numbered 2020-12-29. Patients aged 18 years and older who applied to the emergency department of our hospital, whose polymerase chain reaction positivity was detected in the nasopharyngeal swab and who were followed up in the ICU for at least 72 hours were included in the study (between March 16, 2020 and June 1, 2020). The data of the patients were obtained by scanning of files in the electronic system and archive of the infection control committee. Infections in patients are classified according to the definition of healthcare-associated infections. Patients who had infection within the first 48 hours of admission to ICU or patients transferred from another clinic and had hospital infection at the time of acceptance to ICU were excluded from the study. The data of patients was recorded during the follow-up in the ICU or in other departments to where they were transferred. The data were recorded via case follow-up forms by observing the patients until the date of discharge or death.

Statistical Analysis

SPSS 27.0 (IBM Corporation, Armonk, New York, United States) and PAST 3 (Hammer, Ø., Harper, D.A.T., Ryan, P.D. 2001. Paleontological statistics) programs were used in the analysis of variables. The suitability of univariate data to normal distribution was evaluated using the Shapiro-Wilk francia test, while variance homogeneity was evaluated with the Levene test. Mardia (Dornik and Hansen omnibus) test was used for normal distribution of multivariate data, while Box-M test was used for variance homogeneity. Independent samples t-test was used together with Bootstrap results, while Mann-Whitney U test was used together with Monte Carlo results in comparing the two indepent groups in term of quantitative data. Wilcoxon signed-ranks test was used with Monte Carlo results to compare dependent quantitative variables and duplicate measurements. Comparison of categorical variables was tested with Pearson chi-square and Fisher Exact Monte Carlo simulation techniques, and the column proportions were compared with each other and expressed according to the Benjamini-Hochberg corrected p-value results. Quantitative variables were expressed as mean (standard deviation) and median (percentile 25/ percentile 75) in the tables, while categorical variables were shown as n (%). Variables were analyzed at a 95% confidence level, and a p-value of less than 0.05 was considered significant.

Results

A total of 145 patients diagnosed with COVID-19 pneumonia [55 (37.9%) female and 90 (62.1%) male] were included in the study. The mean age of the patients was 61.18±16 years, and the mean body mass index (BMI) level was 28.04±5.8 kg/m^2. At least one comorbidity was found in 140 (96.6%) patients. The most common comorbidities are hypertension (HT) (34.3%) and diabetes mellitus (DM) (26.4%), and 15.7% of the patients had HT + DM diagnosis together. Different pathogens were isolated in 62 patients in addition to SARS-CoV-2. Secondary infections that developed on the basis of all SARS-CoV-2-related pneumonia were hospital-acquired infections (The earliest occurrence of secondary infections was detected at the 48th hour of intensive care admission.). Thirteen patients had positive endotracheal aspirate (ETA) cultures ventilator associated pneumonia, 56 patients had positive blood cultures, 13 patients had positive urine cultures, 16 patients had positive ETA–and blood cultures (simultaneously), 8 patients had positive blood, urine and ETA cultures (simultaneously), 2 patients had positive ETA and urine cultures (simultaneously), and 2 patients had positive blood and urine cultures (simultaneously) (Table 1).

There was no difference between the patients with or without secondary infection in terms of age, gender, BMI, presence of comorbidity, duration of mechanical ventilation and length of stay (Table 2). Tocilizumab was administered to 44 of 62 patients whose causative agent could be isolated [the mean procalcitonin (PCT) value of the patients using tocilizumab was 4.2±1.2 ng/mL and ferritin ≥700 mg/dL].

The first Acute Physiology and Chronic Health Evaluation-II (APACHE-II) and Sequential Organ Failure Assesment (SOFA) scores, C-reactive protein, white blood count (WBC), neutrophil, PCT, lactate, lactate dehydrogenase and D-dimer levels were found to be similar in patients with or without infection. However, the lymphocyte level of the patients with secondary infection was found to be lower (0.35 vs. 0.53, p=0.026). It was determined that the patients with secondary infection had higher APACHE-II scores and higher PCT levels at the time of sampling for culture (p<0.001 and p=0.028, respectively).

Seventy seven (53.1%) of the patients hospitalized with the diagnosis of COVID-19 pneumonia in the ICU did not survive. All of the patients who died had at least one comorbidity (p<0.021). No difference was found between patients who died or survived in terms of age, gender, BMI,

Table 1. Demographic characteristics, pathogens and focus

	Mean (SD)	Median (min/max)
Age	61.18 (16.00)	61 (18/100)
BMI	28.04 (5.80)	27.34 (16.65/50.78)
	n	**%**
Gender		
Female	55	37.9%
Male	90	62.1%
Mortality		
Alive	68	46.9%
Exitus	77	53.1%
Secondary infection		
No	83	57.2%
Yes	62	42.8%
Pathogens		
Acinetobacter	4	6.5%
Candida	20	32.3%
Klebsiella	9	14.5%
Enterococcus	11	17.7%
Pseudomonas	6	9.7%
E. coli	8	12.9%
Enterobacter	4	6.5%
Isolation of pathogens		
No	35	24.1%
Yes	110	75.9%
Focus of infection		
ETA	13	11.8%
Blood	56	50.9%
Urine	13	11.8%
ETA and blood (simultaneously)	16	14.5%
ETA and urine (simultaneously)	2	1.8%
Blood and urine (simultaneously)	2	1.8%
Blood, urine and ETA (simultaneously)	8	7.3%
Comorbidity		
No	5	3.4%
Yes	140	96.6%
Comorbidity		
HT	48	34.3%
DM	37	26.4%
HT + DM	22	15.7%

Table 1. Continued		
	Mean (SD)	Median (min/max)
Coronary artery disease	4	2.9%
COPD	13	9.3%
Cerebral ischemia/ hemorrhage	1	0.7%
Cancer	9	6.4%
Other	6	4.3%

COPD: Chronic obstructive pulmonary disease, DM: diabetes mellitus, ETA: endotracheal aspirate, HT: hypertansion SD: standard deviation, min: minimum, max: maximum, BMI: body mass index

sources of infection, APACHE-II and SOFA scores (p>0.005) (Table 3). Comparison of the changes in the data of the patients in terms of the presence of secondary infection is shown at Table 4.

Discussion

In this study, it was determined that 140 patients had comorbidity which had a significant effect on hospital mortality, 62 patients had secondary infection and 77 patients died among the 145 patients diagnosed with COVID-19 pneumonia in the ICU of our center.

In a study conducted in the first months of the epidemic in the Lombardy region of Italy, hospital mortality was defined as 48.8% and 53.4% in patients hospitalized in the ICU. In the same study, it was emphasized that COVID-19 mortality increased due to increased length of stay in the ICU and the need for long-term respiratory support (7). In a study conducted in Spain, it was reported that 33% of the COVID-19 patients' in ICUs died due to hospital-acquired infections (8). Yang et al. (9) stated in their study that the mortality rate increased to 81% in their patients who were under mechanical ventilation support.

Ferrando et al. (10) reported that patients with common comorbidities such as HT, obesity, and diabetes had higher APACHE-II and SOFA score and mortality rate was higher in these patients. In another similar study, it was indicated that the overall mortality rate in the ICU was 31% as a result of conditions other than COVID-19- related ARDS (11). It was analyzed whether a secondary infection developed or not with the cultures taken after the increase in PCT levels from the patients hospitalized in the ICU in our study and observed that there was secondary infection in 62 of 145 patients. It was found that APACHE-II and SOFA scores which were evaluated at the time of sampling for culture in the group with secondary infection were found to be significantly higher. In both groups, it was observed that there was a proportional increase between the APACHE-II score and the length of stay in the ICU. Also, all patients who died had at least one comorbidity.

Table 2. Differences in ICU data of patients in the presence and absence of secondary infection			
	Patients without seondary infection (n=83)	Patients with secondary infection (n=62)	p
Age mean (SD)	59.96 (15.59)	62.81 (16.51)	0.293[t]
BMI median (Q1/Q3)	24.69 (27.68/30.12)	24.22 (26.12/29.41)	0.566[u]
Gender, n (%)			
Female	31 (37.3)	24 (38.7)	0.999[c]
Male	52 (62.7)	38 (61.3)	
Mortality, n (%)			
Alive	40 (48.2)	28 (45.2)	0.739[c]
Exitus	43 (51.8)	34 (54.8)	
Comorbidity, n (%)			
No	2 (2.4)	3 (4.8)	0.651[f]
Yes	81 (97.6)	59 (95.2)	
Length of stay (hours), median (Q1/Q3)	89 (171/360)	99 (222/451)	0.382[u]
Ventilator dependent (hours), median (Q1/Q3)	59 (111/308)	60 (174/345)	0.313[u]

[t]Independent samples t-test (Bootstrap), [u]Mann-Whitney U test (Monte Carlo), [c]Pearson chi-square test (Monte Carlo), [f]Fisher Exact test (Monte Carlo), SD: standard deviation, Q1: percentile 25, Q3: percentile 75, BMI: body mass index, ICU: intensive care unit

Table 3. Evaluation of patients with and without secondary infections			
	Patients without secondary infection (n=83)	**Patients with secondary infection (n=62)**	**p[u]**
APACHE-II, median (Q1/Q3)			
First	15 (22/28)	18 (23/29)	0.300
Sampling time	23 (25/29)	26 (31/34)	<0.001
Difference (first-sampling time)	-2 (5/13)	0 (7/13)	0.260
p (for within group comparison)[w]	<0.001	<0.001	
SOFA, median (Q1/Q3)			
First	6 (10/12)	6 (10/12)	0.960
Sampling time	7 (8/12)	8 (12/14)	0.012
Difference (first-sampling time)	-4 (0/5)	-3 (2/5)	0.154
p (for within group comparison)[w]	0.945	0.058	
CRP, median (Q1/Q3)			
First	155 (206/290)	163 (195/286)	0.960
Sampling time	159.42 (208.3/275)	160 (180.5/290)	0.516
Difference (first-sampling time)	-18.58 (0/20)	-26 (0/14)	0.886
p (for within group comparison)[w]	0.655	0.820	
Procalcitonin, median (Q1/Q3)			
First	0.23 (0.76/2.24)	0.25 (0.735/6.7)	0.372
Sampling time	0.12 (0.62/2.08)	0.33 (1.1/4.95)	0.028
Difference (first-sampling time)	-0.19 (0/0)	-0.07 (0/0.29)	0.226
p (for within group comparison)[w]	0.330	0.893	
WBC, median (Q1/Q3)			
First	7.67 (11.3/15.51)	7.97 (10.265/16.57)	0.934
Sampling time	7.97 (10.73/14.16)	8.1 (13.725/16.98)	0.078
Difference (first-sampling time)	-0.84 (0/0.61)	-0.57 (0/4.79)	0.269
p (for within group comparison)[w]	0.953	0.078	
Neu, median (Q1/Q3)			
First	6.31 (9.63/12.81)	6.71 (9.31/14.89)	0.653
Sampling time	6.64 (8.39/12.08)	7.16 (11.755/15.61)	0.114
Difference (first-sampling time)	-0.079 (0/1.07)	-1 (0/4.37)	0.455
p (for within group comparison)[w]	0.538	0.126	
Lym, median (Q1/Q3)			
First	0.53 (0.75/1.23)	0.35 (0.56/1.04)	0.026
Sampling time	0.57 (0.78/1.34)	0.57 (0.955/1.36)	0.378
Difference (first-sampling time)	0 (0/0.2)	0 (0.015/0.67)	0.013
p (for within group comparison)[w]	0.441	<0.001	
Lactate, median (Q1/Q3)			
First	1 (1.4/1.8)	0.9 (1.4/1.9)	0.480
Sampling time	1 (1.5/2.4)	1.3 (1.7/2.6)	0.069
Difference (first-sampling time)	0 (0/0.5)	0 (0.3/0.8)	0.020
p (for within group comparison)[w]	0.269	<0.001	

Table 3. Continued			
	Patients without secondary infection (n=83)	**Patients with secondary infection (n=62)**	**p[u]**
LDH, median (Q1/Q3)			
First	364 (531/701)	298 (457.5/670)	0.225
Sampling time	294 (494/701)	298 (407.5/576)	0.152
Difference (first-sampling time)	-112 (0/0)	-80 (0/41)	0.509
p (for within group comparison)[w]	0.265	0.577	
Ferritin, median (Q1/Q3)			
First	468 (891.6/1492.7)	606.1 (932.6/1587)	0.475
Sampling time	327.5 (763.8/2789)	146.6 (643.15/2557)	0.624
Difference (first-sampling time)	-374.1 (0/381.9)	-669.2 (-4.3/125)	0.227
p (for within group comparison)[w]	0.471	0.570	
D-dimer, median (Q1/Q3)			
First	0.66 (1.78/3.5)	0.85 (1.755/3.95)	0.507
Sampling time	0.84 (1.94/3.65)	0.93 (2.355/4.56)	0.301
Difference (first-sampling time)	0 (0/0.93)	0 (0/0.53)	0.680
p (for within group comparison)[w]	0.105	0.108	

[u]Mann-Whitney U test (Monte Carlo), [w]Wilcoxon signed-ranks test (Monte Carlo), Q1: percentile 25, Q3: percentile 75, *for within group comparison, APACHE-II: Acute Physiology and Chronic Health Evaluation-II, SOFA: Sequential Organ Failure Assesment, CRP: C-reactive protein, WBC: white blood count, LDH: lactate dehydrogenase

In another study, in terms of secondary infection rates, it was reported that the relationship between COVID-19 and other respiratory tract pathogens was higher than reported in previous publications (12). It was stated that 28% of the patients in ICUs in France had secondary infection after admission and the etiological agent of infections were *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Enterobacteriaceae* (13).

There is insufficient study on the prevalence of bacterial or viral secondary infections in patients admitted to the ICU because of ARDS related COVID-19 (14). Secondary infections were reported in 41% of the patients admitted to the ICU in North America (15,16).

Bacterial and fungal secondary infection is common in patients with viral pneumonia, and the rate of secondary infections among patients infected with respiratory viruses is between 11% and 35% (17). In our study; Candida, *Enterococcus*, *Klebsiella*, *Escherichia coli*, *Pseudomonas*, *Acinetobacter* and *Enterobacter* species were isolated in respectively 32.3%, 17.7%, 14.5%, 12.9%, 9.7%, 6.5%, 6.5% of hospitalized patients in the ICU with secondary infection. The results of our study are in accordance with the literature information reporting the bacterial or fungal secondary infection rate of patients infected with COVID-19.

It is known that the development of bacterial and fungal secondary infections with COVID-19 could increase the severity of the disease and mortality (18). Secondary infection caused by bacteria or fungi has a great impact on the progression and prognosis of the disease, especially in critically ill patients. It causes increase in the need for intensive care supply and multiple antibiotic treatment, and most importantly, an increase in mortality (19). In a study regarding secondary infection in SARS-CoV-2 patients, it was indicated that the group with secondary infection had more severe lung lesions histopathologically, and significantly increased proinflammatory cytokines expression (20). The level of pro-inflammatory cytokines associated with severe lung injury increases significantly in COVID-19 patients, and it has been found that there is a 2.5-fold increase in mortality in patients diagnosed with COVID-19 due to the development of secondary infection (21). Regarding laboratory markers of COVID-19 patients were admitted to the ICU, the highest PCT level and platelet count have been associated with mortality. High levels of interleukin 6 were observed in deceased patients. Similarly, ferritin levels were detected to be lower than expected in previously reported hemophagocytic lenfohistiocytosis subtypes (11).

It was determined that in the group without secondary infection, there were higher differences between

Table 4. Comparison of the changes in the data of the patients in terms of the presence of secondary infection in the ICU and mortality

	Patients without infection		Patients with infection		Patients without infection	Patients with infection	Alive	Ex
	Alive	Ex	Alive	Ex	p (alive-ex)	p (alive-ex)	p Isolation (yes-no)	p Isolation (yes-no)
	(n=40)	(n=43)	(n=28)	(n=34)				
Age, mean (SD)	57.28 (16.27)	62.47 (14.67)	63.04 (16.72)	62.62 (16.59)	0.124[t]	0.927[t]	0.163[t]	0.966[t]
BMI, median (Q1/Q3)	24.88 (26.79/31.76)	24.65 (27.76/29.41)	24.65 (26.21/29.39)	24.22 (25.55/31.25)	0.990[u]	0.978[u]	0.630[u]	0.899[u]
Gender, n (%)								
Female	15 (37.5)	16 (37.2)	10 (35.7)	14 (41.2)	0.999[c]	0.975[c]	0.999[c]	0.815[c]
Male	25 (62.5)	27 (62.8)	18 (64.3)	20 (58.8)	-	-	-	-
Comorbidity, n (%)								
No	2 (5)	0 (0)	3 (10.7)	0 (0)	0.229[f]	0.087[f]	0.333[f]	-
Yes	38 (95)	43 (100)	25 (89.3)	34 (100)	-	-	-	-
Length of stay (hours), median (Q1/Q3)	95 (239/369)	82 (130/360)	132 (252/483.5)	95 (176.5/291)	0.269[u]	0.199[u]	0.493[u]	0.657[u]
Mechanical ventilation (hours), median (Q1/Q3)	59.5 (112/281.5)	58 (111/326)	55 (167.5/346.5)	60 (174.5/292)	0.914[u]	0.759[u]	0.637[u]	0.341[u]
Difference (sampling time-first)								
APACHE-II, median (Q1/Q3)	-1 (7/14)	-3 (3/10)	-1 (9/13)	1 (6/12)	0.016[u]	0.552[u]	0.995[u]	0.092[u]
SOFA, median (Q1/Q3)	-2 (1.50/6)	-7 (-3/3)	-3.50 (2/8.50)	-3 (2/4)	0.002[u]	0.249[u]	0.841[u]	0.051[u]
CRP, median (Q1/Q3)	-18.85 (0/50.50)	-18.58 (0/3)	-62.32 (-0.39/1.51)	-15 (0.31/49)	0.477[u]	0.041[u]	0.129[u]	0.214[u]
PCT, median (Q1/Q3)	-0.16 (0/0.02)	-0.19 (0/0)	-0.19 (0/0.26)	0 (0/0.29)	0.707[u]	0.634[u]	0.714[u]	0.180[u]
WBC, median (Q1/Q3)	-0.94 (0/0.36)	-0.50 (0/1.34)	-1.89 (0/5.30)	0 (0/4.79)	0.725[u]	0.494[u]	0.701[u]	0.296[u]
Neu, median (Q1/Q3)	-0.95 (0/0.87)	-0.50 (0/1.55)	-2.59 (0/4.36)	0 (0/4.37)	0.546[u]	0.267[u]	0.908[u]	0.318[u]
Lym, median (Q1/Q3)	0 (0/0.28)	-0.21 (0/0.12)	0 (0.06/0.81)	0 (0/0.53)	0.570[u]	0.540[u]	0.071[u]	0.101[u]
Lactate, median (Q1/Q3)	-0.15 (0/0.60)	0 (0/0.40)	0 (0.40/0.95)	0 (0.15/0.80)	0.716[u]	0.488[u]	0.073[u]	0.187[u]
LDH, median (Q1/Q3)	-113.50 (0/2)	-90 (0/0)	-97.50 (0/27)	-74 (0/67)	0.598[u]	0.505[u]	0.839[u]	0.299[u]
Ferritin, median (Q1/Q3)	-427.99 (0/348.2)	-321.80 (0/506.7)	-796.1 (-446.30/-4.3)	-206.40 (0/1704)	0.567[u]	0.009[u]	0.063[u]	0.815[u]
D-dimer, median (Q1/Q3)	0 (0/1.80)	-0.10 (0/0.08)	-0.02 (0/0.60)	0 (0/0.53)	0.014[u]	0.693[u]	0.294[u]	0.097[u]

[t]Independent samples t-test (Bootstrap), [u]Mann-Whitney U test (monte Carlo), [c]Pearson chi-square test (Monte Carlo), [f]Fisher Exact test (Monte Carlo), SD: standard deviation, Q1: percentile 25, Q3: percentile 75, BMI: body mass index, APACHE-II: Acute Physiology and Chronic Health Evaluation-II, SOFA: Sequential Organ Failure Assesment, CRP: C-reactive protein, PCT: procalcitonin, WBC: white blood count, LDH: lactate dehydrogenase

APACHE-II and SOFA scores measured at the time of admission and sampling for culture. Likewise, there was a significant increase in the levels of ferritin in surviving and deceased patients in the group with secondary infection. According to this finding, it suggests that secondary infections were developed after COVID-19 infections play an important role in the clinical outcomes of patients. In the group without secondary infections, the d-dimer levels of the surviving and deceased patients decreased significantly. We believe that secondary infection in COVID-19 patients may cause an increase in the severity of the disease with systemic inflammation and delay the recovery time.

Conclusion

As a result, secondary infection with different bacteria or fungi on the background of SARS-COV-2 is a serious problem in the COVID-19 pandemic. However, there are few reports of SARS-CoV-2 coexistence with bacterial, fungal, viral infections. The clinical data of secondary infection associated with SARS-CoV-2 play an important role in guiding evidence-based treatment of COVID-19. Critically ill patients who had secondary infections caused by viruses, bacteria, and fungi have a significantly higher rate of mortality and longer length of stay in the ICU than patients without secondary infection. For this reason, it is necessary to reveal the comorbidities of patients with COVID-19, especially in the ICU, as well as the development of secondary infections in the early period. Taking such an approach to COVID-19 patients provides an important insight to the clinician in terms of definitive treatment, accurate prevention and treatment of infectious complications, and helps to effectively reduce the mortality rate of patients infected with the coronavirus.

The study was pallned retrospective.

Ethics

Ethics Committee Approval: University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital Training and Research Hospital garnered on 08/06/2020 under number 2020-12-29.

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: Z.Ç., Y.T.Ş., Design: Y.T.Ş., E.G., Data Collection and Process: Z.Ç., Y.T.Ş., Analysis or Interpretation: Y.T.Ş., E.G., Z.Y., Literature Search: Z.Ç., Y.T.Ş., Writing: Z.Ç., Y.T.Ş

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ORIGINAL RESEARCH / *ÖZGÜN ARAŞTIRMA*

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Can the Development of AKI be Predicted in COVID-19 Patients with Severe Pneumonia?

Ağır Pnömonili COVİD-19 Hastalarında ABH Gelişimi Tahmin Edilebilir mi?

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ABSTRACT *Objective:* Coronavirus disease-2019 (COVID-19) may cause severe respiratory disease, glomerular dysfunction and acute tubular necrosis. Lactate dehydrogenase (LDH), C-reactive protein (CRP), D-dimer, lymphopenia and increased neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR) associated with poor prognosis. We investigated the effects of these mediators on the development of acute kidney injury (AKI).
Materials and Methods: Patients with severe pneumonia with the diagnosis COVID-19 were included in the retrospective study. Three subgroups were created: Group 1: patients who developed AKI at admission or at follow-up to the intensive care unit (ICU), group 2: those without AKI, group 3: Patients who developed AKI on the basis of chronic kidney disease. Demographic data, comorbidities, lactate, D-dimer, CRP, LDH, NLR, PLR, mortality were recorded and compared.
Results: Two hundred fifty six patients were evaluated. Group 2 D-dimer levels before ICU were significantly lower than those in group 3. Group 2 last day D-dimer levels were significantly lower than those of group 3 and group 1. Admission LDH values were higher in the group 1 than in groups 2 and 3. Last day LDH values were higher in the group 1 than in group 2. NLR values were higher in group 3 than in group 2 on the 6th day. Last day PLR values were lower in the group 1 than in group 2. No significant difference was present between the groups in terms of D-dimer, LDH, NLR, PLR levels at the other time points.
Conclusion: The contribution of laboratory findings in determining the risk of AKI has not been clarified.
Keywords: COVID-19, severe pneumonia, acute kidney injury

ÖZ *Amaç:* Koronavirüs hastalığı-2019 (COVİD-19) ciddi solunum yolu hastalığı, glomerüler disfonksiyon ve akut tübüler nekroza neden olabilir. Laktat dehidrogenaz (LDH), C-reaktif protein (CRP), D-dimer, lenfopeni ve artmış nötrofil/lenfosit oranı (NLO), platelet/lenfosit oranının (PLO) kötü prognoz ile ilişkili olduğu bilinmektedir. Bu çalışmada bu mediyatörlerin akut böbrek hasarı (ABH) gelişimi üzerindeki etkilerini araştırmayı amaçladık.
Gereç ve Yöntem: Bu retrospektif çalışmaya COVİD-19 tanısı almış, şiddetli pnömoni gelişen hastalar dahil edildi. Üç alt grup oluşturuldu: Grup 1- yoğun bakım ünitesine (YBÜ) yatışta veya takipte ABH gelişen hastalar, grup 2- ABH olmayanlar, grup 3- kronik böbrek yetmezliği zemininde ABH gelişen hastalar. Demografik veriler, komorbiditeler, laktat, LDH, CRP, D-dimer, NLO, PLO değerleri ve mortalite kaydedildi ve karşılaştırıldı.
Bulgular: İki yüz elli altı hasta değerlendirildi. YBÜ öncesi grup 2'de D-dimer seviyeleri grup 3'ten anlamlı derecede düşüktü. Grup 2'de son gün D-dimer seviyeleri grup 3 ve grup 1'den anlamlı derecede düşüktü. Giriş LDH değerleri grup 1'de grup 2 ve grup 3'e göre daha yüksekti. Son gün LDH değerleri grup 1'de grup 2'ye göre daha yüksekti. Altıncı günde NLR değerleri grup 3'te grup 2'ye göre daha yüksekti. Grup 1'de son gün PLR değerleri grup 2'ye göre daha düşüktü. Diğer zamanlarda D-dimer, LDH, NLO ve PLO seviyeleri açısından gruplar arasında anlamlı bir fark yoktu.
Sonuç: ABH riskini belirlemede laboratuvar bulgularının katkısı açıklığa kavuşturulmamıştır.
Anahtar Kelimeler: COVİD-19, ağır pnömoni, akut böbrek hasarı

Introduction

Coronavirus disease-2019 (COVID-19) is a condition that is caused by the virus termed as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) from Coronaviridae family and that courses with respiratory tract disease and respiratory failure. A critical disease that requires intensive care unit (ICU) monitoring in approximately 5% of the patients emerges accompanied with severe respiratory failure and organ failures including primarily kidney failure. The prevalence rate of acute kidney injury (AKI) was reported to be 4.5-46% in the hospitalized patients with diagnosis of COVID-19 however that rate may rise up between 36.4-76% in the critically ill patients (1,2).

In the autopsy examinations performed in the individuals infected with SARS-CoV-2 virus, the inclusion bodies caused by the virus have been shown also in the glomerular podocytes and proximal tubules including ACE-2 receptors. Nevertheless, non-detection of an immune deposit formation or an evidence of haemorrhage in the renal interstitial field that will cause vasculitis and inflammation suggests that SARS-CoV-2 virus causes AKI and proteinuria by directly entering the glomerular and proximal tubular epithelia by the means of ACE-2 receptor (3).

AKI due to SARS-CoV-2 develops by the entry of the virus into the cell using the ACE-2 and CD147 receptors located on the renal proximal tubules and the ACE-2 receptors located on the glomerular podocytes. It induces glomerular damage such as focal segmental glomerulosclerosis or proximal tubular damage leading to acute tubular necrosis. It impairs renin angiotensin aldosterone system by binding to ACE-2 receptor. It causes the accumulation of angiotensin II by inhibiting the conversion of angiotensin II to angiotensin 1-7. The increased angiotensin II leads to inflammation, vasoconstriction, fibrosis and glomerular dysfunction. At the same time, it induces ischemia and necrosis via formation of fibrin deposits in the glomeruli by activating coagulation. The obstruction of the capillary lumen and diffuse proximal tubule injury occurs due to erythrocyte aggregation mostly without platelets or fibrinoid substances in the virus-infected kidneys. Also increasing cytokine (particularly IL-6) response depending on severe SARS-CoV-2 infection facilitates the glomerular and proximal tubule damage. In addition to all these factors, volume deficit, nephrotoxic treatments, mechanical ventilation and secondary infections also promote the development of AKI in the critically ill patients (4,5).

In the COVID-19 patients, increased neutrophil and decreased lymphocyte counts are associated with more severe disease course, ICU admission and mortality (6-8). Peak platelet value and platelet/lymphocyte ratio (PLR) are the independent risk factors for poor prognosis and prolonged hospital stay, respectively. Furthermore, peak platelet value has been associated with cytokine storm (9). Increased leukocyte count together with decreased platelet and lymphocyte counts are accompanied with myocardial damage and high troponin-T level in the COVID-19 patients (10). Increased lactate dehydrogenase (LDH), C-reactive protein (CRP) and ferritin counts are associated with higher risk for Acute respiratory distress syndrome (ARDS) development and poor prognosis in the COVID-19 patients. Also high D-dimer level is associated with poor prognosis, mortality, increased rate of ARDS development and myocardial damage (10,11).

In the light of all these evidence, we aimed in our study to investigate which inflammatory mediators that increase due to ACE-2 receptor involvement developing after infection with SARS-CoV-2 and subsequently occurring thrombosis tendency and cytokine storm have a higher impact on development of AKI and intensive care monitoring process.

Materials and Methods

Following obtaining the approval for the research from the İstanbul Prof. Dr. Cemil Taşcıoğlu City Hospital Ethics Committee (decision no: 199, date: 16.06.2020), 350 patients diagnosed with confirmed COVID-19 who developed severe pneumonia and admitted to the tertiary stage ICU of University of Health Sciences Turkey, İstanbul Prof. Dr. Cemil Taşcıoğlu City Hospital between the dates 18.03.2020-01.06.2020 were retrospectively examined. All the adult patients diagnosed with confirmed COVID-19 who had severe pneumonia and aged over 18 years were included in the study. The diagnosis of COVID-19 was made with clinical findings and ground glass opacities in thorax computed tomography. In addition, polimerase chain reaction (PCR) of SARS-CoV-2 was performed from all patients. The patients without diagnosis of COVID-19 were excluded from the study. The patients who met the inclusion criteria were included in the study.

The definition of severe respiratory tract infection (pneumonia): The presence of the followings in the patient with fever and signs of respiratory tract infection;

- Breathing rate >30/min and/or,
- Severe respiratory distress (dyspnea, use of extra respiratory muscles) and/or,
- Oxygen saturation in room air <90% (PaO_2/FiO_2<300 in the patient receiving oxygen support) (12).

The Definition AKI (13)

- An increase of 0.3 mg/dL or higher in serum creatinine level or,
- A 1.5 fold or higher elevation in the serum creatinine level compared with basal values known or estimated to occur in the last 7 days or,
- Urine output below 0.5 mL/kg/hour in the last 6 hours,

The patients were divided into 3 subgroups as the patients with developed AKI at baseline (group 1), those without AKI (group 2) and those with AKI on the ground of chronic kidney disease (CKD) (group 3). At the time of initial admission to the ICU; demographic data, comorbid diseases, time from disease onset to ICU admission, admission and discharge Sequential Organ Failure Assessment (SOFA) scores, diuresis amount in the first 6 and 24 hours of the patients as well as lactate, D-dimer, CRP, ferritin, fibrinogen, LDH, neutrophil/lymphocyte ratio (NLR) and PLR values of the patients who developed AKI in the ICU at the day of AKI development and during ICU monitoring were recorded from the patient files. The stage of AKI was assessed in the patients (Table 1) and the facts whether AKI stage increased in the intensive care monitoring process, whether increased AKI stage was associated with laboratory values (ferritin, fibrinogen, D-dimer, NLR, PLR) if it increased and how it was treated (by continuous renal replacement therapy) and whether concurrent multiorgan failure developed, and mortality analysis were recorded from the patient files compared. Differential diagnosis analysis was carried out for total mortality, mortality associated with AKI and non-AKI mortality causes. Invasive (IMV) and non-invasive mechanical ventilation treatments received by the patients, length of stay in the ICU and mechanical ventilation, discharge status (mortality or discharge to the ward) were recorded from the patient files and compared. In addition, the fact whether there was a difference between the patients who had CKD at entrance to the ICU and developed additional AKI in terms of acute phase reactants, oxidative stress and mortality.

Statistical Analysis

The statistical analysis was performed using SPSS 23.0 for Windows. The normality analysis of the continuous variables was carried out by Kolmogorov-Smirnov test accompanying skewness and kurtosis normality tests from the descriptive statistics. All the tests were conducted nonparametrically since the data were not normally distributed in at least one group regarding all study data. The descriptive statistics were expressed as numbers and percentages for categorical variables and given as median (minimum-maximum) for quantitative variables. The difference analysis of the quantitative variables was performed using Mann-Whitney U test in the independent two groups. The rates were compared with chi-square analysis in the independent groups. The statistical alpha significance level was accepted as $p<0.05$.

Results

The study included 256 patients constituted by 142 (55.5%) male and 114 (44.5%) female patients. The female patients had a similar mean age with male patients (p=0.135). AKI group (group 1), non-AKI group (group 2) and the group that developed AKI on the ground of CKD (group 3) included 169, 62 and 25 patients, respectively.

AKI developed in totally 72 patients after entrance to the ICU. AKI emerged due to use of nephrotoxic drugs in 5 of those patients. Aminoglycozide (AG) and colistin were administered alone in 2 and 1 patients, respectively, whereas AG and colistin were administered in combination in 2 patients.

Group 3 had a higher mean age than group 2 and group 1 (p<0.001) and (p=0.022), respectively. Mean age of group 1 was higher than group 2 (p=0.018).

The frequencies of coronary artery disease (CAD), hypertension (HT) and chronic obstructive pulmonary

Table 1. The stages of acute kidney injury (13)

Stage	Serum creatinine level	Urine amount
1	An increase of 1.5-1.9 fold basal value or >0.3 mg/dL	<0.5 mL/kg/hour for 6 hours
2	An increase of 2-2.9 fold basal value	<0.5 mL/kg/hour for 12 hours
3	An increase of 3-fold basal value or >0.4 mg/dL or >0.4 mg/dL or initiation of renal replacement therapy	<0.3 mL/kg/hour for longer than 24 hours or anuria for 12 hours and longer

Table 2. Demographic variables of the groups							
		Group			p		
		Group 1	Group 2	Group 3	Group 2 vs. Group 3	Group 2 vs. Group 1	Group 3 vs. Group 1
		n (%) / mean ± SD					
Sex	Female	75 (44.4%)	30 (48.4%)	9 (36%)	0.293	0.588	0.43
	Male	94 (55.6%)	32 (51.6%)	16 (64%)			
Age (year)		66.5±15.9	66.5±15.9	74.5±11.4	<0.001	0.018	0.02
Co-morbidities							
DM		42 (47.7%)	15 (44.1%)	11 (73.3%)	0.059	0.72	0.067
COPD		27 (38%)	9 (31%)	8 (72.7%)	0.017	0.509	0.03
HT		54 (59.3%)	22 (59.5%)	17 (89.5%)	0.021	0.99	0.013
CAD		29 (39.2%)	6 (23.1%)	10 (71.4%)	0.003	0.138	0.026
Arrhythmia		8 (14%)	3 (12%)	2 (25%)	0.372	0.803	0.421
AF		4 (7.4%)	1 (4.3%)	2 (25%)	0.089	0.618	0.116
CVD		10 (17.9%)	6 (24%)	2 (22.2%)	0.914	0.521	0.754
Alzheimer		11 (18.3%)	3 (12%)	1 (14.3%)	0.872	0.473	0.792
Malignity		18 (56.3%)	11 (45.8%)	4 (40%)	0.755	0.44	0.369
Lung cancer		10 (15.9%)	5 (17.9%)	1 (14.3%)	0.823	0.814	0.913
CKD		-	-	25 (100%)	<0.001	.	<0.001

*Chi-square test, **Mann-Whitney U test, DM: diabetes mellitus, COPD: chronic obstructive pulmonary disease, CAD: coronary artery disease, AF: atrial fibrillation, CVD: cerebrovascular disease, CKD: chronic kidney disease, SD: standard deviation

disease (COPD) were higher in group 3 compared with group 1 (0.026, 0.013 and 0.030, respectively) and group 2 (0.003, 0.021 and 0.017, respectively) (Table 2).

Among AKI patients; the prevalence of AKI patients at entrance to the ICU was higher in group 3 whereas a higher rate of AKI developed in group 1 during ICU monitoring (p=0.014). No significant difference was present between the groups in terms of AKI stage.

The rate of exitus was significantly higher in group 3 and group 1 than group 2 (p=0.019, p=0.012, respectively). The patients of group 3 and group 2 needed ICU admission more lately than group 1 (p=0.011) and (p=0.022), respectively. SOFA values of group 2 at entrance to the ICU were significantly lower than group 3 (p=0.022). No significant difference was present between the groups in terms of entrance and discharge SOFA scores. Lactate values assessed before and on the first day of ICU admission were higher in group 1 than group 2 (p=0.019, p=0.005, respectively). No significant difference was found between the groups in terms of lactate values (Table 3).

PCR positivity was 50% in all patients. PCR positivity was higher in group 2 than group 1 (p=0.014).

Compared with group 2, group 3 and group 1 patients had a significantly higher frequency of oliguria within the first 6 hours of ICU admission (p<0.001, p<0.001, respectively).

Compared with group 2, group 3 and group 1 patients had a significantly higher frequency of oliguria within the first 24 hours of ICU admission (p<0.001, p<0.001, respectively).

Pre-ICU D-dimer levels of group 2 were significantly lower than group 3 (p=0.035). Group 2 showed significantly lower D-dimer levels on the last ICU day compared with group 3 and group 1 (p=0.025, p=0.002, respectively). No significant difference was present between the groups in terms of D-dimer levels on the other time points (Table 4).

LDH values of group 1 patients at entrance to the ICU were significantly higher than group 2 and group 3 patients (p=0.042, p=0.042). LDH values of group 1 patients on the last ICU day were higher than group 2 (p=0.001), (Table 4). No significant difference was present between the groups in terms of ferritin and CRP values.

NLR values of group 3 on the 6th ICU day were higher than group 2 (p=0.017) whereas no difference was found between the groups in terms of NLR values on the other time points (Table 4).

PLR values of group 1 on the last ICU day were lower than group 2 (p=0.017) whereas no difference was found between the groups in terms of PLR values on the other time points (Table 4).

Table 3. Lactate, SOFA, mortality of the groups						
	Group			p		
	Group 1	Group 2	Goup 3	Group 2 vs. Group 3	Group 2 vs. Group 1	Group 3 vs. Group 1
	n (%) / mean ± SD					
Lactate						
Onset	2.6±2.01	1.81±0.72	24.1±65.25	0.561	0.019	0.439
1st day	7.52±42.12	1.98±1.09	10.24±27.66	0.139	0.005	0.94
2nd day	3.5±9.54	1.77±0.34	40.81±85.45	0.151	0.497	0.254
Last day	6.62±17.6	5.97±18.34	17.79±53.16	0.746	0.073	0.246
SOFA						
First day	5.1±3	4.6±2.9	6.1±2.5	0.022	0.28	0.092
Last day	10	3	11	0.317	0.317	0.317
Mortality n (%)						
Exitus	126 (74.6%)	35 (57.4%)	21 (84%)	0.019	0.012	0.304
Alive	43 (25.4%)	26 (42.6%)	4 (16%)			
SOFA: Sequential Organ Failure Assesment, SD: standard deviation						

The administration of high-flow oxygen therapy was significantly higher in group 2 than group 3 patients (p=0.022) whereas no significant difference was determined between the patients in terms of administration of non-invasive ventilation (NIV) and IMV (Table 5).

A higher rate of patients from group 2 were discharged to the ward compared with group 1 (p=0.013) and group 3 (p=0.040) (35%, 19% and 12.5%, respectively) (Table 5).

Discussion

ARDS and mechanical ventilation are important risk factors with respect to development of AKI in the critically ill patients (14). Impaired gas exchange and hypoxia in ARDS causes development of AKI. Beside this, administration of nephrotoxic drugs and volume overload during ICU monitoring may facilitate the development AKI by both worsening ARDS and by also decreasing renal blood flow via increasing intra-abdominal pressure while mechanical ventilation may promote occurrence of AKI by altering renal blood flow (5,15). In addition, age, presence of CKD, diabetes mellitus (DM), HT, leukocytosis and lymphopenia have been accepted as risk factors with respect to development of AKI in COVID-19 patients (16). At the same time, severity of pneumonia is an independent risk factor (17). More elderly patients and higher comorbidity of HT, COPD and CAD in group 3 compared with other two groups in our study were consistent with these evidence, however, comorbidity rate of the patients who developed AKI without CKD on the ground was not higher than non-AKI patients. Although HT, DM and COPD are higher in group 3, the mortality rate is not different from group 1, suggesting that AKI alone significantly increases mortality in COVID-19 patients.

While SOFA score can be more effective than other predictors regarding prediction of mortality in AKI patients admitted in the ICU (18), it is effective as much as Acute Physiology and Chronic Health Evaluation-II and Simplified Acute Physiology score II also in the CKD patients (19). In our patients, SOFA values of AKI group was not significant compared with non-AKI patients, whereas only AKI patients on the ground of CKD had significantly higher SOFA values. However, higher mortality rates of both group 3 and group 1 compared with group 2 may suggest that SOFA indicates mortality in the AKI patients on the ground of CKD.

Even though, lactate value is not a direct indicator of tissue perfusion, any reason creating hypoxia increases lactate level and is associated with poor prognosis. It has been shown that postoperatively assessed serum lactate level particularly ≥4 mmol/L is a reliable indicator regarding development of AKI in low-risk cardiovascular surgery patients (20). Likewise, baseline lactate levels are a predictive indicator regarding development of AKI and mortality in the patients who admitted to the emergency department because of sepsis (21). In our patients, lactate values of group 1 at entrance to the emergency department and on first ICU day were higher than group 2. Mean lactate

Table 4. LDH, D-dimer, NLR, PLR variables of the groups						
	Group			p		
	Group 1	Group 2	Group 3	Group 2 vs. Group 3	Group 2 vs. Group 1	Group 3 vs. Group 1
	n (%)/mean ± SD					
LDH						
Admission	735.3±1466.7	518±329.6	500±234.4	0.733	0.721	0.581
1st day	1620.9±8000.9	625.8±463	560.9±373	0.475	0.042	0.042
2nd day	769.8±1232.9	617.9±660.7	754.1±1037.8	0.914	0.308	0.54
3rd-5th days	985.1±2042.9	487.4±206.2	541.6±321.6	0.944	0.695	0.855
7th-10th days	601.2±585.4	451.9±209.7	436.9±166.9	0.949	0.503	0.682
11th-20th days	1199.9±3823.2	544.4±471.5	587.1±447.4	0.962	0.859	0.667
21st-30th days	605.1±940.8	364.2±113	401	0.343	0.741	0.646
AKI 2	2391.1±12351.4	235	759.6±381	0.114	0.13	0.981
Last day	2651.5±5401.7	2397.1±12494.9	1017.7±1020.7	0.075	0.001	0.4
D-dimer						
Admission	4490.3±12106.5	2902.5±5765.9	5322.9±4118.9	0.035	0.428	0.079
1st day	13131.5±41409.8	8836±23364.1	5515.6±4221.3	0.313	0.103	0.717
2nd day	11148.7±30220.6	17239.7±37586.2	4564.9±4323.2	0.858	0.913	0.993
3rd-5th day	6224.2±13429.7	6766.1±11560.1	3496.5±3604.9	0.362	0.13	0.852
7th-10th day	6393.5±13260.4	4240.8±5309	2616±1689.9	0.652	0.997	0.596
11th-20th day	4095.1±4849.6	3397.1±3697.3	3143.5±3040.4	0.739	0.773	0.681
21st-30th day	5085.3±9380.7	1538.5±607.8	2550	0.121	0.521	0.529
AKI 2	8135.5±13716.8	-	5436.8±5017.8	-	-	0.669
Last day	9887.4±17983.3	5387.1±12970.7	6714.5±7216.7	0.025	0.002	0.826
NLR						
Emergency department	10.46±10.84	25.95±74.36	269.39±743.49	0.071	0.095	0.003
Admission	25.38±101.5	46.16±175.37	123.75±507.7	0.579	0.283	0.153
1st day	73.12±431.92	19.51±19.08	333.73±1006.44	0.198	0.991	0.134
2nd day	134.65±856.93	31.26±71.22	240.31±548.25	0.1	0.616	0.092
3rd-5th day	26.73±92.55	56.43±154.88	156.8±420.07	0.163	0.38	0.146
6th-7th day	36.86±103.15	56.2±236.23	253.57±614.11	0.017	0.089	0.092
7th-10th day	56.78±265.64	53.91±159.92	544±1066.68	0.151	0.139	0.211
11th-20th day	90.08±362.11	96.13±221.4	8.23	0.617	0.351	0.813
21st-30th day	77.2±331.29	46.15±25.24	170.74±458.84	0.157	0.088	0.307
AKI 2	54.92±291.21	31.01±74.2	232.26±834.16	0.218	0.823	0.086
PLR						
Emergency department	258.5±202.8	322±244.4	276.1±245.2	0.353	0.085	0.894
Admission	318.6±276.3	375.2±254.5	352.5±353.8	0.247	0.086	0.951
3rd day	7639.1±87238.4	357.7±238	446.7±285.5	0.21	0.742	0.146
5th day	6395.1±63436.5	381±245.6	441.4±363.9	0.874	0.812	0.709
7th day	356.5±292.2	312.1±216.8	391.4±237.3	0.34	0.657	0.448

Table 4. Continued

	Group				p		
	Group 1		Group 3		Group 2 vs. Group 3	Group 2 vs. Group 1	Group 3 vs. Group 1
	n (%)/mean ± SD						
10th day	301.5±246.1	269.2±204.8	464.7±278.9	0.059		0.58	0.099
20th day	273.3±218.3	198.5±86.9	249.3±62.6	0.296		0.511	0.746
30th day	256.9±201.5	199.5±120.1	182	0.617		0.484	0.651
AKI 2	368±353.7	64	340.6±328.6	0.206		0.184	0.926
Last day	224.9±234.8	287.3±220.3	289.5±289.1	0.745		0.017	0.171

AKI 2: The day when AKI devolops in the ICU. NLR: neurophil/lymphocyte ratio, PLR: platelet/lymphocyte ratio, SD: standard deviation, AKI: acute kidney injury, LDH: lactate dehydrogenase, ICU: intensive care unit

Table 5. NIV, HFNO, IMV, duration of ICU, duration of mechanical ventilation, discharge variables of the groups

		Group			p		
		Group 1	Group 2	Group 3	Group 2 vs. Group 3	Group 2 vs. Group 1	Group 3 vs. Group 1
		n (%)/mean ± SD					
NIV	Yes	31 (21.2%)	12 (26.7%)	3 (15.8%)	0.38	0.455	0.581
	No	115 (78.8%)	33 (73.3%)	16 (84.2%)			
HFNO	Yes	29 (19.9%)	15 (31.9%)	1 (5.3%)	0.022	0.087	0.121
	No	117 (80.1%)	32 (68.1%)	18 (94.7%)			
IMV	Yes	150 (90.4%)	48 (85.7%)	21 (87.5%)	0.832	0.333	0.662
	No	16 (9.6%)	8 (14.3%)	3 (12.5%)			
Duration of ICU (days)		15.1±17.6	12.7±14	8.7±8	0.505	0.167	0.048
Duration of mechanical ventilation (days)		12.2±15.6	10±11.6	7.1±8	0.563	0.236	0.068
Discharge	Yes	31 (19%)	20 (35.1%)	3 (12.5%)	0.04	0.013	0.44
	No	132 (81%)	37 (64.9%)	21 (87.5%)			

*Chi-square test, **Mann-Whitney U test, NIV: non-invasive ventilation, IMV: invasive mechanical ventilation, HFNO: high flow nasal oxygenation, ICU: intensive care unit, SD: standard deviation

value was 7.5 mmol/L on first ICU day in these patients who developed AKI during ICU monitoring process.

The absence of a difference between NLR and PLR values of the patients suggests that NLR and PLR are not differential parameters with respect to development of AKI. NLR value of group 3 on the 6th ICU day was higher than group 2, however, AKI developed in group 3 patients at entrance to ICU.

High values of D-dimer, LDH, NLR, PLR, ferritin and CRP have been associated with more severe disease progression, increased intensive care admission and mortality in COVID-19 patients (22-24). NLR and PLR progressed with higher values in the severe disease group that needed intubation and intensive care compared with those who had not severe disease (25). Therefore they may be differential hematological parameters in predicting development of pneumonia (26).

Similarly, it has been demonstrated that NLR and systemic immune inflammation index (platelet count x neutrophil count/lymphocyte count) progressed with higher values in COVID-19 patients with comorbidity of CKD and that they are effective in determination of the patients with high mortality (27). However, in our study patients, non-detection of a significant change in D-dimer, LDH, NLR, PLR, ferritin and CRP values in group 1 that developed a higher rate of AKI during ICU monitoring may be interpreted such that these monitoring parameters are not related with AKI. Even though D-dimer is a parameter that may increase in numerous medical circumstances, it is a monitoring

parameter that can provide information about thrombotic complications, cytokine storm and disease severity in COVID-19 patients (28-30). In a prospective study (n=41), higher LDH, D-dimer and CRP values were detected in the patients who developed AKI during hospital stay and more severe pulmonary involvement and intensive care admission were determined in these patients (31). In our study, no difference was found between D-dimer assessments between patient groups at entrance and monitoring. However, D-dimer levels were higher in group 3 and group 1 than group 2 on the last ICU day as correlated with disease severity.

Even though, higher LDH values at entrance to ICU in group 1 patients compared with group 2 and group 3 patients, and higher LDH values on the last ICU day in group 1 patients than group 2 points out the relationship between high LDH level and severity of COVID-19 as previously shown (32-34), the absence of a difference between patient groups during monitoring suggests that it has no diagnostic value regarding development of AKI.

Comorbid diseases such as DM, HT, CKD, atherosclerotic heart disease and COPD are risk factors for AKI (13,35). Similarly, HT, DM, obesity, dyslipidemia, cigarette smoking and advanced age are encountered as the most commonly known causes of AKI (36,37). In our study, no difference was observed between AKI patients and non-AKI group in terms of comorbidities whereas comorbid circumstances were frequently in group 3 patients. The length of ICU stay was shorter and mortality rate was high. No difference was identified between the groups regarding use of IMV and NIV. The longer duration of high-flow oxygen therapy and longer ICU stay in group 2 suggest that these patients may be treated with high-flow oxygen therapy for a longer time after being extubated and discharged to the ward.

Conclusion

AKI development courses with high mortality in COVID-19 patients. The nephrotoxicity of the medications should be avoided to prevent development of AKI as well as all critically patients in the ICU. Hypovolemia, hypoxia and hypotension should be managed meticulously. No diagnostic relationship was found between AKI development and intensive care severity parameters.

Ethics

Ethics Committee Approval: The approval for the research obtained from the İstanbul Prof. Dr. Cemil Taşcıoğlu City Hospital Ethics Committee (decision no: 199, date: 16.06.2020).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: R.S.K., Concept: R.S.K., A.A., N.T., Design: R.S.K., A.A., N.T., Data Collection and Process: R.S.K., A.A., E.D., R.G.A., Analysis or Interpretation: R.S.K., A.A., N.T., Literature Search: R.S.K., Writing: R.S.K.

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ÖZGÜN ARAŞTIRMA / *ORIGINAL RESEARCH*

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Bir Üniversite Hastanesinde Farklı Bölümlerde *Legionella* ve Diğer Patojen Mikroorganizmaların Araştırılması: Prospektif Çalışma

Investigation of *Legionella* and Other Pathogenic Microorganisms in Different Departments of a University Hospital: A Prospective Study

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ÖZ *Amaç:* Bu çalışmada, 25 Temmuz 2019-1 Kasım 2019 tarihleri arasında üçüncü basamak sağlık hizmeti sunan bir hastanenin farklı birimlerinden alınan sürüntü örneklerinde *Legionella* spp. ve diğer patojen mikroorganizmaların araştırılması amaçlanmıştır.
Gereç ve Yöntem: Hastanenin laboratuvar, ameliyathane ve farklı yoğun bakım ünitelerinde bulunan mekanik ventilatör, klima filtrelerinin su çıkış noktaları ve lavabo musluklarından 92 sürüntü örneği alındı. Tüm örnekler santrifüjlenerek doğrudan *Legionella* için seçici bir besiyeri olan buffered charcoal-yeast extract agara ve diğer konvansiyonel besiyerlerine inoküle edildi. Kültür ve serolojik testler ile *Legionella* pozitif olan 6 örnek rastgele seçilerek tür düzeyinde tanımlama için 16S rRNA dizi analizi yapıldı.
Bulgular: Kültürlerin 24'ünde (%26,08) *Legionella* spp. kolonisi ile uyumlu üreme gözlendi. Serogrubu belirlenen 6 örnekten sadece üçü moleküler tanımlama ile doğrulandı. Bunların ikisi *Legionella pneumophila* subsp. *pneumophila* diğeri *Legionella anisa* olarak tanımlandı. Mekanik ventilatörlerin filtrelerinden *Penicillium* spp., *Aspergillus flavus, Acinetobacter baumannii, Morganella morganii, Moraxella* spp., *Pseudomonas aeruginosa* ve bir musluk örneğinden *Escherichia coli* izole edildi.
Sonuç: Yüksek riskli hastaların *Legionella* spp. ile potansiyel maruziyeti, örneklem sıklığının artırılması ve etkili kontrol önlemleri ile ortadan kaldırılmalıdır.
Anahtar Kelimeler: *Legionella* spp., patojen, identifikasyon, 16S rRNA

ABSTRACT *Objective:* In this study, it was aimed to investigate *Legionella* spp. and other pathogenic microorganisms in swab samples taken from different units of a tertiary healthcare hospital between July 25, 2019 and November 1, 2019.
Materials and Methods: Ninety-two swab samples were taken from the mechanical ventilator, air conditioner filters, water outlets, and sink faucets in the laboratory, operating room and different intensive care units of the hospital. All samples were centrifuged and inoculated directly onto buffered coal yeast extract agar, a medium selective for *Legionella* and other conventional media. 16S rRNA sequence analysis was performed for identification at the species level by randomly selecting 6 samples that were positive for *Legionella* by culture and serological tests.
Results: Growth compatible with *Legionella* spp. colonies was observed in 24 (26.08%) cultures. Only three of the 6 serogrouped samples were confirmed by molecular identification. Two of these were identified as *Legionella pneumophila* subsp. *pneumophila* and the other as *Legionella anisa*. *Penicillium* spp., *Aspergillus flavus, Acinetobacter baumannii, Morganella morganii, Moraxella* spp., and *Pseudomonas aeruginosa* were isolated from the filters of mechanical ventilators and *Escherichia coli* from a tap sample.
Conclusion: Potential *Legionella* spp. exposure in high-risk patients should be eliminated with increased sampling frequency and effective control measures.
Keywords: *Legionella* spp., pathogen, identification, 16S rRNA

Giriş

Legionella cinsi bakteriler, kapsülsüz, sporsuz ve aerobik üreme özelliğinde olan Gram-negatif kokobasillerdir. Bu cins içerisinde, 50 tür ve bu türlere ait 70 farklı serogrup bulunmaktadır (1). Birçok *Legionella* türünün insan hastalıklarıyla ilişkili olduğu bulunmuştur. Bu enfeksiyonlardan Lejyoner hastalığı, hem hastane kaynaklı hem de toplum kökenli bir halk sağlığı sorunudur. Özellikle toplum kökenli hastalığı olanlar için olgu ölüm oranları %20 civarındayken, sağlık hizmeti ile ilişkili Lejyoner hastalığı olanlar için olgu ölüm oranları %38-53'e kadar yükselmektedir (2).

Lejyoner hastalığına, *Legionella pneumophila* (*L. pneumophila*) türünün alt serogruplarının neden olduğu belirlenmiştir (1,3). *Legionella* türleri, akuatik özellikleri ile göller, nehirler, termal sular gibi sıcak ve soğuk su kaynakları bulunan doğal alanlarda yaşayabilen saprofit mikroorganizmalardır. Habitatları çoğunlukla su olup, bu alanlarda yaşayan amip ve mavi-yeşil alglerde hücre içi paraziti olarak çoğalırlar. Bu bakteriler hastanelerde su ve soğutma sistemlerine, özellikle de musluk, duş başlıkları, ameliyathane ve yoğun bakımlarda mekanik ventilatör ve soğutma sistemleri gibi üremeye elverişli alanlara yerleşerek biyofilm tabakaları içerisinde çoğalabilmektedir (4,5). Patojen *Legionella* türleri, içerisinde bulundukları su ortamlarından, klimalar, musluk ve duş başlıkları, çeşitli tıbbi malzemelerden aerosol yol ile insanlara bulaşarak hastane kaynaklı solunum yolu hastalıklarına yol açabilmektedirler (3). Hastanelerde su kaynaklarının %12-75'inin *Legionella* ile kontamine olduğu belirlenmiştir (6).

Legionella spp. enfeksiyonları ile mücadelede ve özellikle yaz aylarında, hastane ortamında yer alan ve bu bakteri ile kontamine olabilen su depoları, musluklar, duş başlıkları, mekanik ventilatörlerin filtre üniteleri hem mekanik olarak hem de çeşitli dezenfektanlarla (iodoforlar, amonyum bileşikleri, glutaraldehit, formalin) periyodik aralıklarla temizlenmelidir (7).

Bu çalışma ile üçüncü basamak bir sağlık hizmeti sunan bir hastanenin farklı birimlerinden alınan sürüntü örneklerinde *Legionella* türleri ile diğer patojen mikroorganizmaların izolasyonu ve identifikasyonu amaçlanmıştır.

Gereç ve Yöntem

Çalışmada 25 Temmuz 2019-1 Kasım 2019 tarihleri arasında, üçüncü basamak ayaktan ve yataklı teşhis, tedavi ve rehabilitasyon hizmeti sunan bir hastanenin, ameliyathane, anesteziyoloji ve reanimasyon yoğun bakım (ARYÜ) ve öğretim üyeleri odaları (ÖÜO), beyin cerrahi yoğun bakım, dahiliye yoğun bakım ünitesi, göğüs hastalıkları ve nöroloji yoğun bakım üniteleri ve mikrobiyoloji laboratuvarı birimlerinin el yıkama muslukları ve mekanik ventilatörlerin filtre su çıkış noktaları ile merkezi laboratuvarlara ait kullanım musluklarından toplam 92 örnek alınmıştır.

Etik Kurul Onayı ve Kurum İzni

Çalışma, Kahramanmaraş Sütçü İmam Üniversitesi Tıp Fakültesi Klinik Araştırmalar Etik Kurulu tarafından 17.07.2019 tarihli oturumda, karar no: 11 ile onaylanmış ve hastane başhekimliğinden çalışma izni alınmıştır.

Örneklerin Alınması

Ameliyathane ve yoğun bakımlarda bulunan mekanik ventilatör, klima filtrelerinin varsa su çıkış noktalarıyla, lavabo musluklarından 100 mL'lik steril numune şişelerine 100 mL su örneği alınmıştır. Toplanan örnekler önceden steril hale getirilmiş burgu kapaklı cam tüplere konulmuştur. Klima filtrelerinden alınan sürüntü örnekleri ise, steril eküvyon çubuk distile su ile ıslatıldıktan sonra klimanın hava çıkış filtresine çepeçevre sürülerek alınmış ve steril burgu kapaklı cam tüplere konulmuştur. Tüm örnekler tıbbi mikrobiyoloji laboratuvarına yarım saat içinde gönderilmiştir. Hastane suyu soğuk su için, üst limiti 17 °C iken, sıcak su yaz aylarında 40-42 °C, kış aylarında >45 °C ve pH 7,8 civarında değerlendirilmiştir.

Legionella Cinsi Bakterilerin İzolasyon ve İdentifikasyonu

Toplanan su örnekleri santrifüjlendikten sonra *Legionella* cinsi bakterilerin izolasyonu için 0,1 mL özel besiyeri olan buffered charcoal yeast extract (BCYE) (OXOID CM 655, İngiltere) besiyerine ekim yapılmıştır. BCYE agar, tamponlu kömür maya ekstraktı ve L-sistein içeren seçici bir besiyeridir. Besiyerleri ilk izolasyonda %5 oranında CO_2 içeren nemli etüv ortamında ve 37 °C'de 5 gün süre ile inkübasyona bırakılmıştır. BCYE agardaki kültürlerin ilk 24-72 saatte günlük incelemeleri yapılarak üreme durumu kaydedilmiştir. Kültürde yüzeyleri düzgün, hafif bombeli, gri-beyaz veya mavi buzlu-cam görünümü veren koloniler "muhtemel *Legionella* kolonileri" olarak değerlendirilerek Gram boyaması ile mikroskopik morfolojisi incelenmiştir. Gram-negatif ince basil şeklinde olan bakterilere ait kolonilerin BCYE agara pasajları yapılarak üreyen kolonilere katalaz ve oksidaz testleri uygulanmıştır. Gram-negatif, katalaz pozitif ve oksidaz negatif olan *Legionella* spp. kolonileri, *Legionella* lateks aglütinasyon

testi (Oxoid, DR0800, İngiltere) ile tiplendirilmiştir (8,9). Teste göre; *L. pneumophila* serogrup 1, *L. pneumophila* serogrup 2-14 ve tiplendirilemeyen diğer serogruplar *Legionella* spp. olarak değerlendirilmiştir.

Legionella cinsi bakteriler dışında diğer mikroorganizmaların izolasyon ve identifikasyonu için; her bir örnek patojen bakteri izolasyonu amacı ile %5 koyun kanlı agar (BD, ABD) ve eosin methylene blue agara (BD, ABD) ekimleri yapılmıştır. Besiyerleri 37 °C'de 48 saat süre ile aerobik şartlarda inkübe edilmiştir. Maya ve küf türü mantarların üremesi için Sabouraud %4 glukoz içeren agar (Merck millipore, Almanya) kullanılmıştır. Kültür ortamında üreyen bakterilere ait koloniler; Gram boyama, biyokimyasal testler ve BD Phoenix 100 (BD, ABD) identifikasyon sistemleri ile tanımlanmıştır.

16S rRNA Polimeraz Zincirleme Reaksiyonu (PZR) Amplifikasyonu

Legionella spp. izole edilmiş kültürlerden 6 tanesi seçilerek tür düzeyinde tanımlama için moleküler analiz yapılmıştır.

DNA ekstraksiyonu daha önce tarif edildiği gibi single cell lysing buffer (SCLB) yöntemi kullanılarak yapılmıştır (10). 1 mL tris-EDTA buffer (pH 7,4) ve 10 µL 5 mg/mL proteinaz K kullanılarak stok SCLB solüsyonu hazırlanmıştır. Katı besiyerinden iğne öze ile alınan bakteri 40 µL SCLB solüsyonunda homojenize edildikten sonra ısı döngü cihazında 80 °C ve 55 °C'de 10'ar dakika bekletilmiştir. Daha sonra 5000 rpm'de 5 dakika santrifüj edilerek ve süpernatant çalışmada DNA olarak kullanılmıştır. DNA örnekleri çalışma gününe kadar -20 °C'de saklanmıştır.

Toplam hacim 20 µL olacak şekilde; 0,15 µL Taq DNA polimeraz (Solis HOT FIREPol 5 U/µL, Estonya); 0,2 µL dNTP (20 mM); 1,2 µL MgCl2 (25 mM); 10,65 µL deiyonize distile su 0,4 µL primer (10 mM), 2 µL 10x buffer 1 ve 5 µL template DNA'dan oluşan karışım hazırlanmıştır. Amplifikasyon programı 95 °C'de 3 dakikadan sonra 40 siklus 95 °C'de 30 saniye, 56 °C'de 30 saniye, 72 °C'de 1 dakika; ardından 72 °C'de 7 dakika olarak uygulanmıştır. PZR ürünleri %2 agaroz (Vivantis, Malezya) içeren jel elektroforezinde değerlendirilmiştir. Hem amplifikasyon hem de nükleotid dizi analizinde evrensel primerler olan 27F (AGAGTTTGATCMTGGCTCAG) ve 1492R (GGTTACCTTGTTACGACTT) primerleri kullanılmıştır (11). Amplifiye edilmiş ürünler (yaklaşık 1,4 kb), %2 agaroz (Vivantis, Malezya) jel elektroforezi ile çözülmüş ve bir ultraviyole (UV) transillüminatör (UVP EC3 Chemi HR 410 Bioimaging System, Cambridge, UK) altında görüntülenmiştir.

16S rRNA Dizi Analizi

PZR ürünleri, cleanup kit (CleanSEQ, Beckman Coulter, ABD) kullanılarak saflaştırılmış ve üretici talimatları izlenerek big dye direct cycle sequencing kit kullanılarak, Sanger yöntemi (Applied Biosystems 3130 Genetic Analyzer, Fisher Scientific, Waltham, MA, USA) ile nükleotid dizi analizi yapılmıştır. Sanger yöntemi ile belirlenen nükleotid dizileri BLAST (https://blast.ncbi.nlm.nih.gov/) programı yardımıyla analiz edilmiştir.

Filogenetik Küme Analizi

Nükleoitid dizileri BLAST sonuçlarında ≥%98 sorgu kapsamı üzerinde ≥%99 dizi benzerliği ve ilk en yüksek isabet ile ikinci en yüksek isabet arasında ≥%0,8 dizi farklılığına göre tanımlama yapılmıştır (12). Dizi analizi Sequencher 4.5.6 programı (AnnArbor, ABD, https://www.genecodes.com/) kullanılarak yapılmıştır.

Bulgular

Hastanenin yoğun bakım ünitelerinde bulunan mekanik ventilatörlerin filtre su çıkış noktalarından 31 ve lavabo musluklarından 61 olmak üzere toplam 92 sürüntü örneği alınmıştır. Kültürlerin 24'ünde (%26,08) *Legionella* spp. koloni morfolojisi ile uyumlu üreme gözlenmiştir. *Legionella* türlerinin tamamına yakını (23/24) musluklardan izole edilirken sadece bir örnek (1/31) mekanik ventilatör filtre su çıkış noktasından izole edilmiştir. Kültürden izole edilen diğer bakteri ve küf mantarları Tablo 1'de gösterilmiştir. BCYE agarda üreme saptanan *Legionella* spp. kolonileri için lateks aglütinasyon testi yapılmıştır (Şekil 1). Buna göre ameliyathane musluklarından alınan 24 örneğin 19'unda (%79,1) *L. pneumophilia* tespit edilmiştir. Bunların 6'sı (%31,5) serogrup 1; 4'ü (%21) serogrup 2-14 ve 9'u (%47,3) diğer serogrup olarak tanımlanmıştır. ARYÜ mekanik ventilatörlerinden alınan 8 örnekten 1'inde (%12,5) ve ÖÜO'nun lavabo musluklarından alınan 14 örnekten 1'inde (%7,1) diğer serogrup ve mikrobiyoloji laboratuvarı musluklarından alınan 23 örnekten 2'sinde (%8,6) serogrup 2-14 ve 1 (%4,3) tanesinde serogrup 1 saptanmıştır (Şekil 1).

16S rRNA Filogenetik Analizi

Nükleotid dizileri belirlenen altı örneğin üçü (4,5,7) BLAST veri tabanında *Legionella* spp. olarak tanımlanmıştır (https://blast.ncbi.nlm.nih.gov/). İki örnek *Acidovorax temperans*, bir örnek *Boseaeneae*, bir örnek ise *Sphingobium yanoikuyae* olarak saptanmıştır (Şekil 2). Çalışmada izole edilen 4, 5 ve 7

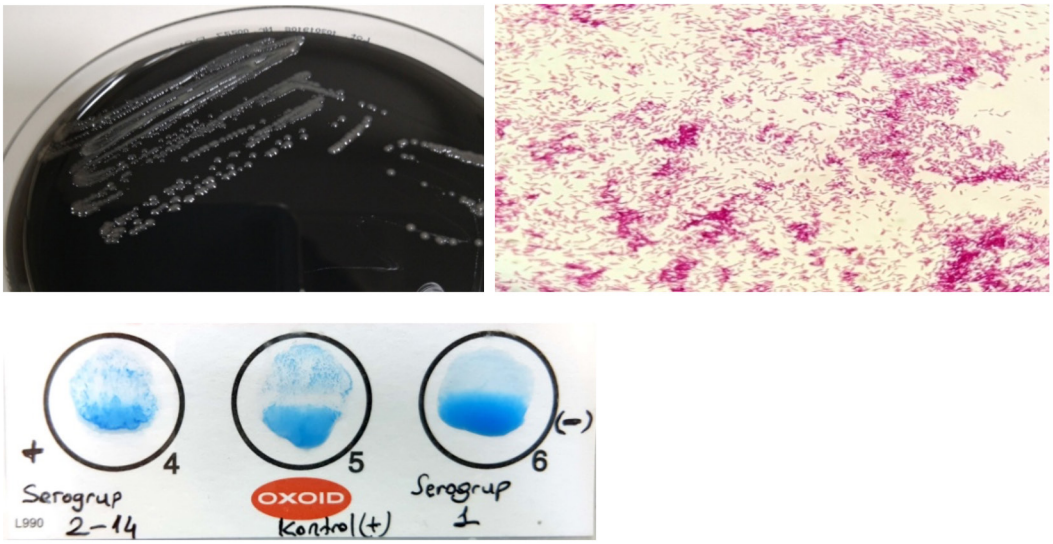
Tablo 1. Kliniklere göre izole edilen mikroorganizmaların ve *Legionella* serogruplarının dağılımı

Örnek no	Kaynak	Toplam örnek sayısı	İzole edilen mikroorganizma	*Legionella pneumophilia*	*Legionella* serogrupları		
				İzolasyon sayısı	Serogrup 1	Serogrup 2-14	Diğer serogrup
1	Ameliyathane mekanik ventilatör filtresi	15					
1[1, 8, 9, 10, 11, 12, 13]			*Penicillium* spp.	-	-	-	-
1[3]			*Penicillium* spp.	-	-	-	-
1[4]			*Aspergillus flavus*	-	-	-	-
1[5]			*Penicillium* spp.	-	-	-	-
1[7]			*Enterobacter cloacae, Moraxella* spp.	-	-	-	-
1[2, 6, 14]			-	-	-	-	-
2	Ameliyathane lavabo muslukları	24		-	-	-	-
2[1, 2, 3, 9, 18]			-	5	+	-	-
2[4]			*Bacillus* spp.	-	-	-	-
2[5]			-	1	-	+	-
2[6]			-	1	-	-	+
2[7]				1	-	-	+
2[8]			*Bacillus* spp.	1	-	-	+
2[9]			-	1	+	-	-
2[10]			*Bacillus* spp.	1	-	-	+
2[11, 14,16, 21, 22, 24]			-	3	-	-	+
2[12,13]			-	2	-	-	+
2[15, 19, 20]			-	3	-	+	-
3	ARYÜ mekanik ventilatör filtresi	8					-
3[1, 6, 8]			*A. baumannii*	-	-	-	-
3[2]			*A. baumannii + K. oxytoca + C.tropicalis*	-	-	-	-
3[3, 4]			*A. baumannii + M. morgani*	-	-	-	-
3[5]			*P. aeruginosa*	1	-	-	+
4	DYBÜ mekanik ventilatör filtresi	3		-	-	-	-
4[1, 2]			-	-	-	-	-
4[3]			*A. baumannii*	-	-	-	-
5	Göğüs/nöroloji YBÜ mekanik ventilatör filtresi	2	-	-	-	-	-
5[1]			-	-	-	-	-
5[2]			*A. baumannii*	-	-	-	-

Tablo 1. Devamı

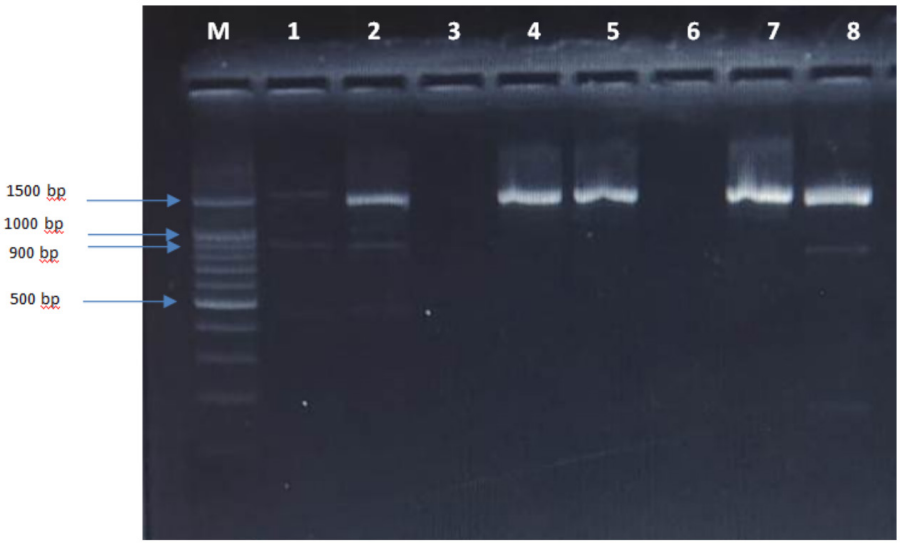
Örnek no	Kaynak	Toplam örnek sayısı	İzole edilen mikroorganizma	*Legionella pneumophilia*	*Legionella* serogrupları		
				İzolasyon sayısı	Serogrup 1	Serogrup 2-14	Diğer serogrup
6	BCYBÜ mekanik ventilatör filtresi	3	-	-	-	-	-
6[1, 2, 3]			*A. baumannii*	-	-	-	-
7	Mikrobiyoloji laboratuvarı muslukları	23	-	-	-	-	-
7[1, 4, 5]			-	-	-	-	-
7[2]			-	1	-	+	-
7[3, 23]			-	2		+	-
7[9]			*E. coli*	-	-	-	-
7[17, 19, 20, 21, 22]			-	-	-	-	-
8	AR öğretim üyeleri odaları lavabo muslukları	14	-	-	-	-	-
8[1, 2, 3, 5-14]			-	-	-	-	-
8[4]			-	1	-	-	+

YBÜ: Yoğun bakım ünitesi, ARYÜ: anesteziyoloji ve reanimasyon yoğun bakım ünitesi, DYBÜ: dahiliye yoğun bakım ünitesi, BCYBÜ: beyin ve sinir cerrahisi yoğun bakım ünitesi



Şekil 1. *Legionella* spp.'nin BCYE agarda koloni görünümü (solda), mikroskop inceleme ile Gram-negatif ince basillerin görünümü (sağda) ve lateks aglütinasyon yöntemiyle serogrup tanısı (aşağıdaki görüntü)
BCYE: Buffered charcoal yeast extract

no.lu örnekler ve 16 referans nükleotid dizisi gen bankasından (https://www.ncbi.nlm.nih.gov/refseq/) indirilerek Sequencher programında hizalanmıştır. Dendrogram MEGA v10 programında (https://www.megasoftware.net/) maximum likelihood yöntemi ile oluşturulmuştur. Programın default parametreleri olan bootstrap filojeni testi, 1000 bootstrap tekrar sayısı, Tamura-Nei modeli kullanılmıştır (13). İki izolatın (4 ve 5) daha önce iyi karakterize edilmiş



Şekil 2. 16S rRNA PZR amplifikasyon ürünleri
PZR ürünleri %2 agaroz jelde yürütüldü. M: Marker (Vivantis 100bp DNA ladder, Malezya), 1 ve 2: *Acidovorax temperans*, 3: *Sphingobium yanoikuyae* 4-5: *Legionella pneumophilia* subsp. *pneumophilia*, 6: *Boseaeneae*, 7: *Legionella anisa*, 8: Pozitif kontrol (*Pseudomonas aeruginosa* ATCC 27853)
PZR: Polimeraz zincirleme reaksiyonu

L. pneumophila Philadelphia 1 ve JCM7571 suşu ile aynı nükleotid dizilerine sahip olduğu ve bir izolatın (7) *L. anisa* olarak ayrı bir dal oluşturduğu gözlenmiştir (Şekil 3).

Gen Bankası Nükleotid Erişim Numaraları

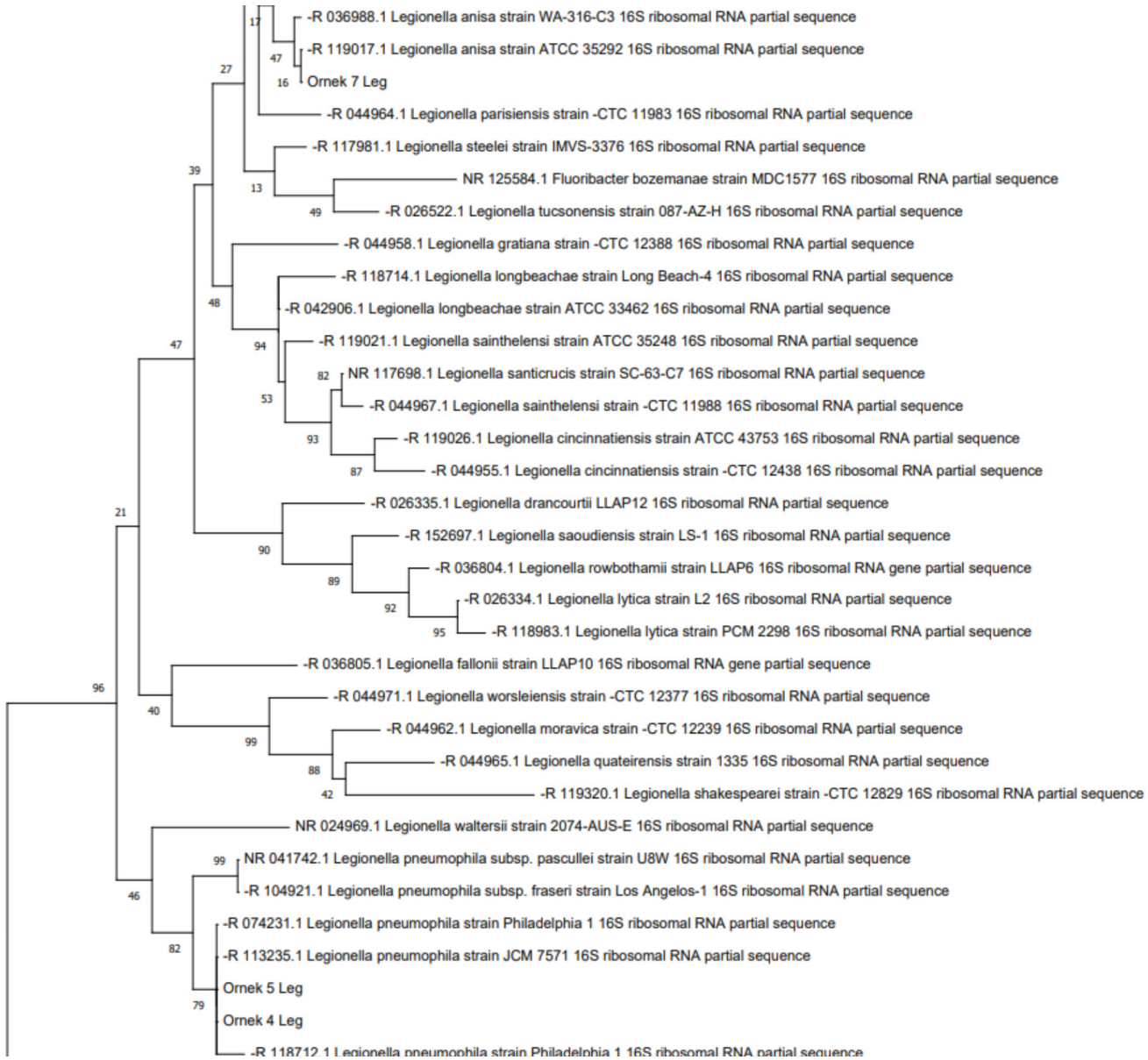
İki *L. pneumophila* ve 1 *L. anisa* izolatının nükleotid dizisi GenBank veri tabanında KSU-Lpfo, KSU-Lpyo ve KSU-Lafo adı ve OL423538-OL423540 erişim numaraları altında saklanmıştır (Tablo 2).

Tartışma

L. pneumophila ve daha az yaygın olarak diğer *Legionella* türlerinin neden olduğu enfeksiyon çevresel bir kaynaktan yayılarak salgın yapma potansiyeline sahiptir (14). Özellikle mekanik ventilatöre bağlı hastalarda *L. pneumophila*, pnömoni ve diğer solunum yolu enfeksiyonlarına neden olan patojenlerden biridir (3). Ayrıca hastanede kalış süresi 1 ile 84 gün arasında değişmekle birlikte ortalama 10,3 güne kadar uzayabilmektedir (14). Çoğu zaman gözden kaçan enfeksiyon etkeninin hem salgına yol açma potansiyeli hem de hastaneye yatış maliyeti göz önünde bulundurularak araştırılması gerektiği görülmektedir. Enfeksiyon ve çevresel kaynak araştırmasının yapıldığı bir çalışmada, mekanik ventilatöre bağlı hastalardan bronş lavaj sıvısı ve hastane musluğu örnekleri alınmıştır. Kültür ve PZR analizlerinde hasta örneklerinin sırasıyla 24 (%8,6) ve 5'inde (%1,8), su kaynaklarının ise 23 (%19,8) ve 8'inde (%6,9) *L. pneumophila* saptanmıştır. Aynı çalışmada tüm pozitif klinik örneklerin ve 14 (%60,8) çevresel örneğin *L. pneumophila* serogrup 1'e ait olduğu gösterilmiştir (15). Ayrıca sigara kullanımı, yaş, yoğun bakımda kalış süresi ve mekanik ventilatör kullanım süresi ile enfeksiyon arasında yakın ilişki bulunmuştur (15). Avrupa'da bildirilen *L. pneumophila*'ya bağlı enfeksiyonların %70'inin *L.*

Tablo 2. *Legionella* spp. izolatlarının tür düzeyinde tanımı ve GenBank erişim numaraları

Örnek no	Örnek yeri	Tür düzeyinde tanımlama	İzolat ismi	GenBank erişim numarası	URL adresi
4 (8^4)	DYBÜ mekanik ventilatör filtresi	*Legionella pneumophilia*	KSU-Lpfo	OL423538	https://www.ncbi.nlm.nih.gov/nuccore/OL423538
5 (2^5)	Göğüs/nöroloji YBÜ mekanik ventilatör filtresi	*Legionella pneumophilia*	KSU-Lpyo	OL423539	https://www.ncbi.nlm.nih.gov/nuccore/OL423539
7 (7^2)	Mikrobiyoloji laboratuvarı musluğu	*Legionella anisa*	KSU-Lafo	OL423540	https://www.ncbi.nlm.nih.gov/nuccore/OL423540



Şekil 3. 16S rRNA dizilerine göre yakından ilişkili *Legionella* türlerinin maksimum olabilirlik yöntemine göre oluşturulmuş dendogramı
*5 ve 4 (2^5, 8^4 no'lu kaynaklar) örnekler yakın ilişkili
**7 no'lu örneğin (7^2 no'lu kaynak) farklı bir tür olduğu görülmektedir

pneumophila serogrup 1, %20-30'nun serogrup 2-16 ve %5-10'un *Legionella* spp. olduğu bildirilmiştir (16). Benzer şekilde 2011-2013 yılları arasında ABD'de yapılan sürveyansa göre *L. pneumophilia* serogrup 1, Lejyoner hastalığının yaklaşık %80'inden sorumlu tutulmuştur (17). Singapur'da yapılan bir çalışmada bakımevi depolama tanklarında %21,1; spa havuzlarında %24,1; sis fanlarında %14,2 ve hızlı ısıtıcılarda %3,3 oranında *Legionella* tespit edilmiştir. Çalışmaya göre spa havuzlarında en fazla serogrup 1 (%13,8), sis fanlarında da diğer serogruplar saptanmıştır (18). Alanya'da 135 otelin su sistemlerinin araştırıldığı çalışmada 52 otelde *Legionella* varlığı tespit edilmiştir. *L. pneumophilia* serogrup 6 (%55,6) ve serogrup 1 (%22,2) en çok izole edilen serogruplar olmuştur (19). Kahramanmaraş'ta ise çeşme musluklarından alınan 130 musluk sürüntü örneğinin üçünde *L. pneumophila* serogrup 2-14, birinde serogrup 1 ve ikisinde serotiplendirilemeyen *Legionella* spp. izole edilmiştir (3). Japonya'da bina su sistemleri ile ilgili araştırmada kültür ve/

veya PZR ile 17 binanın %42'si ve 26 su örneğinin %20'sinin *Legionella* ile kontamine olduğu görülmüştür. Kültür yöntemi ile dört örnekte ve PZR ile 23 örnekte pozitiflik saptanmıştır. Aynı çalışmada; kültürde *L. pneumophila* ve *L. anisa* türleri izole edilirken, PZR ile *L. micdadei* gibi diğer türler de tanımlanmıştır. En çok izole edilen *L. pneumophila* subgrupları ise 1 ve 4 olmuştur (20). *Legionella* türleri içinde *L. anisa* pontiak ateşine neden olan etkenlerden biri olarak kabul edilmektedir (20). Çalışmamızda 92 sürüntü kültürünün 24'ünde (%26,08) *Legionella* spp. izole edilmiştir. İzolatların tamamına yakını (23/24) musluklardan elde edilirken, sadece bir örnek (1/31) yoğun bakım ünitesi mekanik ventilatör filtre su çıkış noktasından izole edilmiştir. Ayrıca kültürden izole edilen 6 örnek rastgele seçilerek moleküler tanımlama yöntemi kullanılmıştır. Altı örnekten 2'si *L. pneumophilia* subsp. *pneumophilia*, 1 örnek *L. anisa* olarak tanımlanmıştır. Diğer 3 örnekte ise *Legionella* dışı akuatik bakteriler saptanmıştır. Mekanik ventilatöre bağlı gelişen pnömonilerde *Klebsiella pneumoniae, Pseudomonas aeruginosa* (*P. aeruginosa*), *Acinetobacter, Escherichia coli* (*E. coli*) ve *Staphylococcus aureus* yaygın olarak saptanırken, nadiren *Mycoplasma pneumoniae* ve *L. pneumophila* gibi bakteriler de izole edilmektedir (21). Çalışmamızda hem *Legionella* hem de diğer patojen mikroorganizmaların izolasyon sayısını artırmak için filtrasyon yapılmadan, santrifüj ile çöküntü kısmından direkt kültür işlemi uygulanmıştır. Mekanik ventilatörlerin filtrelerinden *Penicillium, Aspergillus* tipi küf mantarları ve *Acinetobacter baumannii, Morganella morganii, Moraxella* spp. ve *P. aeruginosa* gibi mikroorganizmalar izole edilmiş, bir musluk örneğinde ise *E. coli* saptanmıştır. *Legionella*, kendisi gibi akuatik bir bakteri olan *P. aeruginosa* ile aynı örnekten izole edilirken, diğer bakterilerin izole edildiği sularda tespit edilememiştir. Bu durum diğer mikroorganizmaların üremesi durumunda *Legionella* ekosisteminin bozulması şeklinde yorumlanabilir. Kusnetsow ve ark.'nın (18) su örneklerinin mikrobiyal ve fizikokimyasal kalitesi ile *Legionella* varlığını araştırdıkları çalışmada, heterotropik bakterilerle herhangi bir ilişki bulunmamıştır. Yine sıcak su sistemlerinin fizikokimyasal ve mikrobiyolojik analizlerinin yapıldığı başka bir çalışmada, yeterli klorlama ve düşük demir içeriğinin *Legionella* eradikasyonunda etkili olduğu belirtilmiştir (20). Leoni ve ark.'na (22) göre, *Legionella* düşük manganez içerikli suda çoğalmaktadır. İtalya'da yapılan bir araştırmaya göre de, su boru sistemlerinin sıcaklığının düşmesi ve suda bakır bulunması sonucunda *Legionella* üretememiştir (23). Ayrıca *L. pneumophilia* serogrup 1, sert sularda çinko, kalsiyum ve magnezyum nedeniyle diğer serogruplara göre daha az, manganez oranı yüksek sularda ise Leoni ve ark.'nın (22) çalışmasının aksine daha fazla izole edilmiştir (23). Sudaki yüksek klor ve düşük su sertliği seviyesi *Legionella* spp. kolonizasyon için uygun bir ortam sağlamaktadır. Amerikan Hastalık ve Önleme Merkezleri'ne göre, *Legionella* için uygun bir yaşam alanı olan kalsiyum ve magnezyum gibi minerallerin neden olduğu kireç ve aşırı klorun neden olduğu korozyonu önlemek için ısıtıcı sistem, tank ve su dağıtım borularının bakımı yapılmalıdır (24). 2007 yılında Sivas'ta 8 hamamdan 64 su örneğinin alındığı çalışmada *Legionella* spp. izole edilememiştir. Bunun nedeni, soğuk su sıcaklığının <20 °C veya sıcak su sıcaklığının >48 °C olması ve suyun sert olması şeklinde açıklanmıştır (25). *Legionella* spp. 32-45 °C optimum sıcaklık aralığında üremektedir (5).

Hastanemizde tüm sıcak su kullanım alanları için hastane arıtma sisteminde demineralize edilmiş yumuşak su; sterilizasyon, mutfak, diyaliz ünitesi ve çamaşırhane gibi ünitelere yumuşak soğuk su verilmektedir. Soğuk su sıcaklığı üst sınırı her zaman 17 °C'de sabit tutulurken, kış aylarında sıcak su 45 °C'nin üzerine çıkmaktadır. Ancak yaz mevsiminde sıcak su sıcaklığı üst sınırı 40-42 °C aralığında sabit tutulmaktadır. Çalışmanın yapıldığı yaz mevsiminde, hastanede sıcak su boru hattında yumuşatılmış su kullanılması ve pH değerinin 7,8 olmasının *Legionella* kolonizasyonu için uygun bir ortam sağladığı düşünülmektedir. *Legionella* enfeksiyonu tanısında kültür altın standart kabul edilse de, özgüllüğü %100, duyarlılığı %10 ile %80 arasında değişmektedir. Özellikle mikroorganizmanın hassas yapısı ve 3-5 günlük uzun bir inkübasyon süresi nedeniyle duyarlılık %50-60'lara kadar düşmektedir (26). Serotiplendirmede, henüz tüm türleri ve serogrupları tespit edebilen ticari bir kit bulunmamaktadır. İdrar antijen testleri sadece serogrup 1'i, direkt floresan antikor testleri ise serogrup 1 ve 6'yı tespit edebilmektedir (26). Kültürde üremeyen türler genellikle yalancı negatifliğe neden olmaktadır. Bunun yanında PZR yöntemi ile test analizi 1 saatten daha kısa sürmektedir. Ayrıca duyarlılık ve özgüllük sırasıyla % 80-100 ve >%90 olarak belirtilmiştir (27). Genellikle hızlı klinik tanı amacıyla alt solunum yolu örneklerinden direkt PZR analizi yapılabiliyorsa idrar antijen testi ile birlikte tanımlama, PZR yapılamıyorsa kültür ve idrar antijen test kombinasyonu ile tanımlama önerilmektedir (27). İsfahan'da yapılan bir sürveyans çalışmasında 11 hastanenin 44 su kaynağında *Legionella* varlığı kültür ve nested PZR (nPZR) yöntemleri ile araştırılmıştır. Kültür yöntemiyle su örneklerinin %50'sinde

Legionella izole edilirken, nPZR ile her hastanenin en az bir örneğinde pozitiflik saptanmıştır. Çalışmada, nPZR ile LEG 448-JRP primer seti kullanılarak örneklerin %66'sında (29/44) *Legionella* türleri tespit edilmiştir (5). ABD'de solunum örneklerinde *Legionella* tespiti için 16S rRNA geninde 386-bp'lik bir ürünü amplifiye eden bir PZR yöntemi geliştirilmiş ve sonuçlar kültür ile karşılaştırılmıştır. Kültürde *Legionella* üreyen örneklerin tamamı PZR testi ile pozitif bulunurken, kültürde üremeyen 12 örnek PZR ile pozitif bulunmuştur. PZR pozitif üç örnek non-*L. pneumophilia* olarak tanımlanmıştır. Çalışmada, salin solüsyonunun *Legionella* kültürünü olumsuz etkilediği belirtilmiştir. Moleküler yöntemler hızlı tanı yöntemleri olmasına rağmen canlı ve ölü mikroorganizmalar ayırt edilememektedir. Ayrıca biyofilm varlığının, konsantrasyon miktarına bağlı olarak reaktifler üzerinde sitotoksik etki yarattığı bildirilmiştir (28). Hastane kaynaklı *Legionella* enfeksiyonunu önlemek ve kontrol altına almak için bir an önce epidemiyolojik araştırmaların başlatılması ve şüphelenilen su kaynağının *Legionella* varlığı açısından incelenmesi büyük önem taşımaktadır (27). Bir eradikasyon yöntemi olan "Aşırı-ısıt ve temizle" yöntemi yaygın olarak kullanılmaktadır. Boyler sıcaklığı 70 °C'ye yükseltilerek tüm su boruları, musluklar ve duş başlıkları en az 3 dakika sıcak su ile yıkanmalıdır (29). Hastanemizde de belirli aralıklarla bu yöntem uygulanmaktadır. Ayrıca soğuk su kulelerinde biyosidal uygulama etkili bulunmuştur (30). Ancak şebeke suyu sistemlerindeki klor içeriği *L. pneumophila* eradikasyonu için yeterli değildir. Amip kistleri üzerinde varlığını sürdüren *Legionella* bakterilerinin yok edilmesi için gereken klor miktarının >50 mg/L olduğu bildirilmiştir (7). Suda amonyak ve serbest klor karıştırılarak içme suyu dezenfeksiyonu serbest klordan daha başarılı bulunmuştur. Bunun yanında ozon ve klor, ozon ve kloramin, UV ve klor ile UV ve kloramin ile dezenfeksiyon yöntemleri de önerilmektedir (7). UV (dalga boyu 253,7 nm) ile ışınlama yönteminin *Legionella*'yı güvenilir şekilde öldürdüğü gösterilmiştir. Ancak *Legionella* ile doğal konakçısı amibin inaktivasyonu arasında büyük farklılıklar gözlenmiş, ikincisi 100 kat daha dirençli bulunmuştur (31). Soğuk su sıcaklığını 20 °C'nin altında tutmak ve minimum su sağlamak için kazanların 60 °C'de ve dağıtım borularının tercihen 55 °C'de tutulması önerilen yöntemler arasındadır (32). Ayrıca su tankları ve su borularının tortu, birikinti, kireç vs. açısından düzenli olarak temizliği ve hasarlı su sistemlerinin onarımı sağlanmalıdır.

Sonuç

Sonuç olarak hastane kaynaklı *Legionella* enfeksiyonlarının önüne geçmek için düzenli epidemiyolojik çalışma ve su sistemlerinde etkin dekontaminasyon uygulaması yapılmalıdır.

Teşekkür: Bakteri dizi analizlerinin nükleotid erişim numaralarını alarak GenBank'a kaydeden Prof. Dr. Fuat Aydın'a teşekkür ederiz.

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The Evaluation of COVID-19 Patients Treated with HFNC in Intensive Care Unit

Yoğun Bakımda HFNO ile Tedavi Edilen COVİD-19 Hastalarının Değerlendirilmesi

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ABSTRACT *Objective:* Since the coronavirus disease-2019 (COVID-19) pandemic caused respiratory failure in many patients, oxygen delivery methods had to be diversified, and their numbers increased. High flow nasal cannula (HFNC), which has been shown beneficial in acute respiratory failure previously, also came to the fore. We investigated the efficacy of HFNC on patients hospitalized in intensive care units due to COVID-19.
Materials and Methods: We retrospectively screened the patients followed up in the intensive care unit due to COVID-19. Patients treated with HFNC performed the study group. We analyzed the relationships among demographics, laboratory results, treatment modalities, complications, and outcomes.
Results: Among the 330 patients including mean ventilation duration with HFNC was 7.84 days. One hundred seventy (51.5%) patients were intubated during HFNC treatment. Only 5 of them were extubated. Intubated patients had higher mean HFNC duration [9.74 days - minimum (min): 2 , maximum (max): 49] compared to non-intubated patients (6.05 days - min: 1, max: 30). There was a significant relationship between mortality and age [Odds ratio (OR): 1.04], Acute Physiology and Chronic Health Evaluation-II score (OR: 1.35), having cancer (OR: 3.89), receiving non-invasive ventilation (OR: 5.94), and presence of secondary bacterial infection (OR: 44.6).
Conclusion: HFNC, whose benefit in acute respiratory failure has been proven, is also widely and successfully used in COVID-19 patients. Comprehensive randomized studies are required to demonstrate the effect of HFNC use on intubation requirement and mortality.
Keywords: Ventilation, mortality, COVID-19, respiratory failure, pneumonia, oxygen therapy

ÖZ *Amaç:* Koronavirüs hastalığı-2019 (COVİD-19) pandemisi nedeniyle solunum yetmezliği gelişen hastalarda oksijen desteği için farklı cihazlar ve yöntemler kullanılmıştır. Bu yöntemlerden birisi de daha önce akut solunum yetmezliğinde faydalı olduğu gösterilen yüksek akımlı nazal kanüldür (HFNO). Bu çalışmada, COVİD-19 nedeniyle yoğun bakım ünitelerinde yatan hastalarda HFNO'nun etkinliğinin araştırılması amaçlanmıştır.
Gereç ve Yöntem: COVİD-19 nedeniyle yoğun bakımda takip edilen hastalar geriye dönük olarak tarandılar. Yoğun bakım yatışı sırasında HFNO ile tedavi edilen hastalar çalışma grubunu oluşturdu. Demografik veriler, laboratuvar sonuçları, tedavi modaliteleri, komplikasyonlar ve klinik sonuçlar arasındaki ilişki incelendi.
Bulgular: Dahil edilen 330 hasta arasında HFNO ile ortalama ventilasyon süresi 7,84 gündü. Yüz yetmiş (%51,5) hasta HFNO tedavisi sırasında entübe edilmişti. Bunlardan sadece 5'i ekstübe olabilmişti. Entübe edilen hastaların ortalama HFNO alma süresi [9,74 gün - minimum (min): 2, maksimum (maks): 49] entübe olmayan hastalara (6,05 gün - min: 1, maks: 30) göre daha yüksekti. Mortalite ile yaş [olasılık oranı (OR): 1,04], Akut Fizyoloji ve Kronik Sağlık Değerlendirmesi-II skoru (OR: 1,35), kanser öyküsü (OR: 3,89), non-invaziv ventilasyon uygulanması (OR: 5,94) ve sekonder bakteriyel enfeksiyon varlığı (OR: 44,6) arasında anlamlı bir ilişki vardı.
Sonuç: Akut solunum yetmezliğinde faydası kanıtlanmış olan HFNO'nun, COVİD-19 hastalarında da yaygın ve başarılı bir şekilde kullanıldığı görülmüştür. HFNC kullanımının entübasyon gereksinimi ve mortalite üzerindeki etkisini göstermek için kapsamlı randomize çalışmalara ihtiyaç vardır.
Anahtar Kelimeler: Ventilasyon, mortalite, COVİD-2019, solunum yetmezliği, pnömoni, oksijen tedavisi

Introduction

High flow nasal cannula oxygen therapy (HFNC) is a relatively new oxygen delivery system for adults. It allows the delivery of oxygen at the desired level reliably. It also provides heated and humidified gas, enhancing patients' comfort, decreasing breathing work, and preventing airway epithelium injury. Nasal usage and its soft and flexible prongs allow a more tolerable procedure for patients. An easy-adjust and straightforward interface makes it -user-friendly- for doctors.

The positive impact of HFNC in acute respiratory failure patients was shown previously in various studies (1-3). Severe acute respiratory syndrome coronavirus-2 pandemic [coronavirus disease-2019 (COVID-19)], as a disease causing acute respiratory failure, resulted in increased need for intensive care units (ICU) and depletion of medical supplies such as mechanic ventilators, ventilation sets, and oxygen masks. Although early intubation was preferred at first, this approach was abandoned, and higher intubation thresholds were used (4). So HFNC became a vital tool for oxygen delivery. Despite previous studies reporting usage rates up to 65 percent, the benefits of HFNC in preventing intubation were not shown (5-7). Nevertheless, higher intubation thresholds and high usage rates of HFNC in the literature suggest it may decrease the intubation rates in case of appropriate use.

In this study, we aimed to investigate the clinical features, and outcomes of COVID-19 patients treated with HFNC in ICUs. The primary outcome of the study is the determine the clinical, laboratory, and radiological findings and outcomes of COVID-19 patients treated with HFNC. The secondary outcome was to identify factors associated with death.

Materials and Methods

We included the adult patients followed in the COVID-19 ICUs of the tertiary health center between 01.08.2020 and 01.01.2021. We gathered the medical information of the patients retrospectively by evaluating their records. We collected the basal demographic data, comorbidities, previous history of long-term oxygen therapy, and continuous positive airway pressure, Acute Physiology and Chronic Health Evaluation-II (APACHE-II) scores, length of hospitalization, polymerase chain reaction test results, computerized thorax tomography findings, and laboratory results. Complications including secondary bacterial pneumonia, pneumothorax, pulmonary thromboembolism (PTE) were recorded. Concomitant non-invasive ventilation (NIV) use, intubation, and extubation information data were collected. We obtained the data from the computerized database of the hospital.

HFNC was performed with Fisher & Paykel HealthCare, Airvo™ 2, and Inspired O2FLO™. GE Healthcare Carescape R860 mechanic ventilator was used for non-invasive and invasive mechanical ventilation.

The study protocol was approved by the Institutional Ethical Committee of Ankara City Hospital (decision no: E1/1463/2021, date: 20.01.2021).

Statistical Analysis

SPSS software version 23.0 was used for statistical analysis. Descriptive analyses were presented using mean ± standard deviation for normally distributed variables and median and minimum (min)-maximum (max) values for skew distributed variables. Categorical variables were expressed as numbers and percentages (%). For comparison between groups, Mann-Whitney U test and t-test were used for continuous variables, and the chi-square test was used for categorical variables. Logistic regression analysis will be used to evaluate the relationship between independent variables.

Selection of Patients

We retrospectively reviewed 987 patients followed in the ICU between 01.08.2020 and 01.01.2021. We excluded 115 patients because they stayed in ICU lower than 48 hours. Two hundred sixty six patients received nasal or mask oxygen. One hundred twenty seven patients were admitted as intubated and 5 patients with tracheostomy to the ICU. One hundred forty four patients were intubated in ICU while they were receiving nasal or mask oxygen. The remaining 330 patients treated with HFNC constituted the study group (Figure 1).

Results

We included 330 patients with a mean age of 66,7 (min 27 - max: 95). Two hundred twenty seven (68.8%) patients were male 103 (31.2%) were female. The mean APACHE-II score was 11.6 (min: 3, max: 28). The most common comorbidities were hypertension (HT) and diabetes mellitus (DM), and coronary artery diseases (CAD) (55.2%, 34.8%, and 20.9%) respectively). Median PaO_2/FiO_2 was 101.6 (40-223). Baseline characteristics of patients are depicted in Table 1.

Table 1. Baseline characteristics				
		HFNC (106)	**HFNC + NIV (224)**	**Total (330)**
Age	Median, min-max	68.0 (31-88)	66.6 (27-95)	66.7 (27-95)
Sex	Female/male (F/M)	39/67	64/160	103/227
Comorbidities (n, perc)				
Hypertension		55 (51.9%)	127 (56.7%)	182 (55.2%)
Diabetes mellitus		37 (34.9%)	78 (34.8%)	115 (34.8%)
CAD		27 (25.5%)	42 (18.8%)	69 (20.9%)
COPD		12 (11.3%)	17 (7.6%)	29 (8.8%)
Cancer		10 (9.4%)	18 (8.0%)	28 (8.5%)
Heart failure		7 (6.6%)	20 (8.9%)	27 (8.2%)
Asthma		7 (6.6%)	13 (5.8%)	20 (6.1%)
CKD		7 (6.6%)	10 (4.5%)	17 (5.2%)
CVD		2 (1.9%)	11 (4.9%)	13 (3.9%)
Demans		6 (5.7%)	4 (1.8%)	10 (3%)
PaO_2/FiO_2 median, min-max*		116 (44-223)	92.5 (40-217)	101.7 (40-223)

HFNC: High flow nasal cannula, NIV: non-invasive ventilation, min: minimum, max: maximum, CAD: coronary artery disease, COPD: chronic obstructive pulmonary disease, CKD: chronic kidney disease, CVD: cerebrovascular disease, n: number, perc: percentage, *PaO_2/FiO_2 was calculated at the beginning of HFNC

The primary laboratory abnormalities were lactate dehydrogenase (LDH), interleukin-6 (IL-6), and C-reactive protein (CRP) levels were increased in 330 (100%), 324 (97.3%), and 319 (97.3%) individuals, respectively. Two hundred eighty four (86.1%) had lymphopenia. Laboratory results are summarized in Table 2.

Computed thorax tomography revealed multilobar ground-glass infiltration consistent with COVID-19 in 327 (99.1%) patients. Two patients had simultaneous PTE at first admission. During follow-up, 3 more patients developed PTE, and 6 patients developed pneumothorax. There may be more concomitant PTE underdiagnosed due to non-contrast computed tomographies.

All patients received favipiravir, 18 patients received remdesivir, and 2 patients received ritonavir-lopinavir as antiviral treatment. We observed that most patients received immunosuppressant therapy due to severe disease. Treatment modalities are presented in Table 3.

The mean ventilation duration with HFNC was 7.84 days. Two hundred twenty-four of 330 (67.9%) patients were applied non-invasive mechanic ventilation concomitantly. Intubation was performed in 170 (51.5%) patients during

Table 2. Laboratory results			
Lab (med, min-max)	**HFNC (106)**	**HFNC + NIV (224)**	**Total (330)**
WBC ($x10^9$/L)	9.13 (2.83-108.7)	9.19 (0.12-22.94)	9.17 (0.12-108.7)
Neutrophile ($x10^9$/L)	7.64 (0.82-17.09)	8.03 (0.04-21.27)	7.90 (0.04-21.27)
Lymphocyte ($x10^9$/L)	0.57 (0.05-82.74)	0.54 (0.02-36.0)	0.55
Sedimentation* (mm/h)	47.5 (5.0-140.0)	38 (3-123)	42 (3-140)
CRP (g/L)	0.13 (0.001-0.360)	0.136 (0.001-0.54)	0.134 (0.001-0.540)
Procalcitonin (mcg/L)	0.19 (0.03-78.83)	0.23 (0.02-35.04)	(0.02-78.8)
IL-6 (pg/mL)	51.4 (2.0-2020)	44.15 (1.30-1703.0)	44.95 (1.3-2020)
LDH (u/L)	516 (159-2058)	552 (179-1396)	(159-2058)
Ferritin (mcg/L)	624 (22-33743)	702 (23-10795)	676 (22-33743)

*199 patients had sedimentation results. CRP: C-reactive protein, min: minimum, max: maximum, WBC: white blood cell, IL-6: interleukin-6, LDH: lactate dehydrogenase, HFNC: high flow nasal cannula, NIV: non-invasive ventilation, min: minimum, max: maximum, med: median

Table 3. Treatment modalities			
Drugs	**HFNC (106)**	**HFNC + NIV (224)**	**Total (330)**
Antivirals			
Favipiravir	106 (100%)	220 (100%)	330 (100%)
Remdesivir	2 (1.9%)	16 (7.1%)	18 (5.5%)
Ritonavir-lopinavir	1 (0.9%)	1 (0.4%)	2(0.2%)
Immun-modulators			
Tocilizumab	23 (21.7%)	28 (12.5%)	51 (15.5%)
Anakinra	7 (6.6%)	23 (10.3%)	30 (9.1%)
Steroid	95 (89.6%)	221 (98.7%)	316 (95.8%)
Pulse	42 (39.6%)	120 (53.6%)	162 (49.1%)
Maintenance*	98 (92.5%)	220 (98.2%)	318 (96.4%)
Others			
Hydroxychloroquine	47 (44.3%)	81 (36.2%)	126 (38.2%)
Colchicine	14 (13.2%)	124 (55.4%)	114 (34.5%)
Convalescent plasma	19 (17.9%)	37 (16.5%)	56 (17%)
Cytokine filter	1 (0.9%)	27 (12.1%)	28 (8.5%)
Immune-globulin	1 (0.9%)	3 (1.3%)	4 (1.2%)

*58% of the patients received maintenance steroid treatment as methylprednisolone and 42% as dexamethasone. Pulse steroid has been administered in different dosages (250 mg, 500 mg, 1 gr). HFNC: High flow nasal cannula, NIV: non-invasive ventilation

HFNC treatment. Only 5 of them were extubated. Intubated patients had higher mean HFNC duration (9.74 days - min: 2, max: 49) compared to non-intubated patients (6.05 days - min: 1, max: 30) (Figure 2).

The mean length of stay in ICU was 13.9 days for all study group. Patients who received NIV stayed in ICU (14.4 days) longer than those who did not receive NIV (12.7 days) (p=0.019). Similarly, the non-NIV group has a lower intubation rate (36.8%) than the NIV received group (58.5%).

There was documented secondary bacterial pneumonia in 71 (41.7%) intubated patients. The most seen agents are *Acinetobacter* spp. (40), *Clostridium striatum, Staphylococcus aureus* (8), and *Klebsiella* spp. (8). We couldn't obtain a respiratory specimen from non-intubated individuals.

Of the 155 patients who transferred to the COVID general ward, 7 were transferred to another ICU for further follow-up, and 5 were discharged home. During ICU stay, 163 patients (49.4%) died. Examination of the relationship between comorbidities and mortality revealed that there was a statistically significant relationship between the presence of heart failure (p=0.007), HT (p=0.04), cerebrovascular disease (p=0.04), and cancer (p=0.01) and mortality. The only treatment modality with a statistically significant relationship

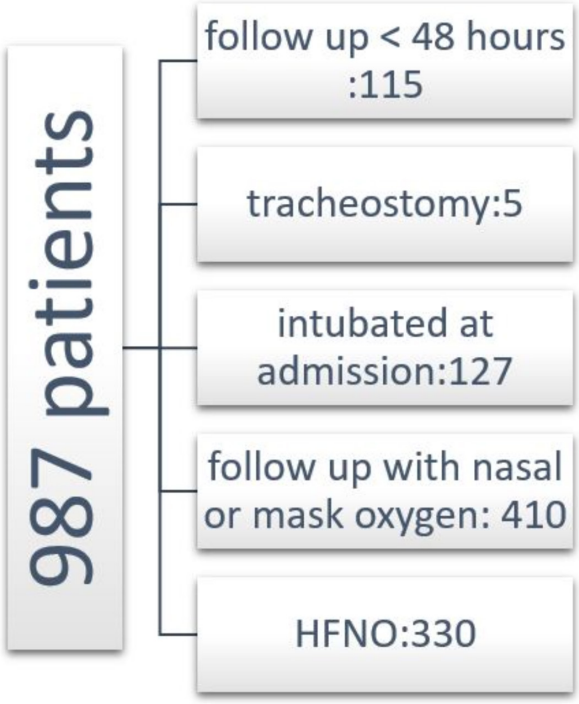

Figure 1. Study design

Table 4. APACHE-II scores							
		HFNC (106)		HFNC+ NIV (224)		Total (330)	
APACHE-II (med, min-max)		10.0 (3-28)		11.0 (3-26)		11.0 (3-28)	
Point	Expected mortality	n	Observed mortality	n	Observed mortality	n	Observed mortality
0-4 point (n, perc)	4%	8 (7.5%)	0%	5 (2.2%)	20%	13 (3.9%)	7.7%
5-9 point (n, perc)	8%	35 (33.0%)	2.9%	66 (29.5%)	16.7%	101 (30.6%)	11.9%
10-14 point (n, perc)	15%	38 (35.8%)	44.7%	95 (42.4%)	66.3%	133 (40.3%)	79.2%
15-19 point (n, perc)	24%	16 (15.1%)	68.8%	40 (17.9%)	90%	56 (17.0%)	83.9%
20-24 point (n, perc)	40%	9 (8.5%)	88.9%	18 (8.0%)	83.3%	27 (8.2%)	85.2%

APACHE-II: Acute Physiology and Chronic Health Evaluation-II, HFNC: High flow nasal cannula, NIV: non-invasive ventilation, med: median, n: number, min: minimum, max: maximum, perc: percentage

with mortality was cytokine filter (p=0.001). Among laboratory results, increased CRP (p=0.004) and procalcitonin (p=0.001) levels were associated with mortality. The range of observed mortality was higher than expected mortality in whole group (7.7%-85.2%, 4%-40%, respectively). While mortality observed in patients with an APACHE-II score below 10 was lower than expected in the HFNC group and slightly higher than expected in the HFNC + NIV group, the mortality rates in patients with an APACHE-II score of 10 and above were much higher than expected in both groups (Table 4). We made logistic regression analysis to determine independent factors associated with mortality. We found that mortality was increasing with age (OR: 1.04), APACHE-II score (OR: 1.35), having cancer (OR: 3.89), receiving NIV (OR: 5.94), and presence of secondary bacterial infection (OR: 44.6).

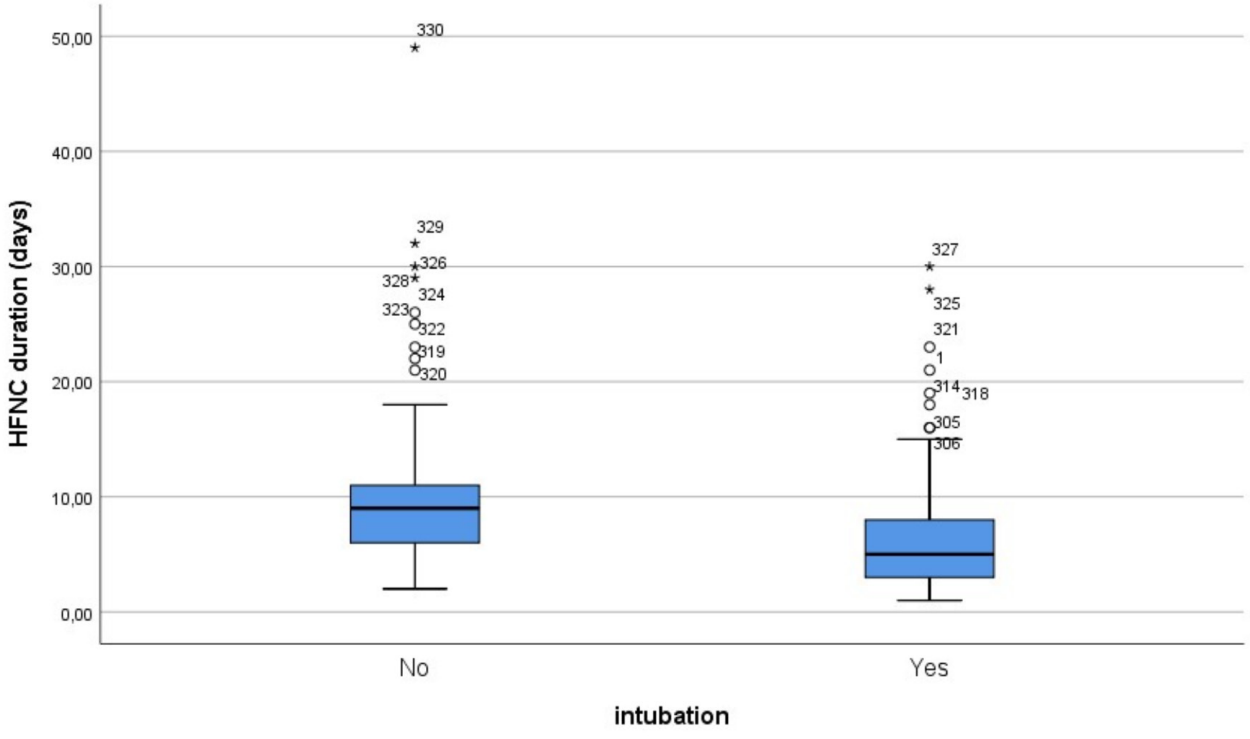

Figure 2. Comparison of HFNC durations between intubated and non-intubated patients
HFNC: High flow nasal cannula

Discussion

In this retrospectively designed study, we investigated clinical, laboratory, and radiological characteristics of COVID-19 patients treated with HFNC hospitalized in the ICU for the primary outcome, and we found that most of the patients were elderly (med: 66.7) and the most common comorbidities were HT, DM, and CAD. LDH, IL-6, and CRP were increased in almost all patients, and the most common radiologic finding was multilobar ground-glass infiltration. While the mean ICU stay of the patients was 13.9 days, HFNC was applied for a mean of 7.8 days; approximately two-thirds of patients received NIV concomitantly and half of them were intubated. During ICU stay, 163 patients (49.4%) died, and logistics regression showed that advanced age, higher APACHE-II score, cancer, receiving NIV, and secondary bacterial infection were significantly associated with mortality as the secondary outcome.

Most of our patients were elderly and had comorbidities consistent with the literature. In a study on the use of HNFC in severe COVID-19 patients, the median age of the patients was 61, and the most common diseases were HT, DM and CAD (8) A meta-analysis investigating ICU admissions of COVID-19 patients also showed that 85% of patients were >70 age years old (9). HT, DM, and CAD were listed as most common comorbidities in several studies (10,11). These findings seem to reflect intensive care patients' general characteristics rather than the use of HFNC. Considering that our patients were also treated with HFNC in the ICU, it is not surprising that the findings were similar.

Though its use is viewed with suspicion as it may cause increased aerosol production initially, NIV has been used in many centers during the COVID-19 period. We also used NIV in many patients with acute respiratory failure due to COVID-19. We found that NIV plus HFNC group had shorter HFNC duration and longer hospitalization time than those receiving HFNC alone. Duan et al. (12) compared HFNC and NIV as first-line therapy. They chose one of these and used the latter as rescue treatment. They stated no difference between groups regarding total HFNC + NIV duration, intubation rate, and mortality (12). In another study, Wang et al. (13) investigated the sufficiency of HFNC in critically ill COVID-19 patients and used NIV as a rescue therapy as well. They reported HFNC failure at 41% and intubation rate at 29% (13). A multicenter study examining the mortality rate of patients who underwent intubation after NIV failure also reported a mortality rate of 43% (14). HFNC and NIV have been applied together or consecutively in various countries. However, this was determined not by evidence or guidelines but by countries' availability to access devices.

We found that 48.5% of patients survived the disease without intubation. Only 2.9% of intubated patients could be extubated, and 49.4% of the patients died in total. In the study mentioned above, Celejewska-Wojcik et al. (8) investigated mortality and intubation rate of COVID patients in ICU receiving HFNC prospectively. They reported that 44% of patients required intubation during follow-up and the overall mortality was 30.2% (8). The intubation rate is similar to our study, but the mortality rate is lower than ours. It may be because our patients are more severe. Although we know that these results cannot conclude that HFNC avoids or delays intubation, we can say that it is used effectively in a severe patient group in this period. In addition, considering the positive results of the HFNC in non-COVID patients in terms of intubation in literature, we can deduce that it will be beneficial in this group as well (1,15,16).

There is a long list of risk factors associated with high mortality, including older age (≥65 years), having obesity, HT, diabetes, chronic heart failure, chronic renal disease, chronic liver disease cancer, high D-dimer, high troponin, lymphopenia, neutrophilia, immunosuppression, acute respiratory distress syndrome, male sex obtained from multiple studies (5,17,18). In terms of risk factors associated with mortality, the results of our study are compatible with the literature. We found that concurrent heart failure, cerebrovascular disease, HT, cancer, increased CRP, increased procalcitonin level, and secondary bacterial pneumonia are associated with mortality have been corrected via logistic regression analysis revealed higher age (OR: 1.04), APACHE-II score (OR: 1.35), cancer (OR: 3.89), receiving NIV (OR: 5.94), and secondary bacterial infection (OR: 44.6) independently increased the mortality. Although the APACHE-II score, which has been used to predict ICU mortality for many years (19), also reflects COVID-19 mortality in low scores; mortality was much higher than expected in patients with a high APACHE-II score of 10 or higher. In two separate studies, it was emphasized that the APACHE-II score underestimated mortality in patients hospitalized in ICU due to COVID-19, supporting our findings (20,21). This may be related to the more severe and fatal course of COVID-19 in the elderly and the fact that the majority of patients hospitalized in ICUs are elderly.

Secondary bacterial infections are a relatively less-investigated topic in the literature. Grasselli et al. (22) had

stated that Gram-negative bacteria and *Staphylococcus aureus* were the most common microorganisms cause ventilator-associated pneumonia and doubled the risk of death. Similarly, Gram-negative bacteria (especially *Acinetobacter* spp., *Klebsiella*) and *S. aureus* were the most common isolated bacteria. Albeit it seems that there was a greater risk for culture-positive patients in terms of mortality ($p<0.001$, OR: 44.7), there may not be a direct relationship since we could collect respiratory samples only in intubated patients.

The high number of patients is one of the strengths of our study. Including the NIV and intubation rates, comorbidities, and treatment data improves the power of reflecting real life. The most important limitation of the study is that it does not include data comparing patients with and without HFNC. However, it should be taken into account that the necessity of providing maximum support to all possible patients during the intensive care patient load is excessive may create an ethical problem in this type of study.

Conclusion

Oxygen support and the delivery route were two of the critical issues of the COVID-19 era. This study showed that HFNC is an essential option for oxygen support as it was used nearly in half of the patients without the need for intubation. Although we couldn't conclude that it decreases the intubation and mortality rates, we believe that further prospectively designed studies may help to determine its contributions.

Ethics

Ethics Committee Approval: The study protocol was approved by the Institutional Ethical Committee of Ankara City Hospital (decision no: E1/1463/2021, date: 20.01.2021).

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: I.Ö.T., H.Z.A., Design: A.M.K., O.K., Data Collection and Process: O.K., Analysis or Interpretation: O.K., A.M.K., I.Ö.T., Literature Search: H.Z.A., Writing: A.M.K., O.K., H.Z.A., I.Ö.T.

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ORIGINAL RESEARCH / *ÖZGÜN ARAŞTIRMA*

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The Predictive Value of Thoracic Computed Tomography on the Mortality of Critically Ill COVID-19 Patients

Bilgisayarlı Toraks Tomografisinin Kritik COVID-19 Hastalarının Mortalitesi Üzerine Tahmin Değeri

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ABSTRACT *Objective:* Although thoracic computed tomography (T-CT) has high sensitivity in the diagnosis of coronavirus disease-2019 (COVID-19), a specific involvement type or region for COVID-19 has not yet been identified in images consistent with viral pneumonia. This study determined the relationship between the degree of involvement in T-CT and mortality in patients with COVID-19.

Materials and Methods: One hundred and fifteen COVID-19 patients admitted to our intensive care unit were included in this study. Obtained T-CTs were evaluated according to the T-CT severity scoring system. Patients were divided into two groups as the mortality and the survival group. The two groups were compared in terms of age and gender, the presence and localization of abnormal T-CT findings and total CT score.

Results: The total CT score was significantly higher in the mortality group than in the survival group (10.88±5.67 vs 8.53±4.89, p=0.048). Bilateral involvement in the T-CT scan was found to be significantly higher in the mortality group.

Conclusion: Total CT scoring has predictive value in determining the survival of patients with a critical COVID-19. Bilateral involvement in the T-CT scans performed in the early period of disease and a total CT score of ≥10 may be indicative of mortality in COVID-19 patients.

Keywords: COVID-19, thoracic computed tomography, mortality, intensive care

ÖZ *Amaç:* Toraks bilgisayarlı tomografisi (T-BT) koronavirüs hastalığı-2019 (COVID-19) tanısında yüksek duyarlılığa sahip olmasına rağmen viral pnömoni ile uyumlu görüntülerde COVID-19 için spesifik bir tutulum tipi veya bölgesi henüz belirlenmemiştir. Bu çalışmada, COVID-19 hastalarında T-BT'de tutulum derecesi ile mortalite arasındaki ilişkinin belirlenmesi amaçlandı.

Gereç ve Yöntem: Bu çalışmaya yoğun bakım ünitesine yatırılan 115 COVID-19 hastası dahil edildi. Elde edilen T-BT'ler, T-BT şiddet skorlama sistemine göre değerlendirildi. Hastalar mortalite ve sağkalım grubu olarak iki gruba ayrıldılar. İki grup yaş ve cinsiyet, anormal T-BT bulgularının varlığı ve lokalizasyonu ve toplam BT skoru açısından karşılaştırıldı.

Bulgular: Toplam BT skoru, mortalite grubunda sağ kalım grubuna göre anlamlı derecede daha yüksekti (10,88±5,67'ye karşı 8,53±4,89, p=0,048). T-BT taramasında bilateral tutulum mortalite grubunda anlamlı olarak daha yüksek bulundu.

Sonuç: Toplam BT skorunun kritik COVID-19 hastalarında sağ kalımı belirlemede prediktif değeri vardır. Hastalığın erken döneminde yapılan T-BT taramalarında bilateral tutulum ve toplam BT skorunun ≥10 olması COVID-19 hastalarında mortalite göstergesi olabilir.

Anahtar Kelimeler: COVID-19, bilgisayarlı toraks tomografisi, mortalite, yoğun bakım

Introduction

The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), also known as coronavirus disease-2019 (COVID-19), originated in December 2019 in Wuhan, China. It has ever since rapidly spread worldwide, causing morbidity and mortality in its way. In March 2020, the World Health Organization designated the COVID-19 outbreak as a pandemic. SARS-CoV-2 primarily targets the respiratory system leading to clinical presentation of patients presenting clinical symptoms ranging from being asymptomatic to severe disease, leading to multi-organ dysfunction and death. In a recent study, patients developing severe disease symptoms often required invasive mechanical ventilation which lead to mortality of 40.8% (1). It is therefore imperative for everyone to diagnose the disease early on which helps in determining the level of care or interventions that could possibly lead to better survival rates. The lung is known to be the first organ affected by the virus in the COVID-19. In the guidelines and recommendations all over the world, if there is clinical and radiological suspicion in diagnosis, individuals with negative polymerase chain reaction (PCR) test have been accepted as COVID-19 cases according to lung computed tomography (CT) findings. In case that direct chest radiography is insufficient for diagnosis or exclusion of COVID-19, non-contrast thoracic CT (T-CT) is frequently used as an imaging method (2). However, in CT scans consistent with viral pneumonia, a specific involvement type or region for COVID-19 has not yet been identified. Despite high sensitivity in the diagnosis of COVID-19 in the screening population, the T-CT images of COVID-19 pneumonia are thought to be non-specific (3). We hypothesized that the type, localization, and intensity of involvement in the lung T-CT of the patients with confirmed COVID-19 has predictive value in determining the survival of critically ill patients in the intensive care unit (ICU). The study aimed to determine the predictive value of the total CT scoring on mortality of patients with a critical COVID-19.

Materials and Methods

Study Design and Population

This study was planned based on retrospective data analysis. The study was approved by the Ethical Review Board of the Kartal Dr. Lütfi Kırdar City Hospital (decision no: 2020/514/180/1, date: 26.06.2020). The records of the critically ill patients, who were admitted to the ICU with a diagnosis of COVID-19 between March 22 and May 22, 2020, were evaluated in the hospital's electronic patient record system. The data of the first 115 patients, whose COVID-19 diagnosis was confirmed with a positive PCR test and for whom T-CT was performed, was taken into analysis. T-CT imaging and PCR swab sampling of all patients were performed during their initial admission to the hospital's emergency department. Patients with lung malignancies, history of lung surgery, tuberculosis, sarcoidosis and similar lung diseases were excluded from the study. Data on age, gender, the Acute Physiology and Chronic Health Evaluation-II (APACHE-II) score, degree of hypoxemia [PaO_2/FiO_2 (P/F) ratio], predicted mortality rates, length of intubation, length of ICU stay, length of hospital stay and the presence of mortality in the ICU were recorded. Each type of involvement on CT was scored according to the involvement rate for each lung lobe. The total score was calculated separately for each patient. Radiological evaluation was conducted independently by two expert radiologists, each being unaware of the other findings.

Radiological Analysis

All CT examinations to screen for SARS-CoV-2 pneumonia were performed with three scanners (Philips ingenuity with 128 sections and Toshiba Alexion with 16 sections) without the use of contrast agents. The main scanning protocol was as follows: Tubevoltage, 120 kVp; tube current modulation, 120 mA-380 mA; detector configuration, 64×0.625 mm or 16×0.625 mm; rotation time, 0.5-0.7 s; slice thickness, 5 mm; and pitch, 0.984. All images were examined in both lungs [width, 1200 Hounsfield units (HU); level, -700 HU] and mediastinal (width, 350 HU; level, 40 HU) settings. The two radiologists with 10-20 years of experience, without clinical informations, examined the chest images CT independently and scored CT findings. İf there was diffent result, they decided by consensus. Images from CT were examined for the presence and distribution of the following abnormalities described for COVID-19, according to a standardized protocol: (a) baseline ground-glass opacities (GGO), (b) nodules (c) linear compaction (d) crazy paving; (e) consolidations; (f) architectural distortions or traction bronchiectasis; (g) pleural effusion; (h) lymphadenopathy; (i) air bronchogram; (j) tree-in-bud sign; (k) white lung (4). The general anatomic distribution (subsegmental, segmental, lobar) zonal predominance (upper, middle, lower lung; central, middle, or peripheral location), and extent (focal,

multifocal and diffuse) of lesions were also recorded. The predominant patterns of abnormalities on the high-resolution CT were divided into consolidation, GGOs network structure, and mixed patterns. A mixedpattern can be described as the presence of crazypaving and airbronchogram. Each of the five lungs lobes were interpreted for the degree of involvement.

The total score CT (4) is determined by scoring the percentage of each of the five lobes affected:

0: None

1: <5% involvement

2: 5-25% involvement (Figure 1)

3: 26-49% involvement

4: 50-75% involvement (Figure 2)

5: >75% participation (Figure 3)

The total score CT is the sum of the individual lobar scores and can range from 0 to 25 (maximum). For comparison, patients were divided into two groups: the mortality group and the survival group. The two groups were compared in terms of age and sex distribution, duration of intubation, ICU stay and hospitalisation, presence and distribution of abnormal CT findings, and total score CT.

Statistical Analysis

The SPSS 26.0 program was used for statistical analysis. The values of mean, standard deviation, median lowest, highest, frequency, and ratio were used in the descriptive statistics of the study data. The distribution of variables was analyzed with the Kolmogorov-Smirnov test. The Mann-Whitney U test was used to assess quantitative independent data while the qualitative-quantitative independent data was analyzed with the chi-square and Fisher's Exact tests. Statistical significance was set at a p-value <0.05. The relation of T-CT involvement types and total CT score with mortality was evaluated using Spearman's rank correlation.

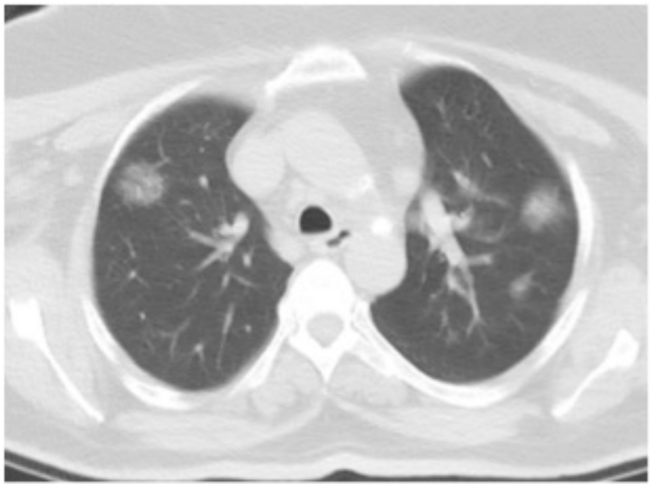


Figure 1. The percentage of lung involvement is approximately 25% by visual assessment

Results

Baseline Characteristics

Gender distribution was as follows: 30.4% (n=35) female and 69.6% (n=80) male with the mean age of 66.20±13.84 years (range; 21 to 94 years). The mean age was comparable in both male (65.36±12.57 years) and female (68.11±16.43 years) groups. Some of the patients had severe respiratory failure at presentation and were directly admitted to the ICU. On the other hand, most of the patients were receiving

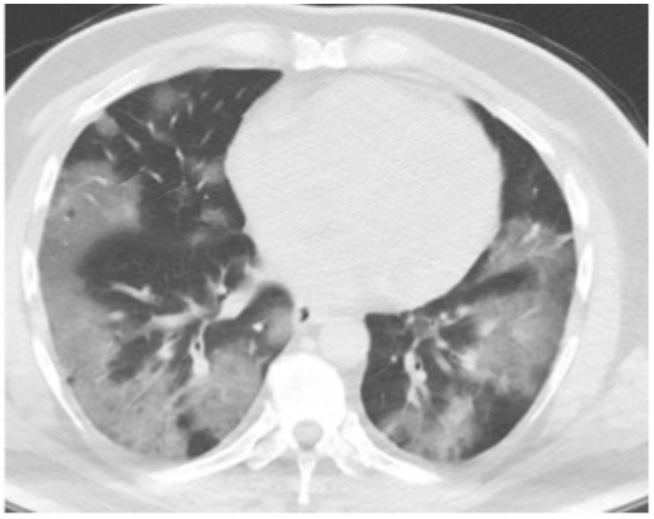


Figure 2. The percentage of lung involvement is approximately 50-75% by visual assessment

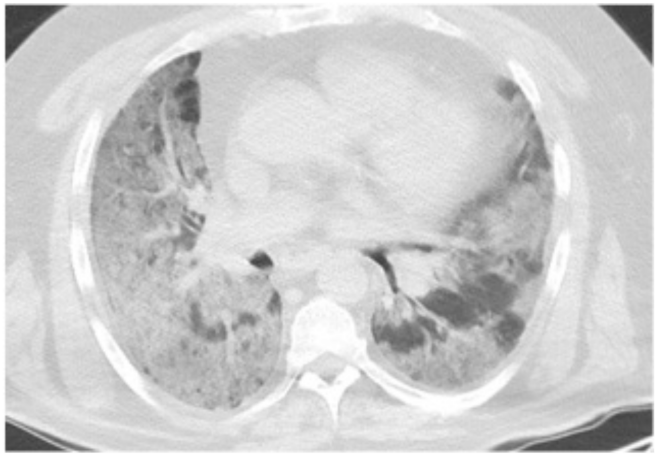


Figure 3. The percentage of lung involvement is approximately >75% involvement by visual assessment

treatment at pandemic clinics, they had to be admitted to the ICU since their condition worsened within 3 to 7 days. In the majority of the patients (101 patients, 87.8%), bilateral involvement was detected. Ninety eight (85.2%) of the 115 patients had multilobar involvement, 92 (80.0%) had peripheral subpleural distribution, and 89 (77.4%) had GGO. While the rate of consolidation was 59.1% (68 patients), the rate of pleural effusion and crazy paving pattern was low [33.9% (39 patients) and 22.6% (26 patients), respectively]. Eighty five (73.9%) of the 115 patients died. The percentage of male patients was higher in the mortality group compared to the survival group ($p<0.05$) (Table 1). When we compared the data of patients who died with the data of those who survived, the mean age was similar ($p>0.05$) between the patient groups. Lengh of intubation was significantly shorter and lengh of hospital stay was significantly longer in the survival group compared to the mortality group. APACHE-II scores, predicted mortality rates, and P/F rates were similar between the two groups (Table 2). Additionally, the patients with pleural effusion had a longer intubation time (8.49±7.50 vs 5.33±6.23 day, $p=0.009$).

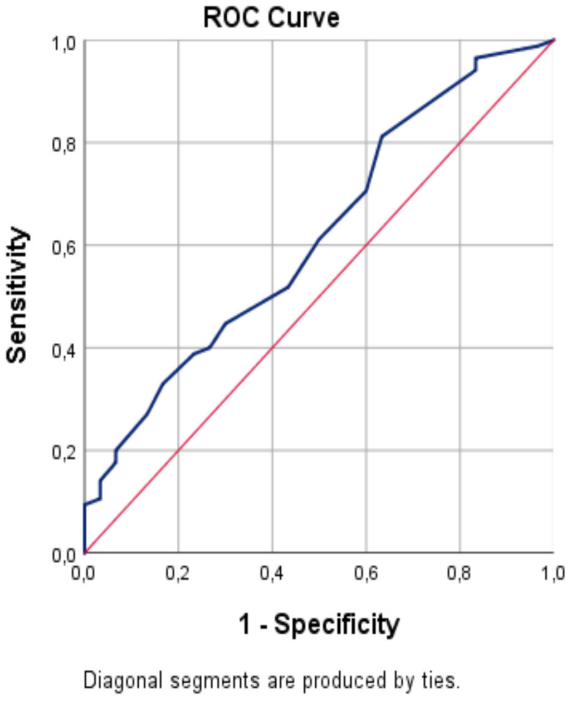
Comparison of Imaging Findings Between Mortality and Survival Groups

In the comparison of T-CT findings between the two groups, bilateral involvement was found to be significantly higher in the mortality group ($p<0.05$), while there was no statistically significant difference between the groups in terms of the rates of multilobar involvement, peripheral subpleural distribution, GGO, crazy paving pattern, consolidation and pleural effusion ($p>0.05$) (Table 1). However, the total CT score was significantly higher in the mortality group than in the survival group (10.88±5.67 vs 8.53±4.89, $p=0.048$). Analyzing the age distribution according to the involvement types detected in T-CTs, the mean age of the patients with crazy paving pattern and pleural effusion was found to be significantly higher than that of the patients without such involvement ($p=0.015$ and $p=0.000$, respectively) (Table 3). Because some of the CT findings were more common in the given age groups, the mortality, and the survival groups were into 3 age groups (≤50, 51-70, and ≥71 years). The data were re-compared statistically according to these age groups. While the rate of bilateral involvement was found to be significantly higher in the 51-70 age group of the mortality group ($p<0.05$), there was no statistically significant difference between the groups in term of the other comparison parameters ($p>0.05$) (Table 4).

When we compared the rate of mortality in terms of the total CT score, we found that the higher the T-CT score was, the greater the mortality rate became. There was a statistically significant positive correlation between the total CT score and mortality ($p<0.05$). The risk of death significantly increased with the increase of CT score value using an estimated cut-off of ≥5.5. The value of the area under the curve for the total score was 0.617 (95% confidence interval: 0.502-0.733) (Figure 4).

Discussion

The main findings of this study are that the total CT scoring has predictive value in determining the survival of



Area Under the Curve

Test Result Variable(s): Total score

Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
,617	,059	,057	,502	,733

The test result variable(s): Total score has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased.

a. Under the nonparametric assumption

b. Null hypothesis: true area = 0.5

Figure 4. Correlation of total CT score and mortality
CT: Computed tomography, ROC: receiver operating characteristic

Table 1. Comparison of the two groups for gender and T-CT findings				
		Survival	Mortality	p
		n (%)	n (%)	
Gender	F	14 (46.7%)	21 (24.7%)	0.025x²
	M	16 (53.3%)	64 (75.3%)	
Bilateral involvement	(-)	8 (26.7%)	6 (7.1%)	0.005x²
	(+)	22 (73.3%)	79 (92.9%)	
Multilobar involvement	(-)	7 (23.3%)	10 (11.8%)	0.125x²
	(+)	23 (76.7%)	75 (88.2%)	
Peripheral subpleural distribution	(-)	8 (26.7%)	15 (17.6%)	0.288x²
	(+)	22 (73.3%)	70 (82.4%)	
Ground glass opacity	(-)	10 (33.3%)	16 (18.8%)	0.102x²
	(+)	20 (66.7%)	69 (81.2%)	
Crazy paving pattern	(-)	25 (83.3%)	64 (75.3%)	0.365x²
	(+)	5 (16.7%)	21 (24.7%)	
Consalidation	(-)	15 (50.0%)	32 (37.6%)	0.237x²
	(+)	15 (50.0%)	53 (62.4%)	
Pleural effusion	(-)	20 (66.7%)	56 (65.9%)	0.938x²
	(+)	10 (33.3%)	29 (34.1%)	
F: Female, M: male, (+): present, (-): absent, T-CT: thoracic computed tomography, x²chi-square test				

Table 2. Comparison of the two groups for age, total T-CT score, lengh of intubation, ICU stay, hospital stay, APACHE-II scores, predicted mortality rates and PaO_2/FiO_2 ratio			
	Survival	Mortality	p
	Mean ± SD	Mean ± SD	
Total T-CT score	8.53±4.89	10.88±5.67	0.048[m]
Age (year)	62.50±18.46	67.51±11.65	0.379[m]
Lengh of intubation (day)	6.13±8.69	7.87±6.51	0.005[m]
Lengh of ICU stay (day)	11.10±7.75	8.49±6.31	0.101[m]
Lengh of hospital stay (day)	17.43±7.06	10.29±7.03	0.000[m]
APACHE-II score	25.43±6.25	28.69±9.42	0.233[m]
Predicted mortality rates (%)	53.26±19.68	59.36±21.53	0.175[u]
P/F ratio	149.54±68.10	130.17±64.88	0.167[u]
P/F ratio: PaO_2/FiO_2 ratio, [m]Mann-Whitney U test, [u]unpaired t-test, APACHE-II: Acute Physiology and Chronic Health Evaluation-II, SD: standard deviation, T-CT: thoracic computed tomography, ICU: intensive care unit			

patients with a critical COVID-19 and a total CT score of ≥10 may be indicative of mortality in patients with COVID-19. Besides the T-CT score, bilateral involvement detected on a single scan may be considered as an indicator for the prediction of the risk for mortality. T-CT can be a diagnostic method for patients with suspected COVID-19 especially when PCR test is negative or PCR tests are not available. At the end of sequential PCR test and low-dose CT scan in 610 patients who presented to the emergency department with the suspicion of COVID-19, the sensitivity and specificity of CT for COVID-19 were found to be 86% (150/174) and 99% (408/411), respectively (5). Studies conducted with a low number of patients that were published at the onset of the pandemic reported that COVID-19 pneumonia produces a T-CT pattern resembling organizing pneumonia, peripheral GGOs, and nodular or mass-like GGOs that are mostly bilateral and multilobar. These publications drew attention to the fact that GGOs are especially located in peripheral,

Table 3. Distribution of gender, T-CT findings and mortality by age

		Age (year)			p
		Range	Median	Mean ± SD	
Gender	F	24.0-89.0	72.00	68.11±16.43	0.181[m]
	M	21.0-92.0	65.50	65.36±12.57	
Bilateral involvement	(-)	24.0-89.0	66.00	61.64±18.93	0.538[m]
	(+)	21.0-92.0	67.00	66.23±12.98	
Multilobar involvement	(-)	24.0-89.0	73.00	66.00±19.25	0.463[m]
	(+)	21.0-92.0	66.00	66.23±12.81	
Peripheral subpleural distribution	(-)	27.0-86.0	64.00	63.09±13.84	0.108[m]
	(+)	21.0-92.0	68.50	66.98±13.81	
Ground glass opacity	(-)	27.0-92.0	70.50	66.27±12.72	0.332[m]
	(+)	21.0-89.0	66.00	65.60±14.17	
Crazy paving pattern	(-)	21.0-92.0	66.00	64.36±14.31	0.015[m]
	(+)	55.0-88.0	72.00	72.50±10.01	
Consolidation	(-)	24.0-92.0	69.00	67.04±14.99	0.353[m]
	(+)	21.0-89.0	65.50	65.62±13.07	
Pleural effusion	(-)	21.0-87.0	65.0	62.58±14.07	0.000[m]
	(+)	56.0-92.0	73.00	73.26±10.33	
Mortality	(-)	21.0-92.0	66.00	62.50±18.46	0.379[m]
	(+)	39.0-89.0	67.00	67.51±11.65	

F: Female, M: male, (+): present, (-): absent, [m]Mann-Whitney U test, T-CT: thoracic computed tomography, SD: standard deviation

Table 4. Distribution of T-CT findings and mortality by different age groups

	≤50 years				51-70 years			≥71 years		
	Mortality (n)				Mortality (n)			Mortality (n)		
		(-)	(+)	p	(-)	(+)	p	(-)	(+)	p
Bilateral involvement	(-)	2	2	1.000[F]	3	2	0.044[F]	3	2	0.123[F]
	(+)	-	6		8	44		9	29	
Multilobar involvement	(-)	2	2	1.000[F]	2	2	0.164[F]	3	6	0.692[F]
	(+)	5	6		9	44		9	25	
Peripheral subpleural distribution	(-)	3	1	0.282[F]	3	10	0.700[F]	2	4	1.000[F]
	(+)	4	7		8	36		10	27	
Ground glass opacity	(-)	1	1	1.000[F]	4	10	0.435[F]	6	7	0.136[F]
	(+)	6	7		7	36		6	24	
Crazy paving pattern	(-)	7	8	-	8	36	1.000[F]	9	20	0.719[F]
	(+)	-	-		2	11		3	11	
Consolidation	(-)	4	3	0.619[F]	4	16	0.728[F]	7	14	0.509[F]
	(+)	3	5		6	31		5	17	
Pleural effusion	(-)	1	1	-	7	32	1.000[F]	9	16	1.000[F]
	(+)	-	-		3	15		6	12	

(+): Present, (-): absent, [F]Fisher's Exact test, T-CT: thoracic computed tomography

posterior or lower lung zones (6-8). However, these T-CT findings are not specific for COVID-19 pneumonia and may vary during the disease (8-11). Later on, in comprehensive meta-analyses conducted the frequency of association of vascular enlargement, interlobular septal thickening, and GGO findings with COVID-19 in the presence of bilateral and multilobar involvement was emphasized (11,12). In fact, T-CT involvement may not be observed in the first days when the symptoms first appear. Wang et al. (9) discovered as a result of the evaluation of repeated T-CT scans in patients with COVID-19 that the T-CT score progressed rapidly from the onset of the disease and peaked up on days 6-11. In their retrospective study conducted on 51 patients with COVID-19, Song et al. (10) reported that the findings of consolidation were more prominent in T-CTs taken on day 4 of symptom onset or later compared to T-CTs obtained within the first 4 days. Therefore, Song et al. (10) concluded that the signs of consolidation signify the disease progression and can be used as a guiding tool for proper treatment protocols or interventions.

The T-CT scans of the patients evaluated in our study were obtained at admission, and the rates of consolidation in the evaluated T-CTs were lower than the other types of involvement, which is consistent with the definition for the early stage of the disease. It was reported in a comprehensive review published in 2021 that although GGOs and vasodilation are common CT changes, severe disease is mostly associated with CT findings such as interlobular septal thickening, traction bronchiectasis, reticulation, pleural effusion, consolidation, and lymphadenopathy (11). Also, these differences are closely associated with involvement at different stages of the disease (13). However, as T-CTs were not repeated during the ICU stay of our patients, it was not possible to follow up how this rate changed in later stages of the disease. Nevertheless, according to our results, the rate of bilateral involvement was higher in the early T-CTs of the patients that died. Wang et al. (9) findings stating that patients with unilateral involvement were discharged within one month of treatment support our results. We believe that since repeating T-CT scanning especially for patients with COVID-19 treated at ICUs would be impractical and financially troublesome, the T-CT scoring obtained at admission to the ICU as in our study is valuable. The total CT scoring system was previously used to define and grade idiopathic pulmonary fibrosis, and it has also been used in T-CT examinations of patients with COVID-19 as well as to define the pulmonary complications of the SARS-CoV virus in the SARS pandemic (4,14). In their retrospective study investigating the determinants of fatality in COVID-19 patients, Li et al. (15) reported that in T-CT scans obtained within the first week of symptom onset, the total severity score and the number of lung lobes affected were significantly higher in patients who died. In addition, the involvement of more than 5 lobes was reported to be associated with serious disease in a comprehensive review published later (11). Li et al. (15) revealed that a total severity score of ≥15 on T-CTs taken within the first week from the onset of the symptoms is a determinant for mortality. Also, in another study, a CT score of ≥18 was associated with mortality (16). Our findings are consistent with Li et al. (15) study. In this study, we also found that the rate of bilateral involvement was significantly higher in the patients who died. On the other hand, our results revealed that GGO, crazy paving pattern, consolidation, and pleural effusion, and age distribution did not differ significantly between the mortality and survival groups, contrary to Li et al. (15) where these rates and the average age were significantly higher in the mortality group. However, different from our study, all patients requiring intensive care follow-up in Li et al. (15) were in critical condition and CTs consisted of CTs taken within the first week of follow-up. The CT images were not obtained at different time points, but during admission to the hospital. In our study, it was determined that the intubation time was significantly longer and the hospital stay was significantly shorter in the mortality group than in the survival group. Similarly, as it is expected, the duration of intubation was also longer in patients with bilateral involvement compared to the others. When CT scanning is performed on every patient or every critically ill patient, who requires follow-up in the ICU, it can give clues about the course of the disease and prevent delayed intubation. In our study, we concluded that patients who deteriorate rapidly and have invasive mechanical ventilation requirements in the early period can be determined by T-CT scoring at the admission phase and aggressive treatment can be started when as soon as necessary. We found the total CT score cut-off value for the prediction of mortality to be 5.5. As different studies reported various cut-off values, it seems to be impossible to mention an agreed value (15,16). This may be a result of the differences in T-CT scoring. What is important is that every institution reveals its T-CT scoring and cut-off value. In this way, it may be possible to predict the mortality risk in

patients with T-CT scores above a given value and to organize close monitoring and even ICU follow-up in the early period. Our findings reveal that although there is no universally accepted cut-off value, total CT score is a useful criterion in determining the prognosis of COVID-19 patients with pulmonary involvement. There are several limitations of this study. The first is that it is a retrospective study. The second limitation is the ignorance of the co-morbidity situations of the groups. Because the number of young patients with low co-morbidity was low, they were not suitable for statistical evaluation. Therefore, patients with younger age and low co-morbidity could be compared with the other patients. The third limitation is that the relationship between T-CT score and ICU admission was not investigated. The strength of the study, on the other hand, is that it includes 115 well-documented patients whose findings were evaluated by two experienced radiologists.

Conclusion

Bilateral involvement in T-CT scans performed in the early period and a total CT score of ≥10 may be indicative of mortality in COVID-19 patients. We believe that in patients with COVID-19 pneumonia, performing T-CT imaging at first admission to the hospital and calculating the T-CT score may help to predict the progression of the cases and decrease mortality by interning these patients in ICU in the early period of disease and providing them close monitoring and early aggressive therapy. We concluded that thoracic CT is a valuable tool for diagnosis and risk stratification of COVID-19 patients both in the emergency department and ICU.

Ethics

Ethics Committee Approval: The study was approved by the Ethical Review Board of the Kartal Dr. Lütfi Kırdar City Hospital (decision no: 2020/514/180/1, date: 26.06.2020).

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

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Relationship Between Intubation and Mortality in COVID-19 Patients with Moderate ARDS, Secondary Bacterial Infection Status

Moderate ARDS'li COVİD-19 Hastalarında Entübasyon ve Mortalite İlişkisi, Sekonder Bakteriyel Enfeksiyon Durumu

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ABSTRACT *Objective:* In many studies on patients with acute respiratory distress syndrome (ARDS) caused by severe acute respiratory syndrome coronavirus-2, the mortality rate was found to be high in intubated patients. The aim of this study was to try to understand how intubation affects mortality in patients with coronavirus disease (COVID) polymerase chain reaction-positive ARDS and to understand the relationship between intubation and mortality in the patient group whose PaO_2/FiO_2 is 100-150 mmHg (moderate) and who have difficulty in intubation decision. *Materials and Methods:* Patient information was obtained by retrospectively examining the hospital computer database and patient files. Three hundred thirteen patients were included in the study. The patients were divided into two groups as intubated and non-intubated according to their intubation status after the first 24 h of their admission to the intensive care unit (ICU) and their intubation status when PaO_2/FiO_2 was 100-150 mmHg (moderate ARDS). *Results:* In the group of patients who were intubated after the first 24 h, the number of mechanical ventilator days was 9.15±8.58 ($p<0.001$), the length of stay (LOS) in the ICU was 14.15±10.33 ($p<0.001$), and the length of hospital stay was 18.33±12.13 ($p<0.05$), it was longer and statistically significant compared to the non-intubated group. Additionally, 140 (80.92%) of these patients died ($p<0.001$). The number of mechanical ventilator days was 8.87±8.51 and the LOS days were 13.53±9.6 in the intubated group with moderate ARDS, which was longer and statistically significant than the non-intubated group ($p<0.001$). Moreover, in 80 (68.4%) of all intubated patients, 60 (37.5%) of the intubated patients with moderate ARDS had secondary bacterial infection ($p<0.001$) and mortality rates were higher ($p<0.001$). *Conclusion:* All intubated patients with coronavirus disease-2019, including those with moderate ARDS, had a higher rate of secondary bacterial infection, as well as a higher mortality rate.
Keywords: Acute respiratory distress syndrome, coronavirus, intubation, secondary bacterial infection

ÖZ *Amaç:* Şiddetli akut solunum sendromu koronavirüs hastalığı (COVID) virüsünün neden olduğu akut solunum sıkıntısı sendromu (ARDS) hastaları üzerinde yapılan çok sayıda çalışmada, entübe hastalarda ölüm oranı yüksek bulunmuştur. Bu çalışmanın amacı, COVID polimeraz zincirleme reaksiyonu pozitif ARDS olan hastalarda entübasyonun mortaliteyi nasıl etkilediği ve $PaO_2/Fi0_2$'nin 100-150 mmHg olduğu (moderate), entübasyon kararında zorlanılan hasta grubunda entübasyon ile mortalite arasındaki ilişkiyi anlamaya çalışmaktır.
Gereç ve Yöntem: Hasta bilgileri hastane bilgisayar veri tabanından ve hasta dosyalarından retrospektif olarak incelenerek elde edildi. Üç yüz on üç hasta çalışmaya dahil edildi. Hastalar yoğun bakıma yatışlarının ilk 24 saatinden sonraki entübasyon durumuna göre ve $PaO_2/Fi0_2$'nin 100-150 mmHg (moderate ARDS) olduğunda entübasyon durumuna göre entübe ve non-entübe olacak şekilde iki gruba ayrıldı.
Bulgular: İlk 24 saatten sonra entübe edilen hasta grubunda mekanik ventilatör gün sayısı 9,15±8,58 ($p<0,001$), yoğun bakım gün sayısı 14,15±10,33 ($p<0,001$) ve hastane gün sayısı 18,33±12,13 ($p<0,05$) idi ve non-entübe gruba göre daha uzun ve istatistiksel olarak anlamlıydı. Ayrıca bu hastaların 140'ı (%80,92) kaybedildi ($p<0,001$). Moderate ARDS'li entübe grupta mekanik ventilatör gün sayısı 8,87±8,51, yoğun bakım gün sayısı ise13,53±9,6 idi ve entübe olmayan gruptan daha

uzun ve istatistiksel olarak anlamlıydı (p<0,001). Ayrıca tüm entübe hastaların 80'inde (%68,4), moderate ARDS'li entübe hastaların ise 60'ında (%37,5) sekonder bakteriyal enfeksiyon mevcuttu (p<0,001) ve mortalite oranları da daha yüksekti (p<0,001).
Sonuç: Tüm entübe COVID-2019'lu hastalarda moderate ARDS'li olgular da dahil olmak üzere sekonder bakteriyel enfeksiyon daha fazla ve mortalite oranları ise daha yüksek tespit edilmiştir.
Anahtar Kelimeler: Akut solunum sıkıntısı sendromu, koronavirüs, entübasyon, sekonder bakteriyel enfeksiyon

Introduction

In the coronavirus disease-2019 (COVID-19) pandemic, physicians, particularly those performing aerosol-generating procedures such as non-invasive ventilation (NIV), a high-flow nasal oxygenation (HFNO), balloon mask ventilation, and intubation, are at a significant risk of developing an infection in the intensive care unit (ICU) (1,2). Endotracheal intubation should be conducted by a clinician who specializes in this field in this patient group, and early intubation should be considered in a patient whose respiratory state worsens (3). The physician's decision to use invasive mechanical ventilation is dependent on his or her clinical judgment, which is impacted by criteria such as oxygen saturation, dyspnea, respiratory rate, chest radiography, and others (4). However, some physicians believe that intubation is linked to a high death rate. A research from China found that intubated COVID-19 patients had a 97% mortality rate, with a mean ventilation period of 4 days (5). Data from an Italian intensive care cohort of 1,591 patients, which was also performed on COVID-19 patients, show that 88% of the patients were intubated, and that those who finished intensive care therapy had a 64 percent mortality rate (6). However, among 1,795 COVID-19 patients who were invasively ventilated, data from a population of inhabitants of England, Wales, and Northern Ireland revealed a 67 percent mortality rate (7). According to a research conducted in New York City and its environs, only 3% of COVID-19 patients who were ventilated invasively survived, while 25% perished (8). When should COVID-19 patients be intubated? There is no clear answer to this question. There is no clear consensus on whether early or late intubation is preferable, or under what circumstances intubation should be conducted. The goal of this study was to examine the link between intubation and mortality in patients with COVID-19 polymerase chain reaction (PCR) positive acute respiratory distress syndrome (ARDS), as well as the effect of intubation on mortality in patients with COVID-19-related ARDS who had a PaO_2/FiO_2 mmHg of 100-150. We believe that knowing the link between intubation timing and mortality might help clinicians make better ventilation decisions in COVID-19 pneumonia.

Materials and Methods

Patients who were followed up owing to COVID-19 in adult ICUs in a tertiary healthcare facility between October 1, 2020 and February 1, 2021 were included in this retrospective analysis. The records of patients admitted to the ICU during the dates mentioned were scanned retrospectively after the study was approved by the Başakşehir Çam and Sakura City Hospital Ethics Committee (decision no: 2021.04.58, date: 14.04.2021).

The study's inclusion criteria were: 1) cases whose COVID-19 diagnosis was confirmed by reverse transcription-PCR, 2) patients diagnosed with ARDS according to Berlin criteria, and 3) patients aged 18 and over. The study's exclusion criteria were: 1) patients under the age of 18, 2) people who do not have ARDS (n=5), 3) pregnant women (n=8), 4) patients with concurrent malignancy (n=35), 5) patients with a history of organ transplantation and/or immunosuppressive drug use (n=36), 7) patients who had a surgical operation in the previous month (n=4), 8) COVID-19 PCR test negative but radiologically diagnosed patients (n=15), 9) patients admitted to the ICU as intubated, and patients intubated within the first 24 hours of admission (n=38).

During the COVID-19 pandemic, our hospital collected data from four adult pandemic ICUs with a total of 16 beds. Symptomatic patients with positive COVID-19 PCR testing are followed in pandemic inpatient care at our hospital, which is a tertiary education and research institution. Patients who require acute care owing to respiratory distress, tachypnea, hypoxia, altered awareness, or hypotension are transported to pandemic ICUs, where their care is continued. Patients

with COVID-19 PCR positive who require intensive care from adjacent provinces and hospitals are also accepted. The hospital's computer database and patient files were used to gather information on the patients. Age, gender, body mass index (BMI), and concomitant sickness status of the patients' sociodemographic data were recorded. On the day of admission to the critical care unit, a complete blood count, kidney (urea, creatinine), and liver function tests (alanine aminotransferase, aspartate transaminase), as well as coagulation indicators, were all conducted. C-reactive protein (CRP), procalcitonin (PCT), and ferritin levels as acute phase reactants, as well as glucose, d-dimer, and lactate dehydrogenesis levels, have all been tracked since the patient's admission to the critical care unit. The Sequential Organ Failure Assessment score (SOFA) and and the Acute Physiology and Chronic Health Evaluation-II (APACHE-II) scores also were taken into account when patients are admitted to the ICU. Mild, moderate, and severe ARDS were assigned to patients diagnosed with ARDS using Berlin criteria. In addition, the forms of oxygen support utilized in critical care were investigated (conventional oxygen support, HFNO), invasive mechanical ventilation, and non-invasive mechanical ventilation. The mechanical ventilation time was measured by keeping a note of when the patients were linked to the ventilator and when they were disconnected. The status of receiving tocilizumab, anakinra, glucocorticoids, intravenous immunoglobulin, plasmapheresis, the development of secondary bacterial infection, the number of days in the ICU, the number of mechanical ventilator days, and the number of hospital days were all recorded using electronic medical records during the follow-up period. Fever, high CRP, elevated PCT, culture results (blood culture, urine culture, tracheal aspirate culture), radiological data, and an infectious diseases consultation 48 hours after admission to the critical care unit were used to determine the presence of secondary bacterial infection. The patients' survival status was recorded during the follow-up period.

Statistical Analysis

The SPSS program was used to do statistical analysis on the study data. To see if the continuous data fit the normal distribution, one sample Kolmogorov-Smirnov test was employed. Quantitative variables in our study will be expressed as mean and standard deviation or median (minimum-maximum) based on their distribution. Numbers and percentages were used to represent categorical variables. For continuous data that fits a normal distribution, the Student t-test will be performed, and for those that do not, the Mann-Whitney U test will be employed. The chi-square test was performed to compare categorical data between two groups.

Results

Three hundred thirteen patients were included in the study. According to their intubation status after the first 24 hours of critical care admission, patients were separated into two groups: intubated and non-intubated. There were 182 males (58.1%) and 131 females (41.9%) among these patients. The average age of the participants was 65.07±14.55. The intubated group had a mean age of 68.79±11.67 ($p<0.001$), a neutrophil level of 10.78±6.89 ($p<0.05$), a white blood cell count of 14.60±10.38 ($p<0.001$), ferritin of 1363.5±1486.18 ($p<0.05$), and APACHE-II score of 18,437,41 ($p<0.05$), and a BMI of 27.98±4.59 ($p<0.001$), all of which were higher than the non-intubated group. In addition, the number of mechanical ventilator days in the intubated group was 9.15±8.58 ($p<0.001$), the number of intensive care days was 14.15±10.33 ($p<0.001$), the number of hospital days was 18.33±12.13 ($p<0.05$) and was longer than the non-intubated group. In addition, 140 (80.92%) of the intubated patients died ($p<0.001$) and the mortality rate was higher than the non-intubated group. The demographics, clinical characteristics, APACHE-II score, SOFA score, intensive care day duration, mechanical ventilator day duration, hospital day duration, BMI, laboratory data, presence of secondary bacterial infection, neutrophil lymphocyte ratio (NLR), and platelet lymphocyte ratio (PLR) values for these patients are listed in Tables 1 and 2. Table 3 summarizes the therapies these patients received as well as the complications they encountered throughout their critical care follow-up. In Table 4, APACHE-II score, SOFA score, intensive care day duration, mechanical ventilator day duration, hospital day duration, BMI, laboratory data, presence of secondary

Table 1. Sociodemographic and clinical characteristics of the study population		
	Mean ± SD/n	%/minimum-maximum
Age	65.07±14.55	18-94
BMI (kg/m^2)	27.06±4.98	18-45
Gender		
Male	182	58.1%
Female	131	41.9%
BMI classification		
Normal	115	36.7%
Overweight	147	46.9%
Obese	35	11.1%
Morbid obese	6	1.9%
Weak	10	3.2%
Comorbidities		
Diabetes mellitus	88	28.1%
Hypertension	139	44.4%
COPD	25	7.9%
Cardiovascular disease	58	18.5%
Chronic renal failure	50	10.4%
Neurodegenerative disease	45	13.4%
Liver failure	8	2.5%
Heart failure	7	2.2%
PaO_2/FiO_2 admission		
Mild ARDS	32	9.9%
Moderate ARDS	160	49.7%
Severe ARDS	121	37.6%
APACHE score	17.17±7.36	8-38
SOFA score at admission	6.32±2.95	3-22
LOS/day	11.81±9.16	1-73
Lenght of stay in hospital/day	16.59±11.74	3-93
Mechanic ventilation days	5.8±7.69	0-52
Entubation	173	55.27%
Mortality	174	55.59%

BMI: Body mass index, COPD: chronic obstructive pulmonary disease, ARDS: acute respiratory distress syndrom, APACHE: Acute Physiology and Chronic Health Evaluation, SOFA: Sequential Organ Failure Assessment score, LOS: lenght of stay in intensive care unit, SD: standard deviation

bacterial infection, NLR, and PLR data were summarized for intubated and non-intubated patients with a PaO_2/FiO_2 of 100-150 after the 24th hour of admission to the ICU. This analysis revealed that 48 (30%) of the patients who were not intubated were male ($p<0.05$). The number of mechanical ventilator days was 8.87±8.51 in the intubated group, while the number of intensive care days was 13.53±9.6, which was greater ($p<0.001$). In this group, 60 (37.5%) patients had secondary bacterial infection, and 79 (49.4%) patients died, with a mortality rate that was greater than in the non-intubated group ($p<0.001$). A logistic regression analysis of clinical and laboratory data was used to predict mortality, and age, presence of secondary bacterial infection, number of mechanical ventilation days, and number of intensive care days were found to be significant for predicting mortality. These data are summarized in Table 5.

Discussion

In this study, we found that patients with ARDS caused by COVID-19 pneumonia who were intubated beyond the first 24 hours of admission to the ICU had a greater fatality rate. Furthermore, intubated patients with a PaO_2/FiO_2 of 100-150 mmHg also had a greater death rate. It's crucial to determine if insufficient oxygenation is caused by a low ventilation-perfusion ratio or by the presence of an intrapulmonary right-left shunt in ARDS caused by COVID-19 pneumonia. In the first situation, increasing the oxygen flow is predicted to result in a significant improvement in oxygenation, hence intubation is avoided in the first place. In cases when insufficient oxygenation is caused by an increase in the intrapulmonary right-left shunt, increasing oxygen delivery has little effect. In this condition, lung-protective ventilation is required, especially with prone placement and, if necessary, extracorporeal membrane oxygenation (9). In our study, 173 of the 313 patients were intubated, and 140 (80.92%) of these intubated patients died. Various studies found that mortality rates for COVID-19-associated ARDS patients who were intubated ranged from 25% to 97 percent (5-8). In several trials, including ours, intubated patients had a higher mortality rate. As a result, the answer to the question of when patients with ARDS linked to COVID-19 should be intubated is still unclear and difficult to determine. When selecting whether or not to intubate, significant respiratory effort and hypoxemia are important considerations. However, measuring esophageal pressure, which can be challenging in a clinical context and is frequently reserved for research, is the most reliable approach to assess high respiratory work. The palpation of phasically rising contractions of the

Table 2. Comparison of the clinical and laboratory results between intubated and non-intubated groups				
	Total (n=313)	**Intubated (n=173)**	**Non-intubated (n=140)**	**p-value**
Age	65.07±14.55	68.79±11.67	60.88±16.29	0.00
Gender (male)	182 (58.1%)	92 (29.4%)	90 (28.8%)	0.05
Glucose (mg/dL)	198.55±103.04	190.09±105.60	208.10±99.58	0.069
BUN (mg/dL)	76.46±58.18	75.9±55.324	77.09± 61.43	0.88
Creatinine (mg/dL)	1.68±03.16	1.44±1.34	1.94±4.38	0.66
AST (U/L)	65.45±212.05	83.16±287.45	45.48±44.17	0.59
ALT (U/L)	49.63±96.03	55.05±110.72	43.50±76.05	0.67
Fibrinogen (mg/dL)	610,71±511,92	640.29±674.18	577.31±210.32	0.872
INR	1.16±0.32	1.15±0.29	1.17±0.36	0.487
D-dimer (mgFEU/mL)	3.38±4.65	3.35±4.86	3.40±4.42	0.62
LDH (U/L)	499.84±383.34	513.83±397.16	484.86±367.82	0.415
Ferritin (ng/mL)	1140,20±1281,75	1363,5±1486,18	887.76±945.34	0.001
WBC (10^9/L)	14.28±15.00	14.60±10.38	11.42 ± 8.85	0.000
HB (g/dL)	12.79±10.70	11.85±2.44	13.85±15.36	0.227
Platelet	248.70±119.70	238.55±125.52	260.15±112.261	0.064
Lymphocyte (10^9/L)	8.09±90.96	0.94±1.10	0.87±0.67	0.750
Neutrophil (10^9/L)	10.37±7.95	10.78±6.89	9.89±8.49	0.031
CRP (mg/L)	130,99±97	135.37±91.66	126.05±102.79	0.119
PCT (ng/mL)	4.75±24.55	5.57±31.7	3.82±12.29	0.887
Mechanic ventilation days	5.8±7.69	9.15±8.58	2.02±4.01	0.000
LOS/day	11.8±9.15	14.15±10.33	9.18±6.74	0.000
Lenght of stay in hospital/day	16.59±11.74	18.33±12.13	14.61±11.0	0.001
SBIP	117 (37.4%)	80 (68.4%)	37 (31.6%)	0.000
SOFA	17.17±7.36	6.5±2.77	6.1±3.13	0.072
APACHE	6.32±2.95	18.43±7.41	15.74±7.05	0.001
NLR	19.38±22.24	18.27±21.55	20.67±22.98	0.184
PLR	452.26±440.16	433.96±402.73	472.92±479.49	0.199
BMI (kg/m^2)	27.06±4.98	27.98±4.59	26.25±5.19	0.001
Mortalite	174 (55.59%)	140 (80.92%)	34 (24.28%)	0.000

BUN: blood urea nitrogen, LDH: lactate dehydrogenase, AST: aspartate transaminase, ALT: alanine aminotransferase, WBC: white blood cell, HB: hemoglobin, PCT: procalcitonin, CRP: C-reactive protein, COPD: chronic obstructive pulmonary disease, ARDS: acute respiratory distress syndrom, APACHE: acute physiology and chronic health evaluation, SOFA: sequential organ failure assessment score, LOS: lenght of stay in intensive care unit, SBIP: secondary bacterial infection positivity, NLR: neutrophil lymphocyte ratio, PLR: platelet lymphocyte ratio, BMI: body mass index

respiratory muscles, notably the sternocleidomastoid muscle, is a simpler method for physicians (10). Because hypoxemia does not always result in end-organ damage, it cannot be used as a sole trigger for intubation (10,11). It's worth noting that tissue oxygen supply is influenced by hemoglobin content and cardiac output in addition to oxygen saturation. Furthermore, the patient's dyspnea is frequently caused by limits in respiratory mechanics rather than oxygenation restrictions (10,11). As a result, deciding whether or not to intubate a patient is a personal decision that should be based on the sum of all of these factors (4,9,10). In COVID-19, there is yet no randomized controlled trial on ventilation therapy. As a result, accurate ventilation recommendations are mostly based on physician expertise and studies in other patient groups (12-14). Based on the oxygenation index (PaO_2/FiO_2) at positive endexpiratory pressure 5 cmH_2O,

Table 3. Applied treatments and complications				
	Total (n=313)	Intubated (n=173)	Non-intubated (n=173)	p-value
Dexamethasone	87 (27.8%)	52 (16.6%)	35 (11.2%)	0.129
Tocilizumab	15 (4.8%)	9 (2.9%)	6 (1.9%)	0.77
Anakinra	42 (13.4%)	18 (5.8%)	24 (7.7%)	0.210
Stem cell therapy	2 (0.6 %)	2 (0.6%)	0	0.5
Methylprednisolone pulse therapy	124 (39.6 %)	70 (22.4%)	54 (17.3%)	0.327
IVIG	19 (6.1%)	12 (3.8%)	7 (2.2%)	0.5
Septic shock	153 (48.9%)	113 (36.1%)	40 (12.8%)	0.000
Survivor	139 (44.4%)	28 (8.9%)	111 (35.5%)	0.000
Acute kidney failure	44 (14.1%)	29 (93%)	15 (4.8%)	0.092
Diabetic ketoacidosis	45 (14.4%)	18 (5.8%)	27 (8.7%)	0.079
Elevated Liver Enzymes	28 (8.9%)	15 (4.8%)	13 (4.2%)	1
Deep vein thrombosis	2 (0.06%)	0	2 (0.06%)	0.132
Pulmonary embolism	6 (1.9%)	3 (1%)	3 (1%)	1
IVIG: Intravenous immunoglobulin				

COVID-19 associated ARDS were categorized into three categories in one study; mild (200 mmHg ≤ PaO_2/FiO_2 <300 mmHg), mild to moderate (150 mmHg ≤ PaO_2/FiO_2 <200 mmHg) and moderate to severe (PaO_2/FiO_2 <150 mmHg) (15). In our study, we also examined the patient groups whose oxygenation index, PaO_2/FiO_2 <100-150 mmHg, which compels clinicians to decide on intubation. We compared patients with this index who preferred invasive mechanical ventilation with groups of patients using NIV and/or HFNO. Seventy nine (49.4%) of 94 (58.4%) patients died in the intubation group with PaO_2/FiO_2 of 100-150 mmHg. In the non-intubated group with PaO_2/FiO_2 150-100 mmHg, 17 (12.14%) of 67 (41.6%) patients were intubated during their stay in the ICU, and only 8 (5%) died. Intubating a patient raises the risk of secondary bacterial infection and lengthens the time spent in the critical care unit, both of which can lead to an increase in mortality. Many COVID-19 patients require intubation due to hypoxemia; these individuals have dyspnea or distress. Shortness of breath does not usually occur until the PaO_2 decreases to 60 mmHg (or much lower) (11). Patients with PaO_2 >40 mmHg (equal to ~75 percent oxygen saturation) have a tough time demonstrating end-organ damage (4). The product of arterial oxygen content and cardiac output determines the amount of oxygen given to the tissues. Initially, oxygen extraction increases and oxygen intake remains normal in patients with restricted oxygen delivery (16). When oxygen delivery falls below a critical level, this extraction mechanism fails, and metabolism shifts from aerobic to anaerobic pathways, impairing important organ function. In critically ill individuals, this critical threshold is not reached until oxygen delivery is 25% of normal (17). The main problem after a patient is put on a ventilator is avoiding complications (18). The best way to minimize ventilator-related complications is to avoid intubation unless necessary (19,20). In addition to increased ventilator-associated pneumonia in intubated patients, the use of sedation-muscle relaxants during long ICU stays may have contributed to the high mortality rate by causing an increase in secondary bacterial infections. According to our findings, secondary bacterial infections develop more frequently in intubated patients. A logistic regression analysis of clinical and laboratory data was used to predict mortality, and age, presence of secondary bacterial infection, number of mechanical ventilation days, and number of intensive care days were found to be significant for predicting mortality. The retrospective nature of this study is one of its limitations. Because the physician made the decision to intubate, the time it took to intubate was vary. The second limiting factor is that the causes of death have not been fully invastigated. More research is needed to see if the onset of symptoms, the time of hospitalization following the beginning of symptoms, the timing of intubation, the intubation $PaO_2/$

Table 4. Comparison of laboratory data of intubated and non-intubated groups with PaO_2/FO_2 =100-150 mmHg				
	Total (n=160)	Intubated (n=93)	Non-intubated (n=67)	p-value
Age	65.14±14.41	68.47±13.7	60.53±14.19	0.000
Gender (male)	92 (57.5%) 68 (42.5%)	44 (47.3%) 49 (52.7%)	48 (71.6%) 19 (28.4%)	0.002
Glucose (mg/dL)	194.07±115.51	192.40±115.18	196.38±116.78	0.89
BUN (mg/dL)	70.95±48.15	75.43±55.34	64.72±35.34	0.59
Creatinine (mg/dL)	1.38±1.04	1.41±1.15	1.33±0.87	0.82
AST (U/L)	81.55±291.48	71.12±262.20	96.01±329.36	0.48
ALT (U/L)	47.69±87.22	43.72±75.34	53.21±101.80	0.53
Fibrinogen (mg/dL)	639.73±686.20	590.16±170.10	708.53±1042,00	0.95
INR	1.16±0.33	1.17±3.31	1.16±0.33	0.16
D-dimer (mgFEU/mL)	3.41±5.18	3.77±5.81	2.91±4.13	0.77
LDH (U/L)	506.55±391.62	501.24±460.52	513.93±271.56	0.22
Ferritin(ng/mL)	1404,78±1840,25	1321,74±1558,88	1520,05±2178,88	0.77
WBC (10^9/L)	12.26±13.40	12.79±16.51	11.54 ±7.22	0.71
HB (g/dL)	12.72±10.64	12.07±2.42	13.62±16.23	0.22
Platelet	259.32±123.98	248.47±125.56	274.37±121.07	0.24
Lymphocyte (10^9/L)	0.85±0.708	0.86±0.77	0.84±0.60	0.39
Neutrophil (10^9/L)	8.86±5.25	8.9±5.3	8.7±5.22	0.92
CRP (mg/L)	125.84±92.37	117.22±84.15	137.78±102.16	0.286
PCT (ng/mL)	5.55±31.76	6.61±40.37	4.09±12.46	0.110
Mechanic ventilation days	5.51±7.76	8.87±8.51	0.86±2.42	0.000
LOS/day	11.83±9.17	13.53±9.6	9.47±7.9	0.000
Lenght of stay in hospital/day	16.81±12.53	17.09±11.9	16.43±13.9	0.37
SBIP	83 (51.9%)	60 (37.5%)	23 (14.4%)	0.000
SOFA	6.08±2.50	6.4±2.79	5.58±1.99	0.11
APACHE	13.55±4.42	13.7±4.31	13.3±5.71	0.72
NLR	17.59±20.16	18.73±23.54	16.02±14.22	0.949
PLR	490.54±526.39	473.97±461.18	513.55±608.38	0.281
BMI (kg/m^2)	27.25±5.33	28.31±4.9	26.49±5.52	0.012
Mortality	87 (54.4%)	79 (49.4%)	8 (5%)	0.000

BUN: Blood urea nitrogen, AST: aspartate transaminase, ALT: alanine aminotransferase, INR: international normalized ratio, LDH: lactate dehydrogenase, WBC: white blood cell, HB: hemoglobin, PCT: procalcitonin, CRP: C-reactive protein, COPD: chronic obstructive pulmonary disease, ARDS: Acute respiratory distress syndrom, APACHE: Acute Physiology and Chronic Health Evaluation, SOFA: Sequential Organ Failure Assessment score, LOS: lenght of stay in intensive care unit, SBIP: secondary bacterial infection positivity, NLR: neutrophil lymphocyte ratio, PLR: platelet lymphocyte ratio, BMI: body mass index

FiO_2 ratio, and pharmacotherapies are all factors that could affect the patient's clinical path. Our study's strength is that we observed that patients with moderate ARDS can survive using oxygenation modalities like high-flow nasal cannula/NIV. Furthermore, there is no other study in the literature that compares intubated and non-intubated patients with ARDS who had a PaO_2/FiO_2 of 150 mmHg.

Conclusion

Deciding whether or not to intubate individuals with COVID-19-associated ARDS is challenging. In this patient group, fear of contaminating health workers should not be a factor in intubation. While substantial oxygenation impairment caused by a large intrapulmonary shunt is a key intubation criterion in classic ARDS, COVID-19 patients often

Table 5. Logistic regression analysis of clinical and laboratory factors for predicting mortality (intubated and non-intubated groups with PaO_2/FO_2 =100-150 mmHg)

	Beta	SE	OR: Exp (B)	Lower 95%	Upper 95%	Sig
Age	-0.046	0.015	0.955	0.928	0.983	0.002
BMI	0.015	0.037	1.015	0.944	1.091	0.693
Gender (male)	-0.321	0.408	0.726	0.326	1.615	0.432
NLR	-0.001	0.017	0.999	0.967	1.032	0.94
PLR	0	0.001	1	0.999	1.001	0.545
PCT	-0.004	0.008	0.996	0.981	1.012	0.649
CRP	-0.001	0.002	0.999	0.994	1.003	0.545
APACHE	0.003	0.046	1.003	0.916	1.098	0.953
SOFA	-0.025	0.087	0.975	0.823	1.155	0.77
SBIP	-0.995	0.414	0.37	0.164	0.833	0.016
Mechanic ventilation days	-0.139	0.04	0.871	0.804	0.942	0.001
LOS/day	-0.014	0.039	0.986	0.914	1.065	0.726
Lenght of stay in hospital/day	0.079	0.028	1.082	1.023	1.144	0.005

BMI: Body mass index, NLR: neutrophil lymphocyte ratio, PLR: platelet lymphocyte ratio, PCT: procalcitonin, CRP: C-reactive protein, APACHE: Acute Physiology and Chronic Health Evaluation, SOFA: Sequential Organ Failure Assessment score, SBIP: secondary bacterial infection positivity, LOS: lenght of stay in intensive care unit, OR: odds ratio, SE: standard error, Sig: significant, Exp (B)-hazard ratio coefficient

respond well to HFNO and/or NIV treatments. Intubation should always be possible due to probable pathophysiological instability and the risk of rapid clinical deterioration, but it should be remembered that invasive mechanical ventilation has a high rate of complications and mortality.

Ethics

Ethics Committee Approval: The study was approved by the Başakşehir Çam and Sakura City Hospital Ethics Committee (decision no: 2021.04.58, date: 14.04.2021).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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Potentially Inappropriate Treatments in Intensive Care Units (INAPPT-ICU): Point Prevalence Study

Yoğun Bakım Ünitelerinde Potansiyel Yersiz Tedaviler (INAPPT-ICU): Nokta Prevalans Çalışması

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ABSTRACT *Objective:* Technological advances increased prolonged life expectancy of the terminal patients, who had end-stage diseases. End-of-life care in intensive care units (ICU) has increased with the rise in admissions of terminal patients to ICU. Our aims in this study were to determine the prevalence of terminal patients, and to find the reasons for potentially inappropriate treatments in ICUs.

Materials and Methods: It was nationwide, multicenter, point prevalence and observational study. All adult patients, who stayed more than 48 h in the ICU, were enrolled. All patients were recorded on an electronic case record form, consisting of data on patient demographics, treatments, family participation and mini survey for physicians. The study was conducted on October 15, 2018 with a follow-up for 30 days.

Results: Of 1127 patients 286 (25%) ICU patients were diagnosed as terminal patients by ICU physicians depending on primary physician statement. Terminal patients relatives requests and physicians legal concerns reduced end-of-life care quality. Terminal patients had significantly increased usage of mechanical ventilation, inotropic drugs, and poor end-of-life care quality ($p<0.001$). Fifty-four percent of the terminal patients didn't have any end-of-life decisions at discharge. Half of the terminal patient relatives requested the full code. Without legal concerns, most of the physicians would apply do not resuscitate (86%), withhold (77%) and withdraw (53%) to terminal patients at the end-of-life.

Conclusion: Terminal patients occupy an important place in the ICU. To increase the quality of terminal patients' end-of-life care in the ICU, advanced care planning and legal arrangements should be conducted properly.

Keywords: Terminal care, inappropriate treatments, intensive care units, advanced care planning, patient care planning

ÖZ *Amaç:* Teknolojik gelişmeler, son dönem hastalıkları olan terminal hastaların yaşam sürelerinin uzamasına neden olmuştur. Yoğun bakım ünitelerinde (YBÜ) yaşam sonu bakım, terminal hastaların YBÜ'ye kabullerindeki yükselme ile artmıştır. Bu çalışmadaki amacımız, terminal hastaların YBÜ'deki prevalansını ve YBÜ'de potansiyel olarak yersiz tedavilerin nedenlerini incelemektir.

Gereç ve Yöntem: Çalışmamız ülke çapında, çok merkezli, nokta prevalans ve gözlemsel olarak yapıldı. YBÜ'de 48 saatten fazla kalan tüm yetişkin hastalar çalışmaya alındı. Tüm hastalar, hasta demografisi, tedaviler, aile katılımı ve hekimler için mini anket ile ilgili verilerden oluşan elektronik bir olgu kayıt formuna kaydedildi. Çalışma, 15 Ekim 2018'de 30 günlük bir takip ile gerçekleştirildi.

Bulgular: Kaydedilen tüm 1127 hastanın 286'sına (%25) primer hekimi beyanına göre YBÜ hekimleri tarafından terminal hasta tanısı konuldu. Terminal hasta yakınlarının talepleri ve hekimlerin yasal kaygılarının yaşam sonu bakım kalitesini düşürdüğü görüldü. Terminal hastalarda mekanik ventilasyon kullanımı, inotropik ilaçlar ve düşük yaşam sonu bakım kalitesi önemli ölçüde fazlaydı ($p<0,001$). Terminal hastaların yüzde %54'ü taburcu olurken herhangi bir yaşam sonu kararı verilmedi. Terminal hasta yakınlarının yarısı tam kod istedi. Yasal kaygılar olmaksızın, doktorların çoğu terminal hastalara yaşamlarının sonunda canlandırma girişiminde bulunmama (%86), tedaviyi durdurma (%77) ve tedaviyi geri çekme (%53) kararı vereceklerini açıkladılar.

Sonuç: Terminal hastalar yoğun bakımda önemli bir yer tutmaktadır. Terminal hastaların YBÜ'deki yaşam sonu bakımının kalitesinin artırılması için önceden yaşam sonu bakım planlaması ve yasal düzenlemelerin doğru yapılması gerekmektedir.

Anahtar Kelimeler: Terminal bakım, yersiz tedaviler, yoğun bakım üniteleri, yaşam sonu bakım planlaması, hasta bakım planlaması

Introduction

Intensive care units (ICU) are life-saving facilities for critically ill patients, using advanced technology and specialized personnel. Especially in high-income countries, increased ICU resources and technological advances resulted in an increase in prolonged life expectancy of the terminal patients (TP), who had end-stage diseases. End-of-life care in ICU has increased with the rise in admissions of TPs to ICU (1). Approximately 20% of deaths occur in ICU (2,3). Dying in ICU might be an advantage when end-of-life (EOL) decisions are regarded or disadvantage when inappropriate treatment is practiced.

The intensive care associations recommended the term "potentially inappropriate" should be used, rather than "futile" to describe treatments that have at least some chance of accomplishing the effect sought by the patient (4). Society of Critical Care Medicine (SCCM) defines inappropriate ICU treatments as "when there is no reasonable expectation that the patient will improve sufficiently to survive outside the acute care setting, or when there is no reasonable expectation that the patient's neurologic function will improve sufficiently to allow the patient to perceive the benefits of treatment" (5). As well as high costs of inappropriate treatments, they also delay other patients' care (6).

It is aimed to prevent long-term hospitalizations in ICU to meet the intensive care needs of more patients and to reduce the expenditures on intensive care. For this purpose, advance directives of TPs have become important issues (7). In the United States, the proportion of advance directives increased from 51% to 90% over the 5-year from 1988 to 1992 (8). To the best of our knowledge, there was no point prevalence study about the potentially inappropriate treatments of TPs in ICUs. Our first objective was to determine the prevalence of TP in ICU. Secondary objectives were to assess the reasons of potentially inappropriate treatments and the quality of EOL care in ICU.

Materials and Methods

Study Design

Inappropriate treatments in intensive care units was a nationwide, multicenter, prospective, observational, point prevalence study conducted on October 15, 2018. All adult patients, whose ICU stay was more than 48 hours, were included in the study. Patients younger than 18 years old and patients admitted for monitorization for less than 48 hours, were excluded. Informed consent was obtained from the family. The study was approved by the Instutional Ethics Committee of İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine (decision no: 172227, date: 10.05.2018). The study was registered to the Clinical Trials, NCT03520270.

Procedures

The announcement of our study and protocol was made through a society website on August 8, 2018. Enrollments to the study were allowed until October 1, 2018. For the study, a password protected safe portal was created with this society. This portal required society membership to save the center information form and patient data. After all enrollments, the electronic case report forms (e-CRF) were sent to the physicians by portal link with the individual number for their ICUs.

Data Records and Definitions

The center information form included name, e-mail, cell phone of the participant, city, name and specialty of the individual responsible of the ICU, number of hospital and ICU beds, type and level of ICU, number of patients who were admitted to the ICU in 2017 and crude mortality of ICU in 2017.

The e-CRF was for all the included patients to use on the study date and follow up for 30 days. The form included demographics of patients, including age, sex, hospital admission date, ICU admission date, type, source and diagnosis of admission, comorbidities, metastasis, the Acute Physiology Chronic Health Evaluation-II (APACHE-II) score Sepsis-related Organ Failure Assessment (SOFA) score, presence of sepsis diagnosis and Glasgow coma score (GCS). Interventions include the use of mechanical ventilation, vasoactive agents, antibiotics, blood or blood product transfusions.

Care related features like defining the goals of care daily, family meeting, family visits, and spiritual support. The ICU physician's diagnose depending on primary doctor's statement, whether the patient is terminal, was asked on a five point Likert scale ranging from completely agree to completely disagree. Also the opinion of the physicians were asked if they would implement an EOL decision for the patient, who did not have any advance directives, if it would be possible legally. EOL decisions included "Do Not Resuscitate" (DNR, not to initiate or perform

cardiopulmonary resuscitation), "Withhold" (not to initiate or escalate a life-sustaining treatment), "Withdraw" (cease or remove a life-sustaining intervention).

After 30 days of initial data collection, discharge date and status, and any EOL decision if implemented was recorded to complete the study. The e-CRFs were sent with detailed explanation of each question. The end date of the study was November 14, 2018, and the portal was allowed to record data until December 31, 2018.

Statistical Analysis

SPSS 15.0 for Windows program was used for statistical analysis. Descriptive statistics of the patients are given as number and percentage for categorical variables, mean (± standard deviation) or median (IQR 25 to 75) for continuous variables. The cohort was divided as terminal or non-terminal according to the intensive care physician's diagnose. TPs were the patients, which physicians agreed or completely agreed with the statement that the patient is terminal. The proportion of TPs was calculated as the prevalence on the study day. Normal distribution was analyzed using Kolmogorov-Smirnov test. Comparisons of terminal and non-TPs were made by Student t-test for independent groups for data showing normal distribution, and by Mann-Whitney U test for non-normally distributed data. Multiple comparisons in normally distributed data were made by ANOVA with Bonferoni post-hoc test. The ratios were compared with the chi-square analysis. In all statistical analyses, the level of significance was considered as two-sided $p<0.05$.

Results

After the announcement in society website, 102 ICU were enrolled until the day of study on October 15, 2018. Eighty-nine of these ICUs (87%) completed the study within 30 days follow up until the end date of the study, November 14, 2018 (Figure 1). Characteristics of the ICUs are presented in Table 1. The total number of enrolled patients was 1127. Of all patients, 25% (n=286) were indicated as TP. Clinical characteristics of patients are presented in Table 2. Most of the admissions were due to medical reasons (73%), and nearly half of these patients had respiratory failure. Number of patients with comorbidities was significantly higher in the TP group, with heart failure being the most prevalent comorbidity. ($p<0.001$) TP had significantly higher admission day APACHE-II, study day SOFA, and significantly lower study day GCS scores than non-TP patients ($p<0.001$). Oxygen treatment, invasive mechanical ventilation, central venous catheter, norepinephrine and dopamine use were significantly higher in TP ($p<0.001$). In addition, the number of patients with sepsis was significantly higher in TP ($p=0.001$), but there was no significant difference between antibiotic use (Table 2).

At the end of the study 34% of the all patients died in the ICU, 37% discharged and 28% were still in the ICU. Thirteen percent of the patients had EOL decisions at discharge.

In quality measures of EOL; daily goals of care determination were significantly low in TP ($p<0.001$). Family meeting in 72 hours was performed in almost all the patients, but only 5% of the ICUs had an open visit. Most of the families (90%) were informed about the terminal state, and half (49.65%) of the families' decisions about EOL were full code (Table 3).

The mini survey was about physicians EOL decisions, if TP did not have any advance directives and it was legally possible. Most of them (86%) would apply DNR, 77% would apply withhold, and 53% would apply withdraw to TP (Table 4).

Table 1. Characteristics of intensive care units

Characteristics of ICU	Results
Mean number of hospital beds	721.52±423.87
Mean number of ICU beds	20.97±20.44
ICU level	
1st level	1 (1.12)
2nd level	4 (4.49)
3rd level	84 (94.38)
ICU type	
Medical/surgical	75 (84)
Medical	11 (12.36)
Surgical	2 (2.25)
Neurology	1 (1.12)
ICU model	
Closed	74 (83.15)
Open	5 (5.62)
Mixed	10 (11.24)
ICU physician's specialty	
Intensive care specialist	60 (67.42)
Anesthesiologist	29 (33.58)
Mean number of patients admitted in 2017	853.38±781.58
Mean 2017 crude mortality	24.81 (15.37)

Data are presented as the mean ± standard deviation or absolute number (percentage). ICU: Intensive care unit

Table 2. Demographic and clinical characteristics of patients				
Variables	**Terminal (n=286)**	**Not terminal (n=841)**	**Total (n=1127)**	**p-value**
Age	70.36±16.12	62.59±18.56	64.56±18.28	<0.0001
Sex				0.521
Male	157 (54.9)	480 (57.1)	637 (55.65)	
Hospital stay before ICU, median	0 (0 to 4)	0 (0 to 3)	0 (0 to 3)	0.399
Admission type				<0.0001
Medical	248 (86)	580 (69)	828 (73)	
Emergency surgery	27 (9.4)	123 (14.6)	150 (13)	
Elective surgery	7 (2.4)	61 (7.3)	68 (0.6)	
Trauma	4 (1.4)	77 (9.2)	81 (0.7)	
Admission reason				0.0014
Respiratory	112 (10.0)	291 (25.8)	403 (35.8)	
Cardiovascular	29 (2.6)	80 (7.1)	109 (9.7)	
Gastrointestinal	19 (1.7)	80 (7.1)	99 (8.8)	
Trauma	4 (0.4)	77 (6.8)	81 (7.2)	
Urogenital	14 (1.6)	35 (3.1)	49 (4.3)	
Metabolic	2 (0.2)	13 (1.1)	15 (1.3)	
Neurological	88 (7.8)	232 (20.6)	320 (28.4)	
Other	18 (1.6)	33 (2.9)	51(4.5)	
Comorbidity				<0.0001
Yes	227 (79.4)	542 (64.4)	769 (68)	
Comorbidity type				
COPD	64 (22.4)	218 (25.9)	282 (25)	0.232
Chirosis	4 (1.4)	11 (1.3)	15 (0.1)	1.00
DM non-insulin	45 (15.7)	87 (10.3)	132 (11)	0.014
DM insulin	24 (8.4)	90 (10.7)	114 (10)	0.263
Heart failure	83 (29)	165 (19.6)	248 (22)	0.001
HIV	1 (0.3)	2 (0.2)	3 (0.2)	1.00
Renal failure	33 (11.5)	76 (9)	109 (0.9)	0.216
Immunosupresive treatment	13 (4.5)	41 (4.9)	54 (0.4)	0.882
Chemotheraphy	29 (10.1)	41 (4.9)	70 (0.6)	0.001
Solid tumor active	56 (19.6)	64 (7.6)	120 (10)	<0.0001
Hematologic cancer	5 (1.7)	17 (2)	22 (1)	0.773
Metastasis	53 (18.5)	45 (5.4)	98 (8)	<0.0001
APACHE-II - admission day	24.48±8.47	20 .67±8.32	21.94±9.72	<0.0001
SOFA - study day	7.97±3.87	5.62±3.41	6.21±3.67	<0.0001
Glasgow coma score	7.90±3.95	10.98±3.83	10.22±4.11	<0.0001
Initiatives				
Oxygene treatment	53 (18.5)	297 (35.3)	350 (31)	<0.0001
Nasal high flow oxygene	3 (1)	28 (3.3)	31 (2.7)	0.042
Noninvasive MV	22 (7.7)	97 (11.5)	119 (10.5)	0.068

Table 2. Continued

Variables	Terminal (n=286)	Not terminal (n=841)	Total (n=1127)	p-value
Invazive MV	222 (77.6)	484 (57.6)	706 (62.6)	<0.0001
Tracheotomy	82 (28.7)	220 (26.2)	302 (26.7)	0.407
Central venous catheter	192 (67.1)	461 (54.8)	653 (57.9)	<0.0001
Other invazive monitorization	76 (26.6)	235 (27.9)	311 (27.5)	0.654
Renal replacement treatment	40 (14)	88 (10.5)	128 (11.3)	0.105
ECMO	1 (0.3)	3 (0.4)	4 (0.3)	1.00
Nasogastric tube	170 (59.4)	430 (51.1)	600 (53.2)	0.015
Percutaneous endoscopic gastrostomy	55 (19.2)	111 (13.2)	166 (14.7)	0.013
Total parenteral nutrition	36 (12.6)	105 (12.5)	141 (12.5)	0.964
Vasoactive agents	163 (57)	243 (28)	406 (36)	
Norepninephrine	114 (39.9)	188 (22.4)	302 (26)	<0.0001
Dopamine	24 (8.4)	21 (2.5)	45 (3)	<0.0001
Dobutamine	13 (4.5)	14 (1.7)	27 (2)	0.006
Epinephrine	10 (3.5)	17 (2)	27 (2)	0.159
Vasopressine	2 (0.7)	2 (0.2)	4 (0.3)	0.268
Other	0	1 (0.1)	1 (0.1)	1.00
Sepsis	112 (39.2)	244 (29)	356 (31.5)	0.001
Antibiotic	70 (75.5)	172 (79.5)	242 (21.4)	0.152
Blood transfusion <24 h	45 (15.7)	143 (17)	188 (16.6)	0.619

Data are presented as the mean ± standard deviation, median (interquartile range), or absolute number (percentage).
ICU: Intensive care unit, COPD: chronic obstructive pulmoner disease, DM: diabetes mellitus, HIV: human immunodeficiency virus, MV: mechanical ventilation, ECMO: extracorporeal membrane oxygenation, APACHE-II: Acute Physiology Chronic Health Evaluation-II, SOFA: Sepsis-related Organ Failure Assessment

Table 3. Quality measures of end-of-life care

Variables	Terminal (n=286)	Not terminal (n=841)	Total (n=1127)	p-value
Daily goals of care	267 (93.4)	822 (97.7)	1,089 (96.6)	0.001
Family meeting in 72 h	281 (98.3)	830 (98.7)	1,111 (98.5)	0.569
Family visit				0.227
Open visit	19 (6.6)	35 (4.2)	54 (4.7)	
1/day	250 (87.4)	736 (87.5)	986 (87.4)	
A few times/week	16 (5.6)	65 (7.7%)	81 (7.1)	
1/ week	1 (0.3)	5 (0.6)	6 (0.5)	
Spiritual support for patient/family	106 (37.1)	384 (45.7)	490 (43.4)	0.011
Family knowledge about terminal period	245 (90.4)	27 (31)	272 (24.1)	0.0001
Family decision about EOL care			363 (32.2)	0.0001
Not asked	96 (34.5)	57 (67.1)	153 (13.5)	
Everything	142 (51.1)	27 (31.8)	169 (14.9)	
Everything except CPR	29 (10.4)	0	29 (2.5)	
Withhold	6 (2.2)	0	6 (0.5)	
Withdraw	5 (1.8)	1 (1.2)	6 (0.5)	

Data are presented as the absolute number (percentage). EOL: End-of-life, CPR: cardiopulmoner resuscitation

Table 4. Mini survey about clinician's end-of-life decisions and patients' discharge status				
	Terminal (n=286)	Not terminal (n=841)	Total (n=1127)	p-value
If you think patient is in EOL period, what would you do?				
Withhold			373 (33)	0.0001
I do	214 (77)	35 (36.8)	249 (22)	
Not sure	14 (5)	25 (26.3)	39 (3.4)	
I do not	50 (18)	35 (36.8)	85 (7.5)	
Withdraw			364 (32.2)	0.0001
I do	146 (53.9)	24 (25.9)	170 (15)	
Not sure	34 (12.5)	21 (22.6)	55 (4.8)	
I do not	91 (33.5)	48 (51.6)	139 (12.3)	
DNR			372 (33)	0.0001
I do	237 (86.2)	42 (43.3)	279 (24.7)	
Not sure	15 (5.5)	23 (23.7)	38 (3.3)	
I do not	23 (8.3)	32 (33)	55 (4.8)	
ICU LOS	30 (13 to 54)	29 (10 to 45)	30 (11 to 49)	0.134
Status after 30 days				0.0001
Discharged	46 (16.1)	375 (44.6)	421 (37.3)	
Death	172 (60.1)	212 (25.2)	384 (34)	
Still in ICU	68 (23.8)	254 (30.2)	322 (28.5)	
EOL decision at discharge			934	0.0001
N/A	148 (53.8)	632 (95.9)	780 (83)	
Withhold	17 (6.2)	2 (0.3)	19 (0.2)	
Withdraw	2 (0.7)	2 (0.3)	4 (0.4)	
DNR	108 (39.3)	23 (3.5)	131 (14)	
Standardized mortality rates	1.49	0.98		

Data are presented as the median (interquartile range) or absolute number (percentage). EOL: End-of-life, DNR: do not resuscitate, ICU: intensive care unit, LOS: length of stay

Status after 30 days; 60% of TP died in the ICU, 16% discharged in the study period and 24% were still in the ICU at the end of the study (p<0.001). TP discharge status was significantly high in medical/surgical type ICU (84%, p<0.005) and third level ICU (92%, p<0.001). More than half of the TP did not have any EOL decisions, 40% had DNR, 6% had withhold, and 1% had withdraw order at discharge.

Discussion

In a large population of multicenter and point-prevalence study, we showed 25% prevalence of TP in the ICUs. In the literature there were surveys about TP prevalence in ICUs in other countries, and our data were consistent with them (4,9,10).

Second important finding of the current study was about the reason of potentially inappropriate treatments in ICU. Physicians legal concerns were the most important reason of avoiding EOL decisions of TPs, and accordingly as well high potentially inappropriate treatment administrations in ICU. Physicians were willing to implement EOL decisions in TP, who did not have any advance directives, if legally possible. But their daily practices were far away from their declaration. In our study EOL decision of TP, who died in ICU (4%), were lower than other studies (11-13). The rates of EOL decisions in Northern and Southern European countries were significantly different (47% vs. 18%) (7). EOL decisions were ranged from 10% in South Asia to 67% in Oceania. They determined that less frequent EOL decisions were made in countries with low-gross national income, and more

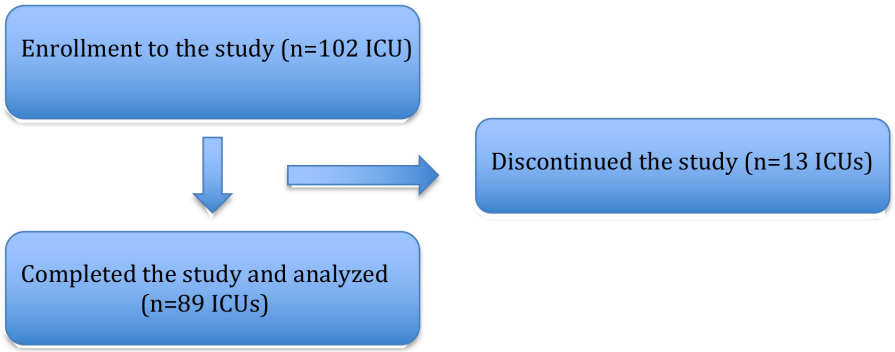

Figure 1. Flow chart
ICU: Intensive care unit

frequently in countries with high-gross national income (14,15). In addition, it was shown that making EOL decision increased 22% in 17 years in European ICUs. The reason for these differences was thought to be due to the changes in attitudes, laws, recommendations and guidelines in Europe regarding EOL practices and the support of European public support in making EOL decisions in the last decade (16).

Other reason of the potentially inappropriate treatments in ICUs was the request of the TPs relatives. Half of the TP relatives EOL decision was full code. Our findings were similar with Palda et al. (9), who showed the most frequent reasons for the potentially inappropriate treatments, were the request of the relatives of the patients (91%) and legal pressure (80%). Some studies showed the reason of the inappropriate treatments in ICUs was poor communication with the patients' families. In our study, we did not find a poor communication between physicians and families.

Other important result of our study was TP ICU length of stay, which was 30 days, was not significantly different from non-TP. Aygencel and Türkoğlu (17) study showed shorter TP ICU length of stay than our study 5 years ago. In the literature, there were studies on limiting the TP ICU length of stay, and avoiding inappropriate treatments, which can be used as a protocol in ICUs (5,18-20). Instead of aggressive treatments, which include ICU admission in the last 30 days of life, SCCM suggests treatments to relieve pain and suffering. Even if such analgesic treatments hasten death, this double effect should not hinder the comfort care (21,22).

Our other result was regarding to the important scoring systems. The most common scoring systems in ICU were APACHE-II, SOFA and GCS. In our study, admission day APACHE and study day SOFA scores were significantly high, and study day GCS was significantly low in TP. Likewise Xia and Wang (23) study found high APACHE and SOFA scores as significant risk factors for poor ICU prognosis. In addition, Villa et al. (24) developed a scoring system including, length of ICU stays, days of mechanical ventilation, days of vasoactive drug use and sepsis, to find the probability of ICU death.

Our other result showed poor EOL care in ICUs. More than half of the TP died in ICU, and 24% was still in ICU after 30 days follow up. These results showed that more than half of the TP had aggressive care rather than comfort care in the last 30 days of their lifes. The best EOL quality of advanced cancer patients was related with avoiding hospitalization and ICU, remaining calm, praying and meditating (25). Patients and families are the gold standard sources for the evaluation of EOL care. According to patients and families, the most important things in the EOL care were; not admitting to ICU in last 30 days of life, communication with clinicians, patient focused decision making, comfort, dignity, personhood, privacy and family support (26,27). Although SCCM suggests family presence in the ICU, in our study most of the families were allowed to visit their patients once a day (28).

Conclusion

In conclusion, there was a high prevalence of TP in ICUs. In order to avoid inappropriate treatments, and to increase the quality of EOL care in ICUs, advance directives should be recorded in patients' files and legal arrangements should be done without delay.

Ethics

Ethics Committee Approval: The study was approved by the Instutional Ethics Committee of İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine (decision no: 172227, date: 10.05.2018). The study was registered to the Clinical Trials, NCT03520270.

Informed Consent: Informed consent was obtained from the family.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: E.E.Ö., H.S., D.M., D.T.A., H.A., F.A., I.Ö.T., Ç.K., D.Ö., M.K.B., Y.D., Consept: E.E.Ö., H.S., I.Ö.T.,Y.D., Design: E.E.Ö., H.S., Y.D., Data Collection or Processing: E.E.Ö., H.S., D.M., D.T.A., H.A., F.A., I.Ö.T., Ç.K., D.Ö., M.K.B., Y.D., Analysis or Interpretation: E.E.Ö., F.A., Y.D., Literature Search: E.E.Ö., Y.D., Writing: E.E.Ö., Y.D.

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ÖZGÜN ARAŞTIRMA / *ORIGINAL RESEARCH*

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COVİD-19 Akut Respiratuvar Distres Sendromu Fenotiplerinde Mekanik Ventilasyon

Mechanical Ventilation in COVID-19 Acute Respiratory Distress Syndrome Phenotypes

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ÖZ *Amaç:* Koronavirüs hastalığı-2019 (COVİD-19) ilişkili akut solunum sıkıntısı sendromu (ARDS) hastalarında kompliyans açısından ARDS fenotipleri tanımlanmıştır. Çalışmamızda COVİD-19 ilişkili ARDS hastalarında mekanik ventilasyon desteği ve sonuçları incelenmiştir.
Gereç ve Yöntem: Retrospektif olarak planlanan çalışma, hesaplanan statik kompliyans değerine göre üç fenotip alt grup belirlenen COVİD-19 ilişkili ARDS hastalarında gerçekleştirildi [tip high (H) = Cstat <40 mL/cmH_2O, tip light (L) = Cstat ≥50 mL/cmH_2O ve tip intermediate (Int) =40≤ Cstat <50 mL/cm H_2O]. Mekanik ventilasyon stratejisinin COVİD-19 ARDS fenotiplerinde mekanik ventilasyon süresi, yoğun bakım ünitesinde kalış süresi ve mortalite üzerindeki etkileri incelendi.
Bulgular: Çalışma hastalarının COVİD-19 ARDS fenotipi açısından %72,3 tip H, %23,4 tip L ve %4,3 tip Int olduğu tespit edildi. Mekanik ventilasyon stratejisinin mekanik ventilasyon süresi (p=0,357), yoğun bakım ünitesinde kalış süresi (p=0,127) ve ölüm oranını (p=0,583) etkilemediği görüldü.
Sonuç: COVİD-19 ilişkili ARDS hastalarında, kompliyans ilişkili fenotipten bağımsız koruyucu ventilasyon stratejisinin uygun olduğunu düşünüyoruz.
Anahtar Kelimeler: COVİD-19, akut solunum sıkıntısı sendromu, mekanik ventilasyon, fenotip

ABSTRACT *Objective:* Coronavirus disease-2019 (COVID-19)-related acute respiratory distress syndrome (ARDS) phenotypes in lung compliance have been described in patients with COVID-19-related ARDS. Our study examined mechanical ventilation support and its results in patients with COVID-19-related ARDS.
Materials and Methods: The retrospectively planned study was performed in patients with COVID-19-associated ARDS who were determined to have three phenotype subgroups based on the calculated static compliance (Cstat) value [type high (H) = Cstat <40 mL/cmH_2O, type light (L) = Cstat ≥50 mL/cmH_2O and type intermediate (Int) =40≤ Cstat <50 mL/cm H_2O]. The effects of mechanical ventilation strategy on the duration of mechanical ventilation, length of stay in the intensive care unit, and mortality in COVID-19 ARDS phenotypes were investigated.
Results: It was determined that the study patients were 72.3% type H, 23.4% type L, and 4.3% type Int in terms of COVID-19 ARDS phenotype. It was observed that the mechanical ventilation strategy did not affect the duration of mechanical ventilation (p=0.357), the length of stay in the intensive care unit (p=0.127), and the mortality rate (p=0.583) in all three phenotypes.
Conclusion: We believe that a phenotype-independent protective ventilation strategy defined according to compliance is appropriate in patients with COVID-19-associated ARDS.
Keywords: COVID-19, acute respiratory distress syndrome, mechanical ventilation, phenotype

Giriş

Yoğun bakım ünitesinde koronavirüs hastalığı-2019 (COVİD-19) ilişkili solunum yetmezliği nedeniyle mekanik ventilasyon desteğinde takip edilen hastaların, COVİD-19 ilişkili olmayan akut solunum yetmezlikli diğer hastalara benzer şekilde mekanik ventilasyon desteğinin planlanması gerektiği, Surviving Sepsis Campaign panelinde önerilmiştir (1). COVİD-19 hastalarının büyük bölümü (%67-85) Berlin kriterlerine (2) göre akut solunum sıkıntısı sendromu (ARDS) nedeniyle yoğun bakım ünitesine kabul edilmiştir (3,4). Ancak COVİD-19 ilişkili ARDS, şiddetli hipoksemi görülse de genellikle normale yakın solunum sistemi kompliyansı olan spesifik bir hastalık olarak karşımıza çıkmıştır (5). Normal kompliyans ve ciddi hipoksemi, normal ARDS hastalarında neredeyse hiç görülmez. ARDS ve kompliyans açısından COVİD-19 ARDS'li hastalar ciddi farklılık göstermektedir (6).

Araştırmacılar, COVİD-19 ilişkili ARDS'nin enfeksiyonun şiddeti, konağın enfeksiyona yanıtı, fizyolojik rezerv, varolan ko-morbiditeler, hipoksemiye reaksiyon ve enfeksiyonun süresiyle ilişkili olarak iki farklı akciğer tutulumu ile karşımıza çıkabileceğini ortaya koydular. Tip light (L) düşük elastans (yani yüksek kompliyans), düşük ventilasyon/perfüzyon oranı, düşük akciğer ağırlığı ve düşük recruitment manevrasına cevap verebilirlik ile karakterize edildi. Tip high (H) ise yüksek elastans, yüksek sağdan sola şant, yüksek akciğer ağırlığı ve yüksek rekrutman manevrasına cevap verebilirlik ile tanımlandı (7).

ARDS'li hastalar için, mekanik ventilasyon stratejisi ve sonuçları henüz tam olarak bilinemezken, COVİD-19 ARDS'li hastalarda tanımlanan bu iki farklı fenotipte mekanik ventilasyon stratejisinin nasıl olması gerektiği hakkında da henüz yeterli yayın bulunmamaktadır.

Çalışmamızda solunum yetmezliği nedeniyle mekanik ventilasyon desteğinde takip edilen COVİD-19 ilişkili ARDS hastalarında mekanik ventilasyon uygulamaları ve sonuçları değerlendirilmiştir.

Gereç ve Yöntem

Çalışma Protokolü

Retrospektif planlanan çalışma, Ondokuz Mayıs Üniversitesi Klinik Araştırma Etik Kurul onayı sonrası (karar no: 2021/270, tarih: 20.05.2021) üniversite hastanesi 20 yataklı 3. düzey yoğun bakım ünitesinde 2021 Ocak ve 2021 Haziran tarihleri arasında takip edilen hasta verilerinin incelenmesi ile gerçekleştirildi.

Hastalar

On sekiz yaş üzeri, Berlin kriterlerine göre ARDS kabul edilen polimeraz zincir reaksiyonu sonucuna göre COVİD-19 (+) hastalar çalışmaya dahil edildi, 18 yaşından küçük hastalar, bilinen kronik akciğer hastalığı ya da göğüs deformitesi bulunan, travma sonrası yada acil cerrahi sonrası muhtemel COVİD-19 ilişkili ARDS'den bağımsız akciğer veya solunum sistemi kompliyansını etkileyebilecek yoğun bakım ünitesine kabul edilen hastalar, terminal kanser hastaları, strok ya da intrakraniyal kanama sonrası yoğun bakım ünitesine kabul edilen COVİD-19 (+) hastalar, ARDS nedeniyle ekstrakorporeal membran oksijenasyonu ihtiyacı bulunan hastalar, yoğun bakıma kabul sonrası ilk 24 saat içinde ölen ve palyatif bakım hastaları çalışma dışı bırakıldı.

Hastaların medikal tedavi desteği, gelişen sekonder enfeksiyon ve alınan örneklerde üreyen mikroorganizma kültür sonuçlarına, serum C-reaktif protein (CRP), ferritin, D-dimer, prokalsitonin sonuçları ve klinik takip verileri değerlendirilerek düzenlenmiştir.

Kliniğimizde mekanik ventilasyon desteği, ilk kabul sonrası SpO_2, arter kan gazı değerleri ve koruyucu mekanik ventilasyon stratejisine göre düzenlenmektedir. Buna göre tidal volüm (VT): 6-8 mL/kg, plato basıncı <28 cmH_2O, ekspirasyon sonu pozitif basınç (PEEP): SpO_2, 6-8 mL VT sağlayan pressure support (PS) ve buna göre plato basıncı <28 cmH_2O olacak şekilde ayarlanmaya çalışılmaktadır. Solunum frekansı dakika ventilasyonu ve $PaCO_2$ değerine göre, basınç-senkronize aralıklı zorunlu ventilasyon (P-SIMV) mod, GE Carescape R860 mekanik ventilatör ile sağlanmaktadır. Kontrol akciğer direkt grafisi ve 30 dakika sonra alınan arter kan gazı, SpO_2 değerine göre mekanik ventilatör desteği revize edilerek takip ve tedavi süreci düzenlenmiştir.

Yoğun bakım takip sürecinde SpO_2 en az %92 olacak şekilde FiO_2 ve PEEP desteği sağlandı. SpO_2 değerine göre PEEP desteği, PS sonucu VT =6-8 mL/kg'yi sağlayan ve plato basıncı <28 cmH_20 olacak şekilde düzenlendi. Eğer PEEP desteği ile hedef SpO_2 sağlanamazsa FiO_2<%60'a kadar oksijen desteği artırıldı. $PaCO_2$ <55 mmHg olacak şekilde dakika ventilasyon düzenlendi. Yüksek PEEP gereksinimi olan ve plato basıncı <28 cmH_20 olacak şekilde VT 6-8 mL/kg sağlanamaması durumunda oto-PEEP oluşturmayacak inspirasyon/ekspirasyon oranı ayarlanarak solunum frekansı arttırıldı ve hedef $PaCO_2$ değeri için dakika ventilasyonu düzenlendi. PaO_2/FiO_2<150 mmHg olan hastalara 8-11 saatlik aralarla prone pozisyonu ile mekanik ventilasyon desteğine devam edildi.

Veri Yönetimi

COVİD-19 ilişkili ARDS'li hastalar ilk yoğun bakım kabul sonrası P-SIMV modda; Cstat = tidal volüm/(plato basıncı - PEEP) formülü ile hesaplanan statik kompliyans, ARDS fenotipi açısından tip H (Cstat <40 mL/cmH_2O), tip L (Cstat ≥50 mL/cmH_2O) ve tip intermediate (Int) (40≤ Cstat <50 mL/cmH_2O) olarak üç gruba ayrıldı (8).

Hastaların ilk kabulündeki Akut Fizyoloji ve Kronik Sağlık Değerlendirmesi-II (APACHE-II) skoru, günlük Sıralı Organ Yetmezliği Değerlendirmesi (SOFA) skoru, COVİD-19 enfeksiyonu için belirlenen hastalık şiddeti ve gelişebilecek komplikasyonları öngörebileceği düşünülen D-dimer, ferritin, CRP, beyaz kan hücresi (WBC), prokalsitonin değerleri, mekanik ventilatör parametreleri, oksijen satürasyon yüzdesi, kan gazı değerleri, COVİD-19 nedeniyle aldığı tedavi rejimi ve süresi, inotrop ihtiyacı, mekanik ventilasyona bağlı kaldığı süre, yoğun bakım süresi, taburculuk şekli (şifa, mortalite), yoğun bakım ünitesinde gelişen organ yetmezlikleri, gelişen komplikasyonlar retrospektif olarak değerlendirildi.

Sonuçlar

Mekanik ventilasyon desteğinin farklı COVİD-19 ARDS fenotiplerinde, mekanik ventilasyon süresine etkisi birinci sonuç; mekanik ventilasyon desteğinin yoğun bakım süresi ve mortalite üzerine etkileri ise ikincil sonuçlar olarak belirlendi.

İstatistiksel Analiz

Veriler, IBM SPSS V21.0 (IBM, New York, ABD) kullanılarak analiz edildi. Normal dağılıma uygunluk tüm hastalar için Kolmogorov-Smirnov testi, alt grup normallik analizleri ise Shapiro-Wilk testi ile incelenmiştir. Üç fenotipik grup arasındaki, kategorik değişkenler ki-kare testi (Pearson chi-square testi) ile, sürekli değişkenler ise Kruskal-Wallis H testi ile değerlendirildi. Mortalite için bağımsız risk faktörlerinin incelenmesinde binary lojistik regresyon analizi kullanıldı.

Subgrup analizlerinde, mekanik ventilasyon desteğinin, mekanik ventilasyon ve yoğun bakım süresine etkisi basit doğrusal regresyon analizi ile, mortalite üzerine etkisi ise Mann-Whitney U testi ile değerlendirildi. Tüm testler için p<0,05 değeri anlamlı kabul edildi.

Bulgular

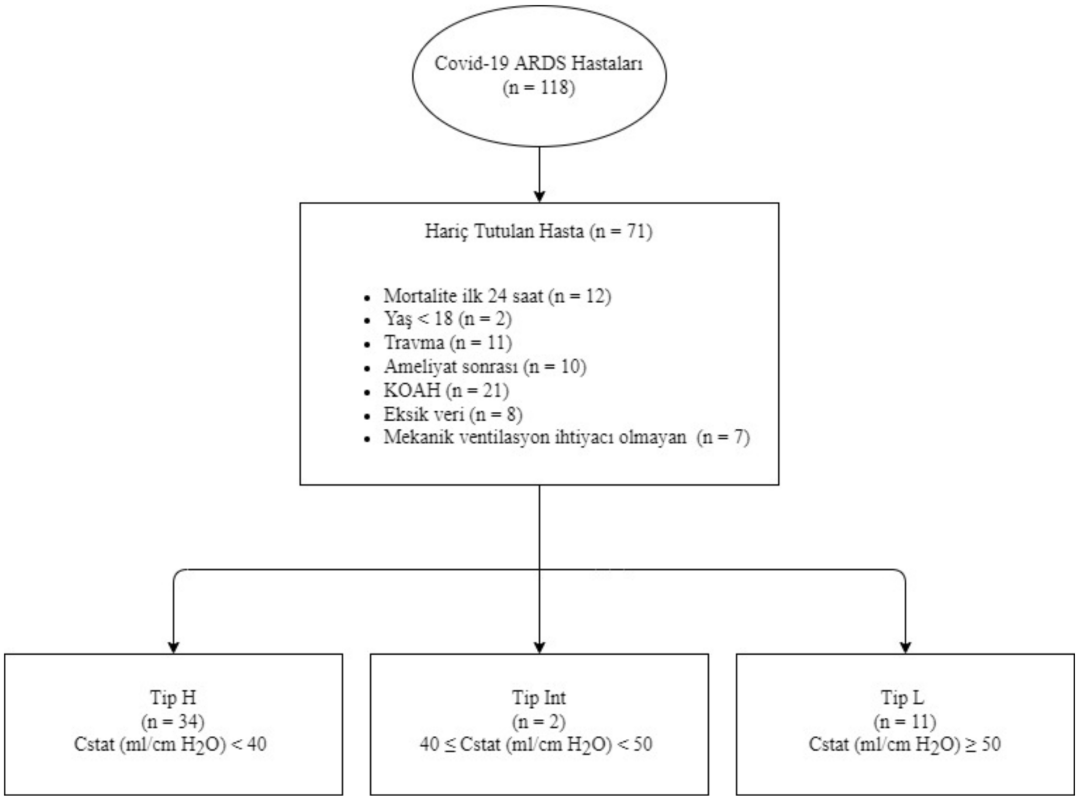
COVİD-19 nedeniyle solunum yetmezliği gelişen ve yoğun bakım ünitesinde takip edilen 118 hastadan 47'si çalışma protokolüne uygun bulunarak çalışmaya dahil edildi (Şekil 1). İnvaziv mekanik ventilatör desteğinde takip edilen çalışma hastalarının COVİD-19 ARDS fenotipi açısından %72,3 tip H, %23,4 tip L, %4,3 tip Int olduğu görüldü. Hastaların demografik verileri, sistemik hastalıkları, yoğun bakım kabulündeki ARDS şiddeti, COVİD-19 enfeksiyonu ile mortalite arasında önceki çalışmalara göre (9) ilişkilendirilen laboratuvar değerleri, APACHE-II ve ortalama SOFA skorları Tablo 1'de özetlenmiştir.

Hastaların yoğun bakım ünitesinde takipleri sürecinde mekanik ventilatör parametrelerinin ortalama değerleri, prone pozisyon ihtiyacı ve kullanılan medikal tedaviler Tablo 2'de özetlenmiştir. Prone pozisyonu uygulanan hastalar ile uygulanmayan hastalar arasında mekanik ventilasyon süresi (p=0,148), yoğun bakım süresi (p=0,161) ve mortalite (p=0,668) oranı benzerdi. Grup içi analizlerinde de prone pozisyonunun tip H ve tip L fenotiplerinde mekanik ventilasyon süresi (p=0,302 ve 0,788), yoğun bakım süresi (p=0,493 ve 0,412) ve mortaliteyi (p=0,656 ve 0,125) etkilemediği görüldü.

Çalışmaya dahil edilen tüm hastalarda en sık tercih edilen mekanik ventilatör modunun P-SIMV modu olduğu (%55,3), bu modu sırasıyla havayolu basıncı tahliye ventilasyonu (*airway pressure release ventilation* - APRV) (%23,4), devamlı pozitif hava yolu basıncı (%17) ve hacim-SIMV (%4,3) modlarının takip ettiği görüldü.

APRV modunda uygulanan yüksek basınç düzeyi, çalışma hastalarında ortalama PEEP düzeyini artırdığı ve ortalama PEEP (cmH_2O) [ortalama ± standart sapma (SS)] düzeyinin, 13,08±8,27 olduğu tespit edildi. APRV uygulanan hastalar değerlendirme dışı bırakıldığında, hastaların ortalama PEEP (cmH_2O) (ortalama ± SS) değeri 8,72±2,27 olarak kaydedilmiştir. APRV modunda uygulanan yüksek basınç değeri tüm hastaların ortalama sürüş basıncı (*driving pressure*) değerinin de düşük hesaplanmasına neden olabileceği düşünülmüştür. Hastaların sürüş basıncı (cmH_2O) (ortalama ± SS) düzeyi 15,08±7,35 iken APRV uygulanan hastalar değerlendirme dışı bırakıldığında sürüş basıncı değerinin (cmH_2O) (ortalama ± SS) 18,62±3,60 olduğu görülmüştür. APRV uygulanan hastalar değerlendirme dışı bırakıldığında COVİD-19 ARDS fenotipi açısından uygulanan mekanik ventilatör parametreleri Tablo 3'te özetlenmiştir.

Çalışmaya dahil edilen 47 hastanın ortalama mekanik ventilasyon süresinin (saat) (ortalama ± SS) 204,5±139,2, yoğun bakım süresinin (gün) (ortalama ± SS) 9,6±6,6, mortalite oranının ise %70,2 olduğu görüldü. COVİD-19 ilişkili ARDS fenotipi açısından ortalama mekanik ventilasyon

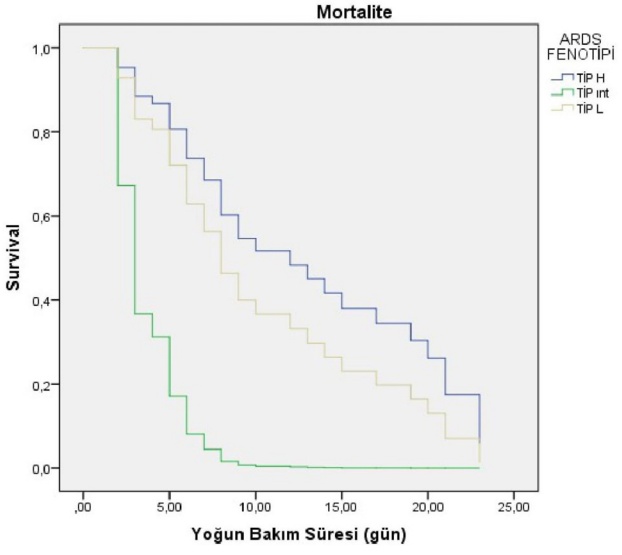


Şekil 1. Hasta seçimini gösteren akış şeması
ARDS: Akut solunum sıkıntısı sendromu, COVİD-19: koronavirüs hastalığı-2019, KOAH: kronik obstrüktif akciğer hastalığı, tip H: tip high, tip L: tip light, tip Int: tip intermediate

sürelerinin (saat) (ortalama ± SS) tip H (218,8±145), tip L (161,4±117,6), tip Int (84±50) (p=0,255); yoğun bakım sürelerinin (gün) (ortalama ± SS) tip H (10,7±7,1), tip L (7,6±4,8), tip Int (3,5±2,1) (p=0,157) ve mortalite (%) oranlarının tip H (70,6), tip L (63,6), tip Int (100) (p=0,583, Şekil 2) benzer olduğu tespit edildi.

COVİD-19 ilişkili ARDS fenotiplerinde, mortalite ile sürüş basıncı düzeyi arasında istatistiksel ilişki yoktu. Ancak, mortalite oranının, APRV uygulanan hastalar değerlendirme dışı bırakıldığında (uygulanan yüksek basıncın, sürüş basıncı düzeyini etkilemesi nedeniyle) sürüş basıncı düzeyi ile ilişkili olduğu görüldü (p=0,023).

Subgrup analizine tip Int (n=2) grubu, hasta sayısının az olması nedeniyle dahil edilmedi. Tip H fenotipe sahip hastalarda mekanik ventilasyon desteğinde uygulanan PEEP (p=0,128), sürüş basıncı (p=0,377), FiO_2 (p=0,233), solunum frekansı (p=0,078) ile mekanik ventilasyon süresi arasında ilişki yoktu. Tip L fenotipe sahip hastalarda da mekanik ventilasyon desteğinde uygulanan PEEP (p=0,407), sürüş basıncı (p=0,291), FiO_2 (p=0,246), solunum frekansı



Şekil 2. Yoğun bakım ünitesinde hasta fenotipleri ve mortalite
ARDS: Akut solunum sıkıntısı sendromu

Tablo 1. COVİD-19 ilişkili ARDS fenotipleri ve hasta özellikleri				
	Tip H (n=34)	**Tip L (n=11)**	**Tip Int (n=2)**	**p**
Yaş (yıl) ortalama ± SS	64,8±11,5	59,3±14,6	67±12,7	0,404
Cinsiyet (kadın) (%)	41,2	81,8	50	0,064
VKİ (kg/m^2) ortalama ± SS	28,4±3,5	24,1±3,9	26,1±5,0	0,042
Sistemik hastalık (%)				
Diabetes mellitus	41,2	54.5	50	0,732
Koroner arter hastalığı	23,5	36.4	-	0,488
Hipertansiyon	55,9	61.6	50	0,882
Kronik böbrek yetmezliği	8,8	-	-	0,542
APACHE-II ortalama ± SS	23,5±10.4	24,1±8,8	36,5±6,3	0,181
SOFA ortalama ± SS	12,8±2.9	10,1±2,1	13,4±5,0	0,127
Cstat (ml/cmH_2O) ± SS	26,2±5.4	93,5±18,6	44,8±4,4	0,000001
PaO_2/FiO_2 ortalama ± SS	134,3±66.1	122,8±48,5	98,6±13,6	0,838
ARDS şiddeti (%)				0,938
Şiddetli	45,5	35,3	50	
Orta	45,5	50	50	
Hafif	9,1	14,7	-	
WBC (mcL) ortalama ± SS	10,5±5,6	11,7±5,3	9,5±2,6	0,760
CRP (mg/L) ortalama ± SS	107,1±87,3	85,1±60,1	104,2±51,9	0,820
D-dimer (ng/mL) ortalama ± SS	2635±2725	4078±4022	1609±1699	0,624
Ferritin (ng/mL) ortalama ± SS	4519±1727	1034±1097	2937±2328	0,261
Prokalsitonin (ng/mL) ortalama ± SS	4,07±13,6	0,55±0,59	0,41±0,03	0,630

COVİD-19: Koronavirüs hastalığı-2019, ARDS: akut solunum sıkıntısı sendromu, SS: standart sapma, APACHE-II: Akut Fizyoloji ve Kronik Sağlık Değerlendirmesi-II, SOFA: Sıralı Organ Yetmezliği Değerlendirmesi, WBC: beyaz kan hücresi, CRP: C-reaktif protein, tip H: tip high, tip L: tip light, tip Int: tip intermediate, PaO_2/FiO_2: parsiyel arterial oksijen basıncı/fraksiyonel inspire oksijen

(p=0,636) ile mekanik ventilasyon süresi arasında ilişki olmadığı tespit edildi. Tip H ve tip L fenotiplerinde yoğun bakım süresi ile PEEP (p=0,135 ve 0,298), sürüş basıncı (p=0,362 ve 0,264), FiO_2 (p=0,117 ve 0,197) ve solunum frekansı (p=0,084 ve 0,454) arasında ilişki gösterilemedi. Mekanik ventilasyon desteği tip H ve tip L fenotiplerinde [(PEEP: p=0,684 ve 0,180), (sürüş basıncı: p=0,133 ve 0,849), (FiO_2: p=0,213 ve 0,487), (solunum frekansı: p=0,646 ve 0,394)] mortaliteyi etkilemedi. Çalışmamızda tüm hastalar için mortaliteyi etkileyen faktörler Tablo 4'te özetlenmiştir. Bu faktörlerin grup içi analizlerinde ise mortaliteyi etkilemediği tespit edildi (p>0,05).

Tartışma

Çalışmamızda her üç fenotipte uygulanan mekanik ventilasyon desteğinin, mekanik ventilasyon süresi, yoğun bakım süresi ve mortalite üzerine etkisinin olmadığı görüldü.

Tip H fenotipe sahip hastalarda istatistiksel olarak anlamlı olmasa da mekanik ventilasyon ve yoğun bakım süresi, tip L ve tip Int'den daha uzundu. Bazı yazarlar tanımlanan bu farklı fenotipleri hastalığın seyri sırasında oluşan akciğer hasarı ile açıklamakta ve tip H'nin aslında tip L'nin ilerlemiş formu olabileceğini öne sürmektedir (6). Tip H fenotipinde görülen uzun mekanik ventilasyon ve yoğun bakım süresi, hastalığın akciğer üzerinde daha uzun süre etki göstermesi nedeni ile açıklanabileceğini düşündürmüştür. Gattinoni ve ark. (10) da COVİD-19 ARDS hastalarında başlangıçta akciğer kompliyansının korunmasına rağmen hipoksi görüldüğünü, hastalığın ilerleyen seyrinde ise hastaların bir kısmında akciğer kompliyansının azalabildiğini bildirmişlerdir. Çalışmamızda tip H fenotipine sahip hastaların daha fazla olduğunu gördük. Bu hastalarımızın ilerleyen dönemde yoğun bakım ünitesine kabulleri sonucu COVİD-19 pnömonisinin tip L'den tip H formuna dönüşme olasılığı nedeniyle meydana gelmiş olabilir.

Tablo 2. ARDS fenotiplerinde mekanik ventilasyon yönetimi ve tıbbi tedavi desteği				
	Tip H (n=34)	**Tip L (n=11)**	**Tip Int (n=2)**	**p**
Mekanik ventilatör modu (%)				0,141
CPAP	27,3	14,7	-	
P-SIMV	18,2	67,6	50	
V-SIMV	9,1	2,9	-	
APRV	45,5	14,7	50	
Mekanik ventilatör parametreleri				
PEEP (cmH_2O) ortalama ± SS	11,5±7,3	16,9±9,8	17,5±10,2	0,344
PS (cmH_2O) ortalama ± SS	13,4±5,7	9±7,9	9,5±10,6	0,271
Pplat (cmH_2O) ortalama ± SS	28,0±3,4	28,0±5,1	30,0±4,3	0,522
DP (cmH_2O) ortalama ± SS	16,5±7,0	11,1±7,6	12,5±3,5	0,118
Frekans/dakika ortalama ± SS	20,0±3,6	20,3±4,8	15,2±5,7	0,221
FiO_2 (%)	63,5±18,8	65,8±28,2	70,8±15,5	0,092
Tıbbi tedavi (%)				
Toculizimab	20,6	9,1	50	0,369
Anakinra	5,9	8,9	-	0,867
İmmün plazma	2,9	-	-	0,823
Prone pozisyon (%)	44,1	27,3	50	0,589

ARDS: akut solunum sıkıntısı sendromu, SS: standart sapma, CPAP: devamlı pozitif hava yolu basıncı, P-SIMV: basınç-senkronize aralıklı zorunlu ventilasyon, V-SIMV: hacim-senkronize aralıklı zorunlu ventilasyon, APRV: havayolu basıncı tahliye ventilasyonu, PEEP: ekspirasyon sonu pozitif basınç, PS: pressure support, Pplat: plato basıncı, FiO_2: fraksiyonel inspire oksijen

Tablo 3. APRV modu hariç ARDS fenotip gruplarında mekanik ventilasyon yönetimi				
	Tip H (n=19)	**Tip L (n=9)**	**Tip Int (n=1)**	**p**
Mekanik ventilatör modu (%)				0,184
CPAP	17,2	50	-	
P-SIMV	79,3	33,3	100	
V-SIMV	3,4	11,7	-	
Mekanik ventilatör parametreleri				
PEEP (cmH_2O) ortalama ± SS	8,7±2,3	8,5±1,9	10	0,790
PS (cmH_2O) ortalama ± SS	15,5±2,9	15,6±3,4	17	0,942
Pplat (cmH_2O) ortalama ± SS	27,7±3,6	25,6±6,1	25	0,562
DP (cmH_2O) ortalama ± SS	19±3,3	17,1±4,4	15	0,346
Frekans/dakika ortalama ± SS	19,6±3,6	20,8±5,1	16	0,435
FiO_2 (%) ortalama ± SS	64,6±20	69,1±27,6	60	0,985

APRV: havayolu basıncı tahliye ventilasyonu, ARDS: akut solunum sıkıntısı sendromu, SS: standart sapma, CPAP: devamlı pozitif hava yolu basıncı, P-SIMV: basınç-senkronize aralıklı zorunlu ventilasyon, V-SIMV: hacim-senkronize aralıklı zorunlu ventilasyon, PEEP: ekspirasyon sonu pozitif basınç, PS: pressure support, Pplat: plato basıncı, FiO_2: fraksiyonel inspire oksijen, DP: sürüş basıncı

2012 Berlin tanımına göre ARDS bilateral akciğer opasiteleri, kardiyojenik bir neden veya aşırı sıvı yüklenmesi ile tam olarak açıklanmayan akut hipoksi (PaO_2/FiO_2 oranı <300 mmHg) durumudur (2). Berlin tanımlamasında ARDS hastalarında akciğer kompliyansı herhangi bir sınıflama için dikkate alınmamaktadır. Ashbaugh ve ark. (11) tarafından 1967 tarihli orijinal ARDS tanımında, incelenen 12 hastanın tümünde akciğer kompliyansı 20 mL/cmH_2O'dan azdı. Yaygın

Tablo 4. Mortalite ilişkili faktörler			
	Olasılık oranı	95% CI	p
APACHE-II ortalama	2,978	1,053-858,659	0,048
SOFA ortalama	1,584	1,136-2,209	0,007
Prokalsitonin (ng/mL) ortalama	2,051	1,011-4,158	0,047
APACHE-II: Akut Fizyoloji ve Kronik Sağlık Değerlendirmesi-II, SOFA: Sıralı Organ Yetmezliği Değerlendirmesi, CI: güven aralığı			

görüş ARDS hastalarında azalmış kompliyans beklentisi olsa da bu netlik kazanamamıştır. Çalışmamızda ortalama Cstat (mL/cmH_2O) (ortalama ± SS)=42,8±30,2 bulunmuş, COVİD-19 ARDS hastalarında yapılan çalışmalar ile benzer olduğu görülmüştür (12-14). Her üç fenotipte de Cstat azalsa da, azalan kompliyans ile PaO_2/FiO_2 oranı arasında anlamı ilişki gösterilememiştir.

Kronik akciğer hastalıkları, ARDS gibi birçok faktör akciğer kompliyansını etkileyebilir (15). Yüksek vücut kitle indeksi (VKİ) bulunan, COVİD-19 ilişkili ARDS'li hastalarda yapılan çalışmalar bu hastaların gerekli tidal volüm ve ventilasyonu sağlayabilmek için daha yüksek basınç desteği, daha yüksek PEEP'ye ihtiyaç duyduğunu ve artan VKİ ile akciğer kompliyansının azaldığı göstermişlerdir (16,17). Demografik veriler ve Cstat karşılaştırıldığında çalışmamızda da tip H fenotipindeki hastaların diğer iki fenotipe göre daha yüksek VKİ'lerinin olduğu görülmüştür.

COVİD-19 ARDS'sinde akciğer hasarı doğrudan viral hasar, trombotik, inflamatuar reaksiyonlar ve konak savunma yanıtı sonrasında gelişmektedir (18). Enflamasyon açısından hiperenflamatuvar ve hipoenflamatuvar ARDS fenotip modelleri de tanımlanmıştır (19). COVİD-19 enflamatuvar alt fenotipleri ile, ARDS kompliyans fenotipleri arasında ilişki olup olmadığı henüz bilinmemektedir. Çalışmamızda enflamasyon belirteçleri olan ve çalışmalarda da mortalite ile ilişkilendirilen (13,20-23) WBC, CRP, ferritin ve D-dimer düzeyleri ile COVİD-19 kompliyans fenotipleri arasında anlamlı ilişki bulunmamıştır. Hastaların klinik takipleri, enflamatuvar belirteçleri doğrultusunda düzenlenen interlökin 1 ve interlökin 6 blokör tedavilerinin de benzer olması, her üç fenotip gelişiminde immün reaksiyon ile ilişki olmadığını düşündürmüştür.

Bilgisayarlı tomografi bulgularına göre üç fenotip tanımlanan [tip 1: Subplevral bölgede fokal tutulum (tip L), tip 2: Homojen olmayan şekilde dağılmış atelektazi ve peribronşiyal opasiteler (tip Int), tip 3: Düzensiz yaygın tutulum (tip H)] COVİD-19 ilişkili ARDS hastalarında, mekanik ventilasyon stratejisinin tip 1 hastalarında 6 mL/kg VT, orta düzey PEEP, tip 2 hastalarında yüksek PEEP, tip 3 hastalarında ise 6 mL/kg tidal volüm ve uygun PEEP stratejisi önerilmiştir (24). Çalışmamızda da ilk kabul sonrası P-SIMV mekanik ventilasyon modunda tüm hastalarımızı koruyucu mekanik ventilasyon stratejisine göre solunum desteği sağladık. Sonraki arter kan gazı PaO_2, $PaCO_2$, pH, SpO_2 değerlerine ve koruyucu mekanik ventilasyon stratejisine göre mekanik ventilatör desteğimizi revize ettik. COVİD-19 ARDS Cstat ilişkili üç alt fenotipte de kan gazı değerlerine göre mekanik ventilatör basınçları, frekans ve FiO_2 (%) ihtiyacı arasında anlamlı fark olmadığını gördük. Her üç fenotipte de mekanik ventilasyon stratejisi sonrası PaO_2/FiO_2 değerine göre prone pozisyon ihtiyacı açısından da anlamlı fark yoktu. Tip H ARDS fenotipli hastalarda istatistiksel olarak anlamlı fark olmasa da diğer iki fenotipe göre APRV modunun daha sık kullanıldığı görüldü. APRV modunda uygulanan yüksek basınç desteği, PEEP ve driving pressure düzeyini etkileyebileceğinden APRV uygulanmayan hastalarda da her üç fenotipte mekanik ventilatör parametreleri arasında istatistiksel fark yoktu.

COVİD-19 ARDS hastalarında koruyucu mekanik ventilasyon stratejisinin mortaliteyi azalttığı ve önceki çalışmalara benzer sürüş basıncı ile mortalite arasında ilişki olduğu gösterilmiştir (8,25,26). Çalışmamızda her üç fenotip için mekanik ventilasyon stratejisi ile mortalite arasında herhangi bir ilişki gösteremesek de tüm çalışma hastalarında önceki çalışmalara benzer şekilde, ancak APRV modu uygulanan hastalar değerlendirme dışı bırakıldığında sürüş basıncı ile mortalite arasında ilişki olduğunu gördük.

Çalışmanın önemli kısıtlılıkları mevcuttur. Çalışma az sayıda hasta ile retrospektif planlanmış ve üç fenotipte hasta sayılarının benzer olmaması çalışmanın istatistiksel olarak gücünü azaltmıştır. Ayrıca hastaların yoğun bakım ünitesine ilk kabul edildikleri mekanik ventilatör değerlerine göre Cstat belirlenmiş ve fenotip sınıflaması yapılmıştır. COVİD-19 ARDS fenotiplendirmesinde tanımlanan ventilasyon perfüzyon oranları ve akciğer ağırlıkları (6) dikkate alınmadan fenotip sınıfları belirlenmeye çalışılmıştır. Elde edilen veriler ile mekanik ventilatör parametrelerinin ilişkisi geriye dönük incelendiğinden standardize edilemez.

Sonuç

Görebildiğimiz kadarıyla çalışmamız haricinde literatürde, COVİD-19 ilişkili ARDS hastalarında akciğer kompliyansını etkileyebilecek diğer nedenleri dışlayarak yapılan kompliyans ve mekanik ventilatör stratejisini inceleyen başka çalışma yoktur. Bu nedenle verilerimizin, COVİD-19 ARDS ilişkili fenotiopler ve mekanik ventilasyon ilişkisini doğru yansıtabileceğini düşünüyoruz. Çalışmamızda her üç fenotipte de mekanik ventilasyon stratejisinin mekanik ventilasyon ihtiyacı, yoğun bakım süresi ve mortalite üzerine anlamlı etkisini gösteremedik. Verilerimiz Surviving Sepsis Campaign panelinde önerilen COVİD-19 ARDS hastalarında mekanik ventilasyon stratejisini desteklemektedir.

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The Effect of Convalescent Plasma Infusion in the Intensive Care Unit on Mortality of COVID-19 Patients: A Retrospective Cohort Study

Yoğun Bakım Ünitesinde Konvelesan Plazma İnfüzyonunun COVİD-19 Hastalarının Mortalitesi Üzerinde Etkisi: Retrospektif Bir Kohort Çalışması

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ABSTRACT *Objective:* This study investigates the effect of convalescent plasma (CP) addition to the standard treatment on mortality in critical coronavirus disease-2019 (COVID-19) patients.
Materials and Methods: This retrospective cohort study was conducted by evaluating the data of 255 critical COVID-19 patients in Marmara University Medical Faculty Hospital, Pandemic Intensive Care Unit (ICU), between April and November 2020.
Results: The patients were divided into two groups, a control group that received standard treatment (153; 60.0%) versus a second group that received CP in addition to standard treatment (102; 40.0%). The ICU mortality rate was found to be lower (p<0.05) in patients receiving CP (38; 37.3%) compared to patients not receiving CP (79; 51.6%). The use of CP was found to reduce the probability of ICU mortality in patients with Acute Physiology and Chronic Health Evaluation-II (APACHE-II) score ≤10 [odds ratio (OR): 0.251; confidence interval (CI) 95%: 0.063-0.994, p=0.049) and APACHE-II score 11-14 (OR: 0.237; CI 95%: 0.066-0.844, p=0.026). CP transfusion, however, did not reduce the mortality in patients with an APACHE-II score of 15 and above. Furthermore, each day of delay in CP transfusion was found to increase the probability of mortality by 1.3 times (OR: 1.369; CI 95%: 1.155-1.622, p<0.001).
Conclusion: The addition of CP to standard treatment in COVID-19 patients followed in ICU reduces mortality.
Keywords: Convalescent plasma, COVID-19, SARS-CoV-2, intensive care unit, mortality

ÖZ *Amaç:* Bu çalışmada yoğun bakım ünitesinde (YBÜ) kritik koronavirüs hastalığı-2019 (COVİD-19) hastalarında standart tedaviye eklenen konvelesan plazma (CP) uygulamasının mortaliteye olan etkisi araştırıldı.
Gereç ve Yöntem: Retrospektif kohort şeklinde planlanan bu çalışma 1 Nisan 2020-1 Kasım 2020 tarihleri arasında Marmara Üniversitesi Tıp Fakültesi Hastanesi, Pandemi YBÜ'de, 255 kritik COVİD-19 hastasının verileri değerlendirilerek gerçekleştirildi.
Bulgular: Hastalar standart tedavi alan hastalar (153; %60,0) ve CP alan hastalar (102; %40,0) olarak 2 gruba ayrıldılar. YBÜ mortalite oranı CP alan hastalarda (38; %37,3), almayanlara göre (79; %51,6) daha düşük bulundu (p<0,05). Akut Fizyoloji ve Kronik Sağlık Değerlendirmesi-II (APACHE-II) skoru ≤10 olan [olasılık oranı (OR): 0,251; güven aralığı (CI) %95: 0,063-0,994, p=0,049)] ve APACHE-II skoru 11-14 olan (OR): 0,237; %95: 0,066-0,844, p=0,026 hastalarda CP tedavisinin YBÜ mortalite olasılığını düşürdüğü belirlendi. APACHE-II skoru 15 ve üzerinde olan hastalarda CP transfüzyonunun mortaliteyi düşürmediği saptandı. Ayrıca CP transfüzyonundaki her bir günlük gecikmenin mortalite olasılığını 1,3 kat arttırdığı (OR: 1,369; CI %95: 1,155-1,622, p<0,001) belirlendi.
Sonuç: YBÜ'de takip edilen COVİD-19 hastalarında standart tedaviye ek olarak CP kullanımı mortaliteyi düşürmektedir.
Anahtar Kelimeler: Konvelesan plazma, COVİD-19, SARS-CoV-2, yoğun bakım ünitesi, mortalite

1. Introduction

Severe acute respiratory syndrome, coronavirus disease-2019 (COVID-19) pandemic caused by coronavirus 2 [severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2)] infection, continues to affect global public health and related healthcare services seriously. More than 376 million confirmed cases and 5,666,064 deaths over 220 countries/regions worldwide reported COVID-19 cases as of February 2022 (1). This number continues to increase rapidly and is expected to threaten more people's daily life, mental and physical health (2).

COVID-19 infection symptoms range from asymptomatic infection, mild to moderate self-limiting respiratory disease to severe progressive pneumonia, multi-organ failure, and death (3,4). Previous studies reported that intensive care unit (ICU) follow-up is required in approximately 14% to 29% of patients who develop COVID-19 pneumonia (5,6). Standard supportive care and various therapeutic strategies ranging from oxygen supplementation and steroid therapy in mild pneumonia to extracorporeal membrane oxygenation (ECMO) in critically ill patients were investigated (4,7). One of the treatment strategies available in this complex and chaotic environment is the infusion of specific antibodies found in recovering patients' plasma to COVID-19 patients (8-12). The use of convalescent plasma in the treatment of other infectious diseases has proven effective; however, it is still under investigation in the context of COVID-19 (13).

The use of CP in the treatment of SARS, Middle East respiratory syndrome (MERS), and H1N1 (2009) patients were reported satisfactory efficacy and safety in the past two decades (13,14). CP transfusion can be a promising treatment for COVID-19 due to the similarities between SARS, MERS, and COVID-19 regarding virological and clinical features (15). Preliminary data from COVID-19 patients reported positive results of CP transfusion (16-18). The United States Food and Drug Administration (FDA) has approved the emergency use of CP for patients with severe or life-threatening COVID-19 (19). CP has a significant potential in the fight against COVID-19, although finding suitable donors, the timing of treatment, and logistical difficulties restrict its use (18,20). Studies investigating the results of CP transfusion in COVID-19 patients have emphasized that its use is beneficial, especially in the early period in hospitalized patients (8,11). However, some have found that it is not effective (9,10,16). Thereby the use of CP in patients followed up in ICU has become controversial. The inability to report the efficacy of CP use can be attributed to the fact that some patients receive it before being admitted to the ICU or patients are admitted to the ICU after the viral replication period has ended. Therefore, studies on the use of CP in COVID-19 patients in ICU are limited (12,17,18).

Complex results and timing of studies investigating the relationship between CP transfusion and the mortality of COVID-19 patients create uncertainty regarding CP's use in treating patients diagnosed with COVID-19 in ICU. Thereby, this study evaluates the effect of CP transfusion in critical COVID-19 patients in the ICU using a standardized approach in a large health center, donor selection, and CP preparation to eliminate this uncertainty.

2. Materials and Methods

2.1. Data Extract Center

This retrospective cohort study was conducted by evaluating the data of COVID-19 patients treated in Marmara University Training and Research Hospital, Pandemic ICU between April 1, 2020, and November 1, 2020.

2.2. Data Collection

The data of patients diagnosed with COVID-19 admitted to the ICU during the study period were collected by scanning the hospital electronic database and patient files.

ICU admission and CP administration, ICU and length of hospital stay, clinical parameters observed during ICU admission, and laboratory results of the patients were screened based on the age, gender, comorbidities, onset of symptoms, and time to hospital admission. The development and stage of acute kidney injury (AKI) according to the AKI criteria determined by Kidney Disease: Improving Global Outcomes, ARDS development, and severity according to the Berlin criteria, Acute Physiology and Chronic Health Evaluation-II (APACHE-II), Sequential Organ Failure Assessment (SOFA) score values calculated in the ICU, treatments (vasoactive drug, antibiotic) and interventions [mechanical ventilation (MV), hemodialysis, plasmapheresis, ECMO], developing secondary infections, duration of MV, and mortality data were evaluated during the ICU follow-up.

2.3. Study Population

The treatment of patients diagnosed with COVID-19 and admitted to the ICU during the study period was planned according to the guidelines published and updated by the Ministry of Health (21).

Requirements for obtaining CP from a recovering patient per guidelines published by the Ministry of Health are as follows: The diagnosis of COVID-19 infection via laboratory test results [polymerase chain reaction (PCR) test positivity studied from nasopharynx swab sample, or serological SARS-CoV-2 antibody positivity]. Clinically (cough, fever, shortness of breath, weakness, etc.) being at least 14 days after recovery, and at least two negative PCR tests studied from nasopharynx swab samples (one of the tests should have been performed within the last 48 hours of the other). Immune plasma donation is accepted from persons with neutralizing anti-SARS-CoV-2 titers 1:80 and above. It is separately labeled and applied as 200 mL divided components by apheresis procedure (22). In patients with expected rapid clinical progression and in patients with poor prognostic parameters, in the presence of tachypnea (respiratory rate >30/min), if the computed tomography findings are compatible with COVID-19 and there is a >50% increase in lung infiltration within 24-48 hours, if SaO_2<90% or PaO_2<70 mmHg was measured despite nasal oxygen support for 5 L/min. or more, if there was a need for vasopressor support, a need for MV, or an increase of at least 2 points in the SOFA score, CP was planned to be performed. Intubation was planned if hypoxemia, dyspnea-tachypnea (>30 breaths/min) continued despite oxygen therapy if accessory respiratory muscles were used (especially sternocleidomastoid) if there was a paradoxical breathing pattern if respiratory alkalosis ($PaCO_2$ <35 mmHg, pH>7.45) was present.

All patients admitted to the ICU with the diagnosis of COVID-19 during the study's planned period were planned to constitute the study sample. Twenty-five thousand one hundred and eighty patients applied to our hospital with the preliminary diagnosis of COVID-19 during the study period. One thousand nine hundred and forty patients diagnosed with COVID-19 were hospitalized. Three hundred and fifty-three patients diagnosed with COVID-19 were admitted to the ICU. It was calculated that at least 116 patients were required for our study with a 95% confidence interval (CI), 80% power, and a planned sample structure of 1/1. A total of 255 patients were included in the study, 102 patients who were followed up in the ICU after the exclusion criteria were applied and CP was transfused, and 153 patients received standard treatment (Figure 1).

2.3.1. Acceptance Criteria

All patients over the age of 18 years who were followed up in the ICU with the diagnosis of COVID-19 were planned to be included in the study.

2.3.2. Exclusion Criteria

Patients whose COVID-19 diagnosis could not be confirmed, ones with multiple ICU admissions, patients referred to an external center, and patients with missing data were excluded from the study.

2.4. Primary Conclusion

The primary objective of the study was to evaluate the effect of CP transfusion added to standard treatment in COVID-19 patients followed in ICU on mortality. The secondary objectives of the study were to evaluate the effect of timing of CP transfusion on mortality in criticaly ill COVID-19 patients and to determine the association of CP use with mortality in patient groups with different disease severity scores.

2.5. Ethical Issues

Institutional permission and ethics committee approval (protocol code: 09.2020.1159, date: 21.01.2021) were obtained from Marmara University Faculty of Medicine Clinical Research Ethics Committee before the research started. The study conforms to the provisions of the 1995 Declaration of Helsinki (as revised in Brazil, 2013).

2.6. Statistical Analysis

The data collected in the study were evaluated with SPSS 22.00 software. Shapiro-Wilk test was used to test the normal distribution of data. Categorical variables were given as frequency (n) and percentage (%), numerical variables as mean ± standard deviation or median and interquartile ranges. Independent samples t-test was used to compare numerical data and the Mann-Whitney U test was used when assumptions of this test could not be met. The chi-square test was used to compare categorical variables and Fisher's Exact test was used when the conditions of the chi-square test could not be met. In patients who underwent CP transfusion, plasma administration day was divided into 4 quarters (4, 5-6, 7-8, ≥9) to determine the relationship between the number of days from the onset of the disease to the administration of convalescent plasma and mortality. In addition, APACHE-II score was divided into 4 quarters (10, 11-14, 15-18, ≥19) to determine the relationship between disease severity and mortality. Logistic regression analysis was used to determine the relationship between the groups and mortality. The significance level was considered as $p<0.05$.

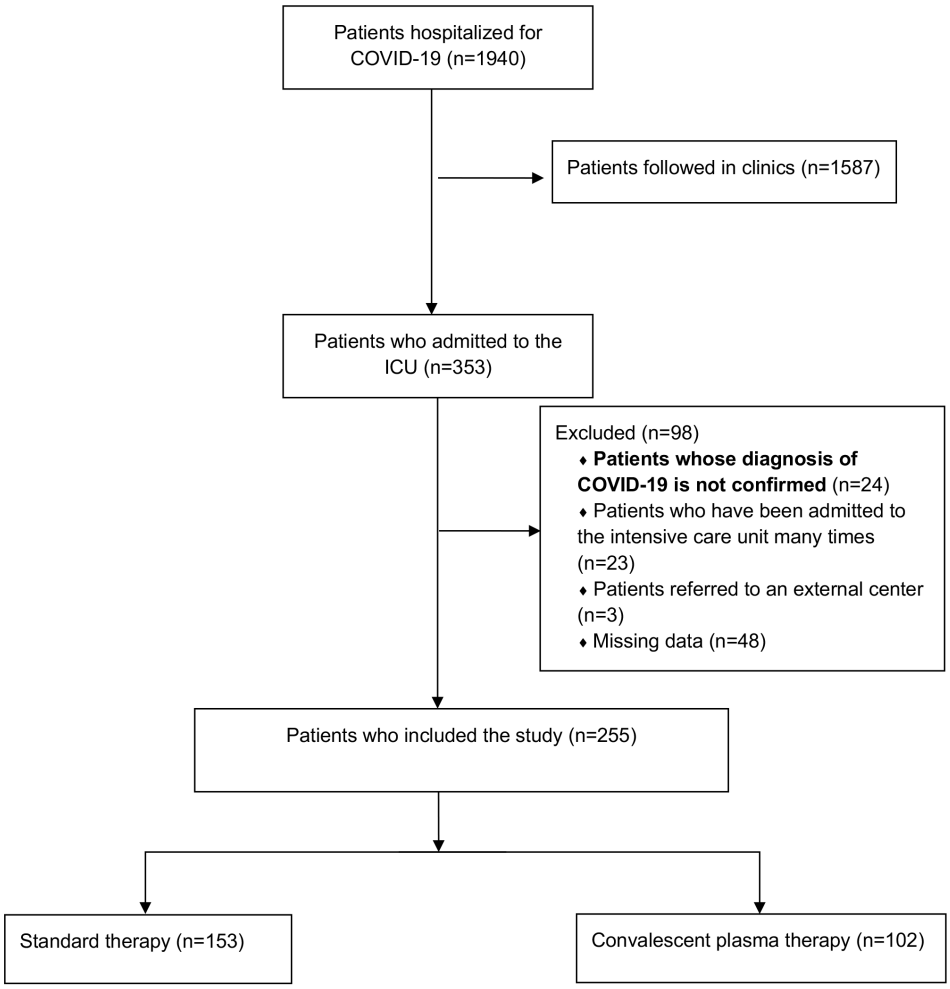

Figure 1. Flow diagram of patients selection
COVID-19: Coronavirus disease-2019, ICU: intensive care unit

3. Results

The general characteristics of the patients are provided in Table 1. The ICU patients were divided into two groups, one that received standard treatment (153; 60.0%) and another that received CP transfusion in addition to the standard treatment (102; 40.0%). Male gender was found to be more common in both groups; gender and age distribution between the two groups were found to be similar. The time from onset of symptoms to hospital admission and admission into ICU were similar in both groups. The prevalence of comorbidities was found to be similar between the two groups. The most common comorbidity was hypertension (HT) in both groups. HT frequency was more common in the group not receiving CP (79; 51.6%) compared to those receiving CP (39; 38.2%) ($p<0.05$). The vast majority of patients in both groups were diagnosed with acute respiratory distress syndrome (ARDS), which was seen in 95.1% (97) of CP receiving patients and 92.8% (142) of non-CP patients. The frequency of mild, moderate, severe ARDS, and PaO_2/FiO_2 ratio of the patients were found to be alike between the groups.

APACHE-II and SOFA scores were found to be alike between the two groups at ICU admission. Heart peak rate and minute respiration rate were higher, while oxygen saturation was lower in the group receiving CP ($p<0.05$). Ferritin, lactate dehydrogenase, and alanine aminotransferase were higher in patients receiving CP. On the other hand, D-dimer, troponin, brain natriuretic peptide, and creatinine were higher in the group not receiving CP when the patients' first laboratory parameters after ICU admission

Table 1. Demographic characteristics and admission symptoms of the patients			
Parameter	**Plasma- 153 (60) n (%) Median (IQR)**	**Plasma+ 102 (40) n (%) Median (IQR)**	**p-value**
Age (years), mean ± SD	64.27±15.21	61.59±14.22	0.158
Gender			0.168
Male	100 (65.4)	75 (73.5)	
Female	53 (36.4)	27 (26.5)	
Duration between symptom-hospital (day)	4 (2-7)	4 (3-6)	0.147
Duration between hospital-ICU (day)	4 (3-8)	4 (2-6)	0.141
Comorbidity	121 (79.1)	70 (68.6)	0.059
Hypertension	79 (51.6)	39 (38.2)	0.036
Diabetes	59 (38.6)	31 (30.4)	0.181
Cardiovascular disease	50 (32.7)	33 (32.4)	0.956
COPD	26 (17.0)	13 (12.7)	0.356
Malignancy	19 (12.4)	8 (7.8)	0.245
CRF	17 (11.1)	5 (4.9)	0.084
Cerebrovascular disease	23 (15.0)	9 (8.8)	0.143
Other	4 (2.6)	6 (5.9)	0.162*
Admission symptom			
Fever	59 (38.6)	54 (52.9)	0.024
Shortness of breath	103 (66.7)	80 (78.4)	0.042
Cough	53 (34.6)	46 (45.1)	0.093
Myalgia-arthralgia	25 (16.3)	23 (22.5)	0.214
Diarrhea	15 (9.8)	16 (15.7)	0.159
Nausea-vomiting	8 (5.2)	10 (9.8)	0.162
Headache	5 (3.3)	9 (8.8)	0.056
Other	9 (5.9)	10 (9.8)	0.243
ARDS	142 (92.8)	97 (95.1)	0.461
Mild ARDS	25 (16.3)	12 (11.8)	0.310
Moderate ARDS	52 (34.0)	39 (38.2)	0.488
Severe ARDS	65 (42.5)	46 (45.1)	0.680
PaO_2/FiO_2	110 (78-182)	120 (80-180)	0.752

IQR: Interquartile range, ICU: intensive care unit, COPD: chronic obstructive pulmonary disease, CRF: chronic renal failure, ARDS: acute respiratory distress syndrome, PaO_2: partial pressure of oxygen, FiO_2: fraction of inspired oxygen, *Fisher's Exact test

were examined (p<0.05). Procalcitonin, C-reactive protein, lymphocyte count, lymphocyte percentage, neutrophil/lymphocyte ratio, fibrinogen, and aspartate aminotransferase levels were found to be homogeneous between the two groups (Table 2).

Fifty-two (51.0%) patients who received CP during ICU follow-up and 108 (70.6%) patients who did not receive CP were mechanically ventilated (p<0.05). There were no differences between the two groups in terms of the duration of MV. High flow nasal cannula, non-invasive MV, and awake prone position frequency were higher in patients receiving CP. On the other hand, intubation prone position frequency was lower in patients not receiving convalescent plasma (p<0.05). Hemodialysis, cytokine filter, ECMO, and stem cell applications were alike in both groups. The drugs administered to the patients were similar in both

Table 2. Clinical and laboratory characteristics of the patients			
Parameter	**Plasma- 153 (60)**	**Plasma+ 102 (40)**	**p-value**
APACHE-II	15 (8-19)	15 (10-18)	0.774
SOFA	6 (4-8)	5 (3-7)	0.053
HR (per min)	97±24	107±23	<0.001
Systolic tension (mmHg)	121 (105-140)	120 (108-139)	0.429
Diastolic tension (mmHg)	68 (60-75)	70 (60-76)	0.761
Respiratory rate (per min)	32 (27-38)	36 (32-40)	<0.001
SpO_2 (%)	92 (88-95)	88 (84-90)	<0.001
Laboratory parameters			
Lymphocyte count (10^3 µL)	0.7 (0.5-1.1)	0.6 (0.4-0.8)	0.055
Lymphocyte (%)	7.0 (3.8-11.1)	6.4 (4.2-11.0)	0.579
Neutrophil/Lymphocyte ratio	12.0 (7.0-22.5)	13.8 (8.0-21.0)	0.333
Procalcitonin (ng/mL)	0.55 (0.16-1.76)	0.31 (0.14-1.30)	0.088
CRP (mg/L)	150 (89-224)	128 (96-195)	0.273
Ferritin (ng/mL)	527 (215-936)	647 (404-1137)	0.024
LDH (U/L)	478 (333-643)	573 (414-711)	<0.001
D-dimer (µg/mL)	1.97 (1.05-3.70)	1.24 (0.69-2.10)	<0.001
Fibrinogen (mg/dL)	591±187	574±171	0.470
Troponin (pg/mL)	33 (14-80)	17 (9-35)	<0.001
proBNP (pg/mL)	1284 (390-5605)	729 (178-1789)	0.002
Creatinine (mg/dL)	1.02 (0.71-1.72)	0.81 (0.63-1.31)	0.017
AST (U/L)	51 (35-81)	56 (37-77)	0.826
ALT (U/L)	33 (18-50)	39 (21-63)	0.021

APACHE-II: Acute Physiology and Chronic Health Evaluation-II, SOFA: Sequential Organ Failure Assessment, HR: heart rate, SpO_2: Peripheral capillary oxygen saturation, CRP: C-reactive protein, LDH: lactate dehydrogenase, proBNP: brain natriuretic peptide, AST: aspartate transaminase, ALT: alanine transaminase

groups, with no significant differences between them. The most commonly administered drug was favipiravir in both groups. Other commonly administered agents were steroids, antibiotics, and tocilizumab (Table 3).

Forty-eight percent of the group receiving CP during ICU follow-up and 49% of the group not receiving CP developed AKI. The proportion of patients who developed AKI and its stages were found to be similar between the two groups. The incidence of secondary infection was 48.0% (49) in the CP group and 59.5% (91) in the non-CP group (p>0.05). The prevalence of pneumothorax, another complication, did not differ significantly between the two groups. Pneumothorax was detected in 4 (3.9%) patients and 13 (8.5%) patients who did not receive CP (Table 3). Rash and redness were reported in 2 (1.96%) patients who underwent CP transfusion. No other adverse effects and no severe complications were observed.

Mortality differed significantly between groups (Table 3). The 28-day mortality rate was lower in patients receiving CP (35; 34.3%) compared to those not receiving CP (73; 47.7%) (p<0.05). Furthermore, the ICU mortality rate was found to be lower (p<0.05) in patients receiving CP (38; 37.3%) compared to those not receiving CP (79; 51.6%). Length of ICU stay did not differ significantly between groups, although the length of hospital stay was longer in patients receiving CP [19 days; (14-17)] compared to patients not receiving CP [16 days (10-24)]. CP treatment was found to reduce the risk of ICU mortality in patients with APACHE-II score ≤10 [odds ratio (OR): 0.251; CI 95%: 0.063-0.994, p=0.049] and APACHE-II score 11-14 (OR: 0.237; CI 95%: 0.066-0.844, p=0.026) as a result of subgroup analyses conducted by dividing the patients into quarters according to APACHE-II score. CP transfusion did not significantly affect mortality probability in patients with APACHE-II score of 15 and above (Table 4).

Table 3. Interventions and treatments administered to the patients, developing complications and mortality			
Parameter	**Plasma- 153 (60) n (%) Median (IQR)**	**Plasma+ 102 (40) n (%) Median (IQR)**	**p-value**
Treatment			
Favipiravir	149 (97.4)	102 (100.0)	0.128*
Steroid	123 (80.4)	87 (85.3)	0.314
Tocilizumab	59 (38.6)	38 (37.3)	0.833
Cytokine hemoadsorption	23 (15.0)	18 (17.6)	0.578
Stem cell	6 (3.9)	1 (1.0)	0.159
Antibiotic	116 (75.8)	71 (69.6)	0.272
Vasopressor	104 (68.0)	51 (50.0)	0.004
Ventilation			
HFNC	31 (20.3)	62 (60.8)	<0.001
Awake prone positioning	34 (22.2)	59 (57.8)	<0.001
NIMV	5 (3.3)	26 (25.5)	<0.001
MV-intubation	108 (70.6)	52 (51.0)	0.002
Prone intubated	21 (13.7)	30 (29.4)	0.002
ECMO	6 (3.9)	6 (5.9)	0.469
Complication			
Seconder infection	91 (59.5)	49 (48.0)	0.072
AKI	75 (49.0)	49 (48.0)	0.878
AKI 1	21 (13.7)	19 (18.6)	0.292
AKI 2	12 (7.8)	12 (11.8)	0.094
AKI 3	42 (27.5)	18 (17.6)	0.071
Hemodialysis	38 (24.8)	19 (18.6)	0.244
Mortality			
Mortality ICU	79 (51.6)	38 (37.3)	0.024
28-day mortality	73 (47.7)	35 (34.3)	0.034
Duration of MV	6 (4-13)	6 (4-11)	0.877
Length of stay in the ICU	8 (5-14)	10 (6-14)	0.116
Length of stay in the hospital	16 (10-24)	19 (14-27)	0.015

IQR: Interquartile range, HFNC: high flow nasal cannula, NIMV: non-invasive mechanical ventilation, MV: mechanic ventilation, ECMO: extracorporeal membrane oxygenation, AKI: acute kidney injury, ICU: intensive care unit, *Fisher's Exact test

A significant relationship was determined between the time from onset of symptoms to plasma therapy and ICU mortality from subgroup analysis of patients receiving CP treatment. It was determined that CP transfusion was performed later in patients with mortality [8 days (6-9)] compared to patients without mortality [6 days (4-7)] (p<0.001). Each day of delay in CP transfusion increases the probability of mortality by 1.3 times according to the analysis obtained (OR: 1.369; CI 95%: 1.155-1.622, p<0.001). It was determined that there was no difference in mortality in the first four days between the patients who received CP treatment (OR: 0.410; CI 95%: 0.094-1.789). The probability of mortality increased approximately 3.5-fold in patients receiving treatment in 7-8 days (OR: 3.492; CI 95%: 1.012-12.051, p=0.048), and the increase in the probability of mortality was 5.6-fold (OR: 5.657, CI 95%: 1.792-17.854, p=0.003) in patients receiving CP treatment in 9 or more days as a result of the subgroup analyses conducted by

Table 4. Relationship between APACHE-II score and transfusion timing with mortality in patients receiving convalescent plasma therapy			
Parameter	**OR**	**CI %95**	**p-value**
APACHE-II score			
APACHE-II ≤10	0.251	0.063-0.994	0.049
APACHE-II 11-14	0.237	0.066-0.844	0.026
APACHE-II 15-18	0.500	0.191-1.310	0.500
APACHE-II ≥19	2.857	0.712-11.462	0.139
CP therapy			
CP therapy day	1.369	1.155-1.622	<0.001
CP subgroups			
CP ≤4 day	References		
CP 5-6 day	0.410	0.094-1.789	0.236
CP 7-8 day	3.492	1.012-12.051	0.048
CP ≥9 day	5.65	1.79-17.85	0.003
OR: Odds ratio, CI: confidence interval, APACHE-II: Acute Physiology and Chronic Health Evaluation-II; CP: convalescent plasma			

dividing the day data starting CP transfusion into quarters (Table 4).

4. Discussion

It was found that CP treatment in COVID-19 patients followed up in ICU reduced mortality in patients with low APACHE-II score (≤10) and had no effect on mortality in critical patients with a high APACHE-II score (≥15). Besides, CP transfusion timing was associated with mortality. It was found to increase in the patients who underwent CP transfusion on the 7th day and after compared to the patients who underwent CP transfusion within the first four days.

The mechanism of action of CP transfusion is well defined. The specific antibodies present in CP bind to the virus and neutralize its virulent activity. The use of virus-neutralizing antibodies reduces viral load and prevents SARS-CoV-2 from entering uninfected cells (23). Thus, CP can suppress the peak viremia within seven days of infection, followed by virus cleansing with the onset of patients' immune response (24). This theoretical basis explains why CP transfusion in the early period of COVID-19 is more effective than late transfusion. Another critical issue in CP activity is the amount of neutralizing antibodies it contains. The use of CP with low antibody levels may cause a weaker response than desired in humoral immunity. US-FDA recommends the measurement of neutralizing antibody titers in CP. A titer of 1:160 is recommended if the measurement is possible. An antibody titer of 1:80 is also indicated to be acceptable if the measurement cannot be performed according to US-FDA. In addition, it is recommended that appropriate donors are selected to obtain effective CP, and CP is collected in licensed blood institutions under standard procedures and regulations for plasma collection (25).

The results of previous studies investigating the relationship between the use of CP and mortality in COVID-19 patients are contradictory (8-12,16,26-28). Some studies have reported a decrease in mortality similar to our results (8,11,16,27), whereas others have reported that CP transfusion is ineffective on mortality (9,10,12). The mortality rate of CP transfused patients was found to decrease by 51% compared to standard treatment in a systematic analysis of CP transfusion in COVID-19 (27). Mortality after 7 and 30 days of CP transfusion was analyzed; it was found that CP transfusion reduced mortality in a large study evaluating the data of patients with severe or life-threatening COVID-19 who received at least one unit of CP transfusion at hospitalization (16). These results support CP efficacy as a therapeutic tool in COVID-19. However, a Cochrane analysis including 20 studies concluded that the effect of CP transfusion on mortality is uncertain contrary to the above results (28). CP transfusion was not found to be superior to placebo in patients diagnosed with COVID-19 pneumonia when the 30-day clinical results were examined in a multicenter study excluding mild and moderate pneumonia cases (10). CP transfusion was not associated with 28-day mortality in another multicenter study involving patients with severe COVID-19 pneumonia (9). These complex results may

have been caused by the lack of standardization and control procedures regarding the donor selection process, the level of antibodies in CP units, the different timing of transfusion, and the severity of the disease in patients. This may even explain the different outcomes seen in similar patient groups.

The optimal timing of CP treatment is unknown (29). It is known to have higher efficacy when transfused early in the course of an infectious disease in the past (30). In agreement with our results, previous results show that each one day delay for CP transfusion increases the probability of mortality in patients by 36%. In agreement with our results, previous results show that each one day delay for CP transfusion increases the probability of mortality in patients by 36%. A meta-analysis study found that COVID-19 patients treated with early CP transfusion were more likely to survive (31). It was concluded in another study that CP reduced mortality in patients who underwent transfusion within 72 hours (11). Another recent study established that CP transfusion within 72 hours in the early stages of COVID-19 reduced the risk of progression to severe respiratory disease by 48% in elderly adult patients (8). A multicenter study conducted in the USA determined that the mortality of patients who received CP transfusion within the first 72 hours was lower than that of patients who underwent later CP transfusion (32). These results indicate that the therapeutic effect of CP transfusion is associated with transfusion timing.

Another parameter affecting the results in patients undergoing CP transfusion is disease severity. The fact that CP transfusion was found to reduce mortality in patients with low APACHE-II scores and not associated with mortality in patients with high scores supports this hypothesis. The results of our study are consistent with previous studies. CP use was associated with clinical improvement in severe cases in a similar study; however, it was not associated with critical patients' mortality (12). A meta-analysis study concluded that mild COVID-19 cases benefited more from CP transfusion when compared to critical cases (31). The advanced pathological process accounts for the lack of CP efficacy in critical cases with high APACHE-II scores (26). The mortality estimation obtained with the APACHE-II score is found to be lower when applied to COVID-19 patients compared to normal ICU patients (33). This can be explained by the fact that Glasgow coma score, an important component of the APACHE-II score, remains high in COVID-19 infection. In COVID-19 patients, the nervous system is typically less affected than the respiratory system (33). Additionally, a study established that neutralizing immunoglobulin G autoantibodies against interferon was not detected in asymptomatic or mild COVID-19 cases but was in 10.2% of critical COVID-19 cases, emphasizing the possibility of potential harm related to CP (34). These autoantibodies may cause a defective type I interferon response, contributing to the severity of the disease. Transfer from donor to critical COVID-19 patient with CP may lead to the exacerbation of the case. The longer ICU stay in patients undergoing CP can be explained by the lower mortality in patients undergoing CP. Low CP mortality may have caused more living patients to stay in the ICU and the ICU stay to be longer in patients who underwent CP.

The study has some limitations such as the implementation of standardized treatment protocols according to the recommendations of the current guidelines published by the Ministry of Health of all patients, the evaluation of factors such as secondary infection that may have an effect on the prognosis, AKI development, and the absence of data loss in the patients included in the study due to the completion of the entire treatment process in our hospital in addition to the strengths of our study. First, it lacks dynamic clinical and laboratory data due to its retrospective design. Furthermore, this retrospective design can inevitably result in some confounding factors (for example, biased patient selection). The data were collected from the electronic health record database. This prevented the possible level of detail with manual medical record review. All of our patients were treated in a single health center from a single geographical region. Therefore, the factors associated with the results may vary in other geographical regions despite the diversity in our patient population. The relationship between the quality of donor plasma and the efficacy of CP treatment could not be evaluated due to the lack of detailed data on neutralizing antibody titer in CP units. The significant difference between the groups in prone positioning, both awake and after intubation, may have affected mortality. The possibility of obesity contributing to death in COVID-19 patients was excluded from the study due to a lack of data on body mass index.

5. Conclusion

The inclusion of CP to the standard treatment in COVID-19 patients with similar demographic and clinical features followed in ICU resulted in reduced mortality compared to

only standard treatment. The use of CP is reliable, and the rate of complications is low. CP efficacy is influenced by the timing of transfusion and the severity of the case. This study concludes that early CP transfusion reduces mortality in critically ill COVID-19 patients.

Ethics

Ethics Committee Approval: Institutional permission and ethics committee approval (protocol code: 09.2020.1159, date: 21.01.2021) were obtained from Marmara University Faculty of Medicine Clinical Research Ethics Committee before the research started.

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Concept: M.S.S., F.G., B.B., S.T.K., B.D.O., İ.C., Design: M.S.S., F.G., B.B., S.T.K., B.D.O., İ.C., Data Collection or Processing: M.S.S., F.G., B.B., S.T.K., B.D.O., İ.C., Analysis or Interpretation: M.S.S., F.G., B.D.O., İ.C., Literature Search: M.S.S., F.G., B.D.O., İ.C., Writing: M.S.S., F.G., B.D.O., İ.C.

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