TÜRK YOĞUN BAKIM DERGİSİ

TURKISH JOURNAL OF INTENSIVE CARE

CİLT / VOLUME 19
ÖZEL SAYI / SUPPLEMENT 1
ARALIK / DECEMBER 2021

TYBD
Türk Yoğun Bakım Derneği
Turkish Society of Intensive Care

E-ISSN: 2602-2974

ÖZGÜN ARAŞTIRMALAR/ORIGINAL RESEARCHES

galenos yayınevi

TURKISH JOURNAL
OF INTENSIVE CARE

CİLT / VOLUME 19
ÖZEL SAYI / SUPPLEMENT 1
ARALIK / DECEMBER 2021

TYBD
Türk Yoğun Bakım Derneği
Turkish Society of Intensive Care

TÜRK YOĞUN BAKIM DERGİSİ

Yazışma Adresi / Correspondence Address

Türk Yoğun Bakım Derneği
İnönü Cad., Işık Apt., No: 53 Kat: 4 Gümüşsuyu, 34437 Taksim, İstanbul, Türkiye
Tel.: +90 212 292 92 70
Faks: +90 212 292 92 71
E-posta: dergi@yogunbakim.org.tr - info@yogunbakim.org.tr
URL: http://www.yogunbakimderg.com

galenos yayınevi

Galenos Publishing House
Owner and Publisher
Derya Mor
Erkan Mor

Publication Coordinator
Burak Sever

Web Coordinators
Fuat Hocalar
Turgay Akpınar

Graphics Department
Ayda Alaca
Çiğdem Birinci
Gülşah Özgül

Finance Coordinator
Sevinç Çakmak

Project Coordinators
Aysel Balta
Duygu Yıldırım
Gamze Aksoy
Gülay Akın
Hatice Sever
Melike Eren
Meltem Acar
Özlem Çelik Çekil
Pınar Akpınar
Rabia Palazoğlu

Research&Development
Melisa Yiğitoğlu
Nihan Karamanlı

Digital Marketing Specialist
Seher Altundemir

Yayınevi İletişim/Publisher Contact
Adres/Address: Molla Gürani Mah. Kaçamak Sk. No: 21/1
34093 İstanbul, Türkiye
Telefon/Phone: +90 (212) 621 99 25
Faks/Fax: +90 (212) 621 99 27
E-posta/E-mail: info@galenos.com.tr/yayin@galenos.com.tr
Web: www.galenos.com.tr
Yayıncı Sertifika No/Publisher Certificate Number: 14521
Online Yayınlanma Tarihi/Online Publication Date: Aralık 2021/December 2021
E-ISSN: 2602-2974

Üç ayda bir yayımlanan süreli yayındır.
International scientific journal published quarterly.

TURKISH JOURNAL
OF INTENSIVE CARE

CİLT / VOLUME 19
ÖZEL SAYI / SUPPLEMENT 1
ARALIK / DECEMBER 2021

TYBD
Türk Yoğun Bakım Derneği
Turkish Society of Intensive Care

TÜRK YOĞUN BAKIM DERGİSİ

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.

Türk Yoğun Bakım Dergisi, **Emerging Sources Citation Index (ESCI), ProQuest Health & Medical Complete, EBSCO Database, Gale, Index Copernicus, CINAHL, Tübitak/Ulakbim, Türk Tıp Dizini, Türkiye Atıf Dizini, Hinari, GOALI, ARDI, OARE, AGORA, J-Gate, IdealOnline** ve **Türk Medline**'da indekslenmektedir.

Açık Erişim Politikası

Dergide açık erişim politikası uygulanmaktadır. Açık erişim politikası Budapest Open Access Initiative (BOAI) http://www.budapestopenaccessinitiative.org/ kuralları esas alınarak uygulanmaktadır.

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.

Abone İşlemleri

Türk Yoğun Bakım Dergisi, Türk Yoğun Bakım Derneği'ne üye olan ve tüm ilgili öğretim elemanlarına ücretsiz olarak dağıtılmaktadır. Derginin tüm sayılarına ücretsiz olarak www.yogunbakim.org.tr adresinden tam metin ulaşılabilir. Dergiye abone olmak isteyen kişiler Türk Yoğun Bakım Derneği'ne başvurmalıdır.

Adres: İnönü Cad. Işık Apt. No: 53 Kat: 4, 34437 İstanbul, Türkiye

Tel. : +90 212 292 92 70

Faks : +90 212 292 92 71

Web sayfası: www.yogunbakim.org.tr

E-posta: dergi@yogunbakim.org.tr - info@yogunbakim.org.tr

Baskı İzinleri

Editör: Prof. Dr. Perihan Ergin Özcan

Adres: İnönü Cad. Işık Apt. No: 53 Kat: 4, 34437 İstanbul, Türkiye

Tel.: +90 212 292 92 70

Faks: +90 212 292 92 71

Web sayfası: www.yogunbakimderg.com

E-posta: dergi@yogunbakim.org.tr - info@yogunbakim.org.tr

Reklam

Reklam ile ilgili başvurular Türk Yoğun Bakım Derneği'ne yapılmalıdır.

Adres: İnönü Cad. Işık Apt. No: 53 Kat: 4, 34437 İstanbul, Türkiye

Tel.: +90 212 292 92 70

Faks: +90 212 292 92 71

Web sayfası: www.yogunbakimderg.com

E-posta: dergi@yogunbakim.org.tr - info@yogunbakim.org.tr

Yayınevi Yazışma Adresi

Galenos Yayınevi Tic. Ltd. Şti.

Adres: Molla Gürani Mah. Kaçamak Sk. No: 21/1 34093 İstanbul, Türkiye

Tel.: +90 212 621 99 25

Faks: +90 212 621 99 27

E-posta: info@galenos.com.tr

Web sayfası: www.galenos.com.tr

Yazarlara Bilgi

Yazarlara Bilgi dergi sayfalarında ve www.yogunbakimderg.com web sayfasında yayınlanmaktadır.

Materyal Sorumluluk Reddi

Türk Yoğun Bakım Dergisi'nde yayınlanan tüm yazılarda görüş ve raporlar yazar(lar)ın görüşüdür ve Editör, Editörler Kurulu ya da yayıncının görüşü değildir; Editör, Editörler Kurulu ve yayıncı bu yazılar için herhangi bir sorumluluk kabul etmemektedir.

TURKISH JOURNAL
OF INTENSIVE CARE

CİLT / VOLUME 19
ÖZEL SAYI / SUPPLEMENT 1
ARALIK / DECEMBER 2021

TYBD
Türk Yoğun Bakım Derneği
Turkish Society of Intensive Care

TÜRK
YOĞUN
BAKIM
DERGİSİ

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.

Turkish Journal of Intensive Care is indexed in **Emerging Sources Citation Index (ESCI), ProQuest Health & Medical Complete, EBSCO Database, Gale, Index Copernicus, CINAHL, Tübitak/Ulakbim Turkish Medical Database, Turkiye Citation Index, Hinari, GOALI, ARDI, OARE, AGORA, J-Gate, IdealOnline** and **Turk Medline**.

Open Access Policy

This journal provides immediate open access to its content on the principle that making research freely available to the public supports a greater global exchange of knowledge.

Open Access Policy is based on rules of Budapest Open Access Initiative (BOAI) http://www.budapestopenaccessinitiative.org/. By "open access" to [peer-reviewed research literature], we mean its free availability on the public internet, permitting any users to read, download, copy, distribute, print, search, or link to the full texts of these articles, crawl them for indexing, pass them as data to software, or use them for any other lawful purpose, without financial, legal, or technical barriers other than those inseparable from gaining access to the internet itself. The only constraint on reproduction and distribution, and the only role for copyright in this domain, should be to give authors control over the integrity of their work and the right to be properly acknowledged and cited.

Subscription

The Turkish Journal of Intensive Care is sent free of charge to the subscribers and to relevant academic members. All published volumes in full text can be reached free of charge through the web site www.yogunbakim.org.tr. Requests for subscription should be addressed to Turkish Society of Intensive Care.

Address: İnönü Cad. Işık Apt. No: 53 Kat: 4, 34437 İstanbul, Turkey

Phone : +90 212 292 92 70

Fax : +90 212 292 92 71

Web page: www.yogunbakim.org.tr

E-mail: dergi@yogunbakim.org.tr - info@yogunbakim.org.tr

Print Permissions

Editor: Prof. Dr. Perihan Ergin Özcan

Address: İnönü Cad. Işık Apt. No: 53 Kat: 4, 34437 İstanbul, Turkey

Phone: +90 212 292 92 70

Fax: +90 212 292 92 71

Web page: www.yogunbakimderg.com

E-mail: dergi@yogunbakim.org.tr - info@yogunbakim.org.tr

Advertisement

Applications for advertisement should be addressed to Turkish Society of Intensive Care.

Address: İnönü Cad. Işık Apt. No: 53 Kat: 4, 34437 İstanbul, Turkey

Phone: +90 212 292 92 70

Fax: +90 212 292 92 71

Web page: www.yogunbakimderg.com

E-mail: dergi@yogunbakim.org.tr - info@yogunbakim.org.tr

Publisher Corresponding Address

Galenos Yayınevi Tic. Ltd. Şti.

Address: Molla Gürani Mah. Kaçamak Sk. No: 21/1 34093 İstanbul, Turkey

Phone: +90 212 621 99 25

Fax: +90 212 621 99 27

Web page: www.galenos.com.tr

E-mail: info@galenos.com.tr

Instructions to Authors

Instructions to authors are published in the journal and on the web page www.yogunbakimderg.com.

Material Disclaimer

The author(s) is (are) responsible from the articles published in the Turkish Journal of Intensive Care. The editor, editorial board and publisher do not accept any responsibility for the articles.

TURKISH JOURNAL
OF INTENSIVE CARE

CİLT / VOLUME 19
ÖZEL SAYI / SUPPLEMENT 1
ARALIK / DECEMBER 2021

TYBD
Türk Yoğun Bakım Derneği
Turkish Society of Intensive Care

TÜRK
YOĞUN
BAKIM
DERGİSİ

YAZARLARA BİLGİ

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.

Türkçe yazılarda Türk Dil Kurumu'nun Türkçe Sözlüğü ve Yazım Kılavuzu temel alınmalıdır.

Yazıların Gönderilmesi

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].

YAZI ÇEŞİTLERİ

Özgün Araştırmalar

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.

TURKISH JOURNAL
OF INTENSIVE CARE

CİLT / VOLUME 19
ÖZEL SAYI / SUPPLEMENT 1
ARALIK / DECEMBER 2021

TYBD
Türk Yoğun Bakım Derneği
Turkish Society of Intensive Care

TÜRK
YOĞUN
BAKIM
DERGİSİ

YAZARLARA BİLGİ

Türkçe yazılarda, yazının İngilizce başlığı da mutlaka yer almalıdır; yabancı dildeki yayınlarda ise yazının Türkçe başlığı da bulunmalıdır.

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.

Gereç ve Yöntem bölümü, çalışmanın tekrar edilebilmesi için yeterli ayrıntılar içermelidir. Kullanılan istatistik yöntemler açık olarak belirtilmelidir.

Bulgular bölümü de çalışmanın tekrar edilebilmesine yetecek ayrıntıları içermelidir.

Tartışma bölümünde, elde edilen bulguların doğru ve ayrıntılı bir yorumu verilmelidir. Bu bölümde kullanılacak literatürün, yazarların bulguları ile direkt ilişkili olmasına dikkat edilmelidir.

Teşekkür mümkün olduğunca kısa tutulmalıdır. Her türlü çıkar çatışması, finansal destek, bağış ve diğer editöryal (istatistik analiz, İngilizce/Türkçe değerlendirme) ve/veya teknik yardım var ise metnin sonunda sunulmalıdır.

Metinde fazla kısaltma kullanmaktan kaçınılmalıdır. Tüm kısaltılacak terimler metinde ilk geçtiği yerde parantez içinde belirtilmelidir. Özette ve metinde yapılan kısaltmalar birbirinden bağımsız olarak ele alınmalıdır. Özet bölümünde kısaltması yapılan kelimeler, metinde ilk geçtiği yerde tekrar uzun şekilleri ile yazılıp kısaltılmalıdırlar.

4) Kaynaklar

Kaynakların gerçekliğinden yazarlar sorumludur.

Kaynaklar metinde geçiş sırasına göre numaralandırılmalıdır. Kullanılan kaynaklar metinde parantez içinde belirtilmelidir.

Kişisel görüşmeler, yayınlanmamış veriler ve henüz yayınlanmamış çalışmalar bu bölümde değil, metin içinde şu şekilde verilmelidir: [isim(ler), yayınlanmamış veri, 19...].

Kaynaklar listesi makale metninin sonunda ayrı bir sayfaya yazılmalıdır. Altıdan fazla yazarın yer aldığı kaynaklarda 6. isimden sonraki yazarlar için "et al" ("ve ark") kısaltması kullanılmalıdır. Dergi isimlerinin kısaltmaları Index Medicus'taki stile uygun olarak yapılır. Tüm referanslar Vancouver sistemine göre aşağıdaki şekilde yazılmalıdır.

a) Standart Makale: Intiso D, Santilli V, Grasso MG, Rossi R, Caruso I. Rehabilitation of walking with electromyographic biofeedback in foot-drop after stroke. Stroke 1994;25:1189-92.

b) Kitap: Getzen TE. Health economics: fundamentals of funds. New York: John Wiley & Sons; 1997.

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.

Birden fazla editör varsa: editors.

d) Toplantıda Sunulan Makale: Bengtsson S, Solheim BG. Enforcement of data protection, privacy and security in medical informatics. In: Lun KC, Degoulet P, Piemme TE, Reinhoff O, editors. MEDINFO 92. Proceedings of the 7th World Congress on Medical Informatics; 1992 Sep 6-10; Geneva, Switzerland. Amsterdam: North-Holland; 1992. p. 1561-5.

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.

f) Tez: Kaplan SI. Post-hospital home health care: the elderly access and utilization (thesis). St. Louis (MO): Washington Univ; 1995.

5) Tablolar, Grafikler, Şekiller, Resimler

Tüm tablolar, grafikler veya şekiller ayrı bir kağıda basılmalıdır. Her birine metinde geçiş sırasına göre numara verilmeli ve kısa birer başlık yazılmalıdır. Kullanılan kısaltmalar alt kısımda mutlaka açıklanmalıdır. Özellikle tablolar metni açıklayıcı ve kolay anlaşılır hale getirme amacı ile hazırlanmalı ve metnin tekrarı olmamalıdır. Başka bir yayından alıntı yapılıyorsa yazılı baskı izni birlikte yollanmalıdır. Fotoğraflar parlak kağıda basılmalıdır. Çizimler profesyonellerce yapılmalı ve gri renkler kullanılmamalıdır.

Özel Bölümler

1) Derlemeler: Dergiye derlemeler editörler kurulu daveti ile kabul edilmektedir. Derginin ilgi alanına giren derlemeler editörlerce değerlendirilir.

2) Olgu Sunumları: Nadir görülen ve önemli klinik deneyimler sunulmalıdır. Giriş, olgu ve tartışma bölümlerini içerir.

3) Editöre Mektuplar: Bu dergide yayınlanmış makaleler hakkında yapılan değerlendirme yazılarıdır. Editör gönderilmiş mektuplara yanıt isteyebilir. Metnin bölümleri yoktur.

Yazışma Adresi

Tüm yazışmalar dergi editörlüğünün aşağıda bulunan posta veya e-posta adresine yapılabilir.

Türk Yoğun Bakım Derneği

Adres: İnönü Cad. Işık Apt. No: 53 Kat: 4, 34437 İstanbul, Türkiye

Tel.: +90 212 292 92 70

Faks: +90 212 292 92 71

Web sayfası: www.yogunbakimderg.com

E-posta: dergi@yogunbakim.org.tr

info@yogunbakim.org.tr

TURKISH JOURNAL
OF INTENSIVE CARE

CİLT / VOLUME 19
ÖZEL SAYI / SUPPLEMENT 1
ARALIK / DECEMBER 2021

TYBD
Türk Yoğun Bakım Derneği
Turkish Society of Intensive Care

TÜRK
YOĞUN
BAKIM
DERGİSİ

INSTRUCTIONS TO AUTHORS

Turkish Journal of Intensive Care is the periodical of the Turkish Society of Intensive Care. The journal is an independent, peer-reviewed international, published quarterly in April, August, December.

Submitted manuscripts to Turkish Journal of Intensive Care are subjected for double-blind peer-review. The journal publishes articles in Turkish and English languages.

The abbreviation of the Turkish Journal of Intensive Care is "Turk J Intensive Care". It should be denoted as it when referenced.

It publishes original experimental and clinical researches, case reports, invited reviews, editorial comments, letters to editor on topics related to intensive care, and poster abstracts presented in national intensive care congresses/meetings. The scientific board guiding the selection of the papers to be published in the journal consists of elected experts of the journal and if necessary, selected from national and international authorities.

Turkish Language Institution dictionary and orthography guide should be taken as basic for literary language for Turkish manuscripts.

Submission of Manuscripts

Turkish Journal of Intensive Care does not charge any article submission or processing charges.

Manuscripts can only be submitted electronically through the web site http://www.journalagent.com/tybdd/ after creating an account. This system allows online submission and review.

The ORCID (Open Researcher and Contributor ID) number of the correspondence author should be provided while sending the manuscript. A free registration can be done at http://orcid.org

The manuscripts are archived according to International Committee of Medical Journal Editors (ICMJE), Index Medicus (Medline/PubMed) and Ulakbim-Turkish Medicine Index rules. Rejected manuscripts, except artwork are not returned.

In clinical trials in which the approval ethics committee is prerequisite, the certificate of approval (including approval number) will be requested by the editor/assistant editors.

The authors should guarantee that their manuscript has not been published and/or is under consideration for publication in any other periodical. Only those data presented at scientific meetings in form of abstracts that does not exceed 200 words could be accepted for consideration if notification of the scientific conference is made. The signed statement of scientific contributions and responsibilities of all authors, and statement on the absence of conflict of interests are required.

Patients have a right to privacy. Identifying information, including the patients' names should not be published in written descriptions, and photographs, unless the information is scientifically essential and the patient (or parent or guardian) gives written informed consent for publication.

Identifying the patient details should be omitted if they are not essential. Complete anonymity is difficult to achieve, however, informed consent should be obtained if there is any doubt. For example, covering eyes with a band in the photographs is not sufficient to ensure confidentiality.

Authors should indicate in manuscript that the procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964, revised 2013. In experimental animal studies the authors should indicate that the procedures followed were in accordance with animal rights (Guide for the care and use of laboratory animals. www.nap.edu/catalog/5140.html) and obtain animal ethics committee approval. The approval of the ethics committee and the fact that informed consent was given by the patients should be indicated in the Materials and Methods section.

The scientific and ethical liability of the manuscripts belongs to the authors and the copyright of the manuscripts belongs to the Turkish Journal of Intensive Care. Authors are responsible for the contents of the manuscript and accuracy of the references. All manuscripts submitted for publication must be accompanied by the Copyright Transfer Form [copyright transfer]. Once this form, signed by all the authors, has been submitted, it is understood that neither the manuscript nor the data it contains have been submitted elsewhere or previously published and authors declare the statement of scientific contributions and responsibilities of all authors.

The Review Process

All manuscripts submitted to the Turkish Journal of Intensive Care are screened for plagiarism using the 'iThenticate' software. Results indicating plagiarism may result in manuscripts being returned or rejected.

All manuscripts are reviewed by editor, related associate editor and at least two experts/referees. The authors of the accepted manuscript for publication should be in consent of that the editor and the associate editors can make corrections without changing the main text of the paper.

Manuscripts format should be in accordance with Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication (available at http://www.icmje.org/)

In case of any suspicion or claim regarding scientific shortcomings or ethical infringement, the Journal reserves the right to submit the manuscript to the supporting institutions or other authorities for investigation. The Journal accepts the responsibility of initiating action but does not undertake any responsibility for an actual investigation or any power of decision.

The Editorial Policies and General Guidelines for manuscript preparation specified below are based on "Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals (ICMJE Recommendations)" by the International Committee of Medical Journal Editors (2016, archived at http://www.icmje.org/).

Preparation of research articles, systematic reviews and meta-analyses must comply with study design guidelines:

CONSORT statement for randomized controlled trials (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/);

PRISMA statement of preferred reporting items for systematic reviews and meta-analyses (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/);

STARD checklist for the reporting of studies of diagnostic accuracy (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/);

STROBE statement, a checklist of items that should be included in reports of observational studies (http://www.strobe-statement.org/);

MOOSE guidelines for meta-analysis and systemic reviews of observational studies (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).

MANUSCRIPT TYPES

Original Researches

Manuscript should not exceed 5000 words. All pages of manuscript should be numbered at right top corner except the title page. In order to be comprehensible, papers should include sufficient number of tables and figures.

TURKISH JOURNAL
OF INTENSIVE CARE

CİLT / VOLUME 19
ÖZEL SAYI / SUPPLEMENT 1
ARALIK / DECEMBER 2021

TYBD
Türk Yoğun Bakım Derneği
Turkish Society of Intensive Care

TÜRK
YOĞUN
BAKIM
DERGİSİ

INSTRUCTIONS TO AUTHORS

The style for title page, references, figures and tables should be unique for all kind of articles published in this journal.

1) Title Page (Page 1)

This page should include the titles of the manuscript, knowledge about author(s), key words and running titles.

English title should take place for every article in the title page. Likely, Turkish title should be mentioned for articles in foreign language.

Turkish and English key words and running titles should also be included in the title page.

The names and full postal addresses (including institutions addresses) of authors and the author to whom correspondence is to be addressed should be indicated separately. Especially as e-mail addresses will be used for communication, e-mail address of the corresponding author should be stated. In addition, telephone and fax numbers must be notified.

If the content of the paper has been presented before, the time and place of the conference should be denoted.

If there are any grants and other financial supports by any institutions or firms for the study, information must be provided by the authors.

2) Summary (Page 2)

In the second page, Turkish and English summaries of the manuscript (maximum 200 words for each), and the key words should take place.

The summary consists of the following sections separately: Objective, Materials and Methods, Results, Conclusion. Separate sections are not used in the summaries for the review articles, case reports and educational articles. For these articles, the summaries should not exceed 200 words and briefly present the scope and aims of the study, describe the salient findings and give the conclusions.

The references should not be cited in the summary section. As far as possible, use of abbreviations are to be avoided. If any abbreviations are used, they must be taken into consideration independently of the abbreviations used in the text.

3) Text (According to the length of the summaries Page 3 or 4 and etc.)

The typical main headings of the text are as follows: Introduction, Materials and Methods, Results, Discussion.

The introduction, part should include the rationale for investigation and the background of the present study. Results of the present study should not be discussed in introduction part. Materials and methods section should be presented in sufficient detail to permit the repetition of the work. The statistical tests used should be stated. Results should also be given in detail to allow the reproduction of the study.

Discussion section should provide a thorough interpretation of the results. It is recommended that citations should be restricted to those which relate to the findings of the authors.

Acknowledgements should be as brief as possible. Any technical or financial support or editorial contributions (statistical analysis, English/Turkish evaluation) towards the study should appear at the end of the article.

The excessive use of abbreviations is to be avoided. All abbreviations should be defined when first used by placing them in brackets after the full term. Abbreviations made in the abstract and text are separately taken into consideration. Abbreviations of the full terms that are made in the abstract must be re-abbreviated after the same full term in the text.

4) References

Accuracy of reference data is the author's responsibility. References should be numbered according to the consecutive citation in the text. References should be indicated by parenthesis in the text.

Personal communications, unpublished observations, and submitted manuscripts must be cited in the text as "(name(s), unpublished data, 19...)".

The reference list should be typed on a separate page at the end of the manuscript and if there are more than 6 authors, the rest should be written as 'et al' or 've ark.' Journal titles should be abbreviated according to the style used in the Index Medicus. All the references should be written according to the Vancouver system as follows:

a) Standard Journal Article: Intiso D, Santilli V, Grasso MG, Rossi R, Caruso I. Rehabilitation of walking with electromyographic biofeedback in foot-drop after stroke. Stroke 1994;25:1189-92.

b) Book: Getzen TE. Health economics: fundamentals of funds. New York: John Wiley & Sons; 1997.

c) Chapter of a Book: 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.

If more than one editor: editors.

d) Conference Papers: Bengtsson S, Solheim BG. Enforcement of data protection, privacy and security in medical informatics. In: Lun KC, Degoulet P, Piemme TE, Reinhoff O, editors. MEDINFO 92. Proceedings of the 7th World Congress on Medical Informatics; 1992 Sep 6-10; Geneva, Switzerland. Amsterdam: North-Holland; 1992. p. 1561-5.

e) Journal on the Internet (e-Publishing): 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.

f) Thesis: Kaplan SI. Post-hospital home health care: the elderly access and utilization (thesis). St. Louis (MO): Washington Univ; 1995.

5) Tables, Graphics, Figures, and Pictures

All tables, graphics or figures should be presented on a separate sheet. All should be numbered consecutively and a brief descriptive caption should be given. Used abbreviations should be explained further in the figure's legend. Especially, the text of tables should be easily understandable and should not repeat the data of the main text. Illustrations that already published are acceptable if supplied by permission of authors for publication. Photographs should be printed on glossy paper. Figures should be done professionally and no gray colors be used.

Special Parts

1) Reviews: The reviews within the scope of the journal will be taken into consideration by the editors; also the editors may solicit a review related with the scope of the journal from any authorized person in the field.

2) Case Reports: Case reports should present important and unique clinical experience. It consists of the following parts: Introduction, case, discussion.

3) Letters to the Editor: Views about articles published in this journal. The editor invites responses to letters as appropriate. Letters may be shortened or edited. There are no separate sections in the text.

Address for Correspondence

All correspondences can be done to the following postal address or to the following e-mail address, where the journal editorial resides:

Türk Yoğun Bakım Derneği

Address: İnönü Cad. Işık Apt. No: 53 Kat: 4, 34437 İstanbul, Turkey

Phone: +90 212 292 92 70

Fax: +90 212 292 92 71

Web page: www.yogunbakimderg.com

E-mail: dergi@yogunbakim.org.tr

info@yogunbakim.org.tr

TURKISH JOURNAL
OF INTENSIVE CARE

CİLT / VOLUME 19
ÖZEL SAYI / SUPPLEMENT 1
ARALIK / DECEMBER 2021

TYBD
Türk Yoğun Bakım Derneği
Turkish Society of Intensive Care

TÜRK
YOĞUN
BAKIM
DERGİSİ

İÇİNDEKİLER/CONTENTS

ÖZGÜN ARAŞTIRMALAR / ORIGINAL RESEARCHES

TURKISH JOURNAL
OF INTENSIVE CARE

CİLT / VOLUME 19
ÖZEL SAYI / SUPPLEMENT 1
ARALIK / DECEMBER 2021

TYBD
Türk Yoğun Bakım Derneği
Turkish Society of Intensive Care

TÜRK
YOĞUN
BAKIM
DERGİSİ

İÇİNDEKİLER/CONTENTS

Turk J Intensive Care 2021;19(Suppl 1):1-7
DOI: 10.4274/tybd.galenos.2021.41736

ORIGINAL RESEARCH / *ÖZGÜN ARAŞTIRMA*

Ayşe Vahapoğlu,
Döndü Genç Moralar,
Ferhat Çengel,
Zuhal Çavuş,
Ülkü Aygen Türkmen

Evaluating the Correlation Between Thoracic Ultrasound and Thoracic Computed Tomography Scores of Patients with Severe COVID-19 Pneumonia Receiving Intensive Care

Yoğun Bakımda Şiddetli COVID-19 Pnömonili Hastalarda, Toraks Ultrason ve Toraks Bilgisayarlı Tomografi Skorlamaları Arasındaki Korelasyonun Değerlendirilmesi

Received/Geliş Tarihi : 19.10.2020
Accepted/Kabul Tarihi : 20.01.2021

Ayşe Vahapoğlu, Döndü Genç Moralar, Zuhal Çavuş, Ülkü Aygen Türkmen
University of Health Sciences Turkey, Gaziosmanpaşa Training and Research Hospital, Clinic of Anaesthesiology and Reanimation, İstanbul, Turkey

Ferhat Çengel
University of Health Sciences Turkey, Gaziosmanpaşa Training and Research Hospital, Clinic of Radiology, İstanbul, Turkey

Ayşe Vahapoğlu MD, (✉),
University of Health Sciences Turkey, Gaziosmanpaşa Training and Research Hospital, Clinic of Anaesthesiology and Reanimation, İstanbul, Turkey

E-mail : aysevahapoglu@yahoo.com
Phone : +90 505 819 47 64
ORCID ID : orcid.org/0000-0002-6105-4809

ABSTRACT *Objective:* The coronavirus disease-2019 (COVID-19) pandemic has turned into a global health issue in a short time because of its increasing mortality and high infection rate. Since thoracic computed tomography (CT) cannot be performed and it is not possible to transfer COVID-19 patients followed-up in the intensive care unit (ICU), follow-up, and diagnosis using lung ultrasound (LUS) has been highly advantageous nowadays. The aim of this study was to assess the correlation between the thoracic CT score and LUS score and to determine their association with mortality.

Materials and Methods: Patients admitted to the ICU, diagnosed to have COVID-19 pneumonia, underwent an initial thoracic CT examination and who underwent LUS during admission to the ICU were included in the study. The clinical parameters, demographic characteristics, prognosis, LUS, and thoracic CT scores of the patients were recorded prospectively. The survivors and deceased patients' demographic characteristics were compared.

Results: The mean age of the 29 patients included in this study was 61.93±14.21 years, and the male-to-female ratio was 18/11 (62.1%/37.9%). A strong positive correlation was between the thoracic CT score and LUS score (r=0.964; p<0.001). The thoracic CT and LUS scores of the survivors were 15.5±2.7 and 27.3±4.9, respectively, while those of the deceased patients were 14.1±3.4 and 25.6±5.8, respectively, and the two groups found no significant difference.

Conclusion: A strong positive correlation was found between the thoracic CT score and LUS score of COVID-19 patients admitted to the ICU. This result shows that LUS is easily preferred for patients who require imaging for diagnosis and follow-up under intensive care conditions. The mortality rates of COVID-19 patients could not be predicted by either thoracic CT score or LUS score.
Keywords: Critical care, COVID-19 pneumonia, computed tomography, lung ultrasound

ÖZ *Amaç:* Koronavirüs hastalığı-2019 (COVID-19) pandemisi, artan mortalite ve yüksek enfeksiyon oranı nedeniyle hızlı bir şekilde küresel bir sağlık sorununa dönüşmüştür. Bilgisayarlı tomografisi (BT) yapılamadığı ve yoğun bakımda takip edilen COVID-19 hastalarının transferinin mümkün olmadığı için akciğer ultrasonu (LUS) ile takip ve tanı günümüzde oldukça avantajlı hale gelmiştir. Bu çalışmanın amacı torasik BT skoru ile LUS skoru arasındaki ilişkiyi değerlendirmek ve mortalite ile ilişkisini tespit etmektir.

Gereç ve Yöntem: Yoğun bakım ünitesine (YBÜ) kabul edilen, COVID-19 pnömonisi tanısı alan, ön toraks BT incelemesi yapılan ve YBÜ'ye kabul sırasında LUS yapılan hastalar çalışmaya dahil edilmiştir. Hastaların klinik parametreleri, demografik özellikleri, prognozu, LUS ve toraks BT skorları prospektif olarak kaydedilmiştir. Hayatta kalanlar ve ölen hastaların demografik özellikleri karşılaştırılmıştır.

Bulgular: Bu çalışmaya dahil edilen 29 hastanın yaş ortalaması 61,93±14,21 yıl ve erkek-kadın oranı 18/11 (%62,1/37,9) idi. Torasik BT skoru ile LUS skoru arasında güçlü bir pozitif korelasyon vardı

(r=0,964; p<0,001). Sağ kalanların torasik BT ve LUS skorları sırasıyla 15,5±2,7 ve 27,3±4,9 iken, ölen hastalarınki sırasıyla 14,1±3,4 ve 25,6±5,8 idi ve iki grup arasında anlamlı bir fark bulunmamıştır.
Sonuç: YBÜ'ye yatırılan COVID-19 hastalarının torasik BT skoru ile LUS skoru arasında güçlü pozitif korelasyon bulunmuştur. Bu sonuç, yoğun bakım koşullarında tanı ve takip için görüntüleme gerektiren hastalarda LUS'nin rahatlıkla tercih edildiğini göstermektedir. COVID-19 hastalarının ölüm oranları ne torasik BT skoru ne de LUS skoru ile tahmin edilememiştir.
Anahtar Kelimeler: Yoğun bakım, COVID-19 pnömoni, bilgisayarlı tomografi, akciğer ultrasonu

Introduction

The world currently faces a pandemic that is rapidly spreading due to complications in the respiratory system that results in pneumonia, caused by a new coronavirus (severe acute respiratory syndrome coronavirus 2) and called coronavirus disease-2019 (COVID-19) in 2019 (1). It is estimated that 5 to 10% of the infected cases need critical care 15 to 20% of them have severe pneumonia (2).

Imaging modalities mainly help diagnos and manage COVID-19 suspected patients (3). Chest radiograph displays low-density pneumonia foci (viral pneumonia), most of which involve bilateral mid-lower zones in this disease. However, chest X-ray shows low the sensitivity (30-60%) (4), and pneumonia is not excluded by normal chest radiograph (1). It has been proven that computed tomography (CT) findings can diagnose most of the cases with screening test of an initial false-negative reverse transcriptase-polymerase chain reaction (RT-PCR) (5-7). COVID-19 patients present with bilateral multilobar ground-glass opacification, crazy-paving pattern and consolidation etc. with a peripheral distribution (8). Although CT is a highly sensitive and specific imaging technique, it has some disadvantages, especially for critically ill patients who are monitored in intensive care. The transfer of a COVID-19 patient from the intensive care unit (ICU) for CT, who is monitored in invasive mechanical ventilation (IMV), has drawbacks both in terms of the spread of infection and the patients' exposure to ionized radiation due to the patient's critical condition. The CT scanner needs to be thoroughly cleaned after each suspected case of COVID-19, to prevent the spread of the infection to other patients and healthcare staff (9).

Lung ultrasound (LUS), which is currently used as a diagnostic tool in emergency departments (1), is a promising imaging tool for COVID-19, considering both the peripheral involvement of the lung and the disadvantages of CT and plain radiograph (8). This imaging modality is quick, portable, easy to learn, repeatable, with high inter-rater and intra-rater reproducibility (10). Due to its ease of use at the bedside (11), it can also be guiding in the management of the disease and follow-up in patients having a high mortality risk who are monitored with IMV (12) in the intensive care unit. Although COVID-19 patients receiving invasive ventilation will often have non-recruitable lung lesions early on, recruitable lesions may develop later in the disease course (9). LUS could titrate ventilator settings in positive end-expiratory pressure (PEEP) -induced lung recruitment, and also facilitates successful weaning from mechanical ventilation (12). Its easy repeatable can also be useful in the early diagnosis of complications. this study evaluated the correlation between the baseline LUS score and CT score of severe COVID-19 patients who were followed up in the ICU was determined as the primary end point and its correlation with mortality was determined as the secondary end point.

Materials and Methods

Patients

The study was approved by the Clinical Research Ethics Committee of Gaziosmanpaşa Training and Research Hospital (decision no: 87, date: 28.05.2020). Written informed consent was obtained from the patients to be included in the study and/or their relatives. The study was conducted prospectively between June 2020 and July 2020. The inclusion criteria were as follows: among patients and/or their relatives those who gave written consent, who were over 18 years of age, hospitalized in intensive care with a diagnosis of COVID-19 pneumonia, had a definite diagnosis by PCR, had an initial thorax CT examination, and underwent LUS at admission to intensive care. The exclusion criteria were as follows: patients under 18 years of age who did not give written consent, had no definitive diagnosis by PCR, previous lung resection, no thorax CT and LUS at admission to intensive care. Thorax CT scoring was performed by an experienced radiologist, while LUS scoring was performed an experienced anesthesia and reanimation specialist. The demographic characteristics, clinical parameters, prognosis, thorax CT and LUS scores of the patients were recorded

prospectively. The correlation between thorax CT score and LUS score was evaluated.

Radiological Evaluation

LUS Score

An intensive care specialist experienced in this field performed LUS using a 2- to 5-MHz transducer (Esaote MyLabSeven, Getz Healthcare Malaysia). A probe cover was used to cover the transducer, and disinfectant wipes were used to clean the ultrasound device and transducer after each use. LUS examinations were performed in the supine position at the bedside, and twelve-zone examinations were performed. Each hemithorax is separated into 6 quadrants: lateral, posterior, and anterior zones (separated by the anterior and posterior axillary lines) each divided in lower and upper portion (Figure 1). the LUS pattern was used to score each zone as follows: the presence of lung sliding with A-lines or below two isolated B-lines, scored 0; when multiple well-defined B-lines presented, scored 1; the presence of multiple coalescent B-lines, scored 2; the presence of a tissue pattern characterized by dynamic air bronchograms (lung consolidation), scored 3. The sum of the scores was calculated by recording and using the worst ultrasound pattern found in each zone (total score =36).

CT Technique and Image Interpretation

The low dose protocol of our hospital with a 128-slice multi-detector CT scanner (Optima; General Electric Healthcare, Wisconsin, USA) was used to obtain the thorax CT scans in the study. All CT scans were performed during a single breath-hold without contrast administration. A radiologist with 9-year experience in interpreting thorax CT imaging (FC), on a PACS imaging workstation reviewed all CT images (Infinitt PACS; Infinitt Healthcare, Seoul, Korea).

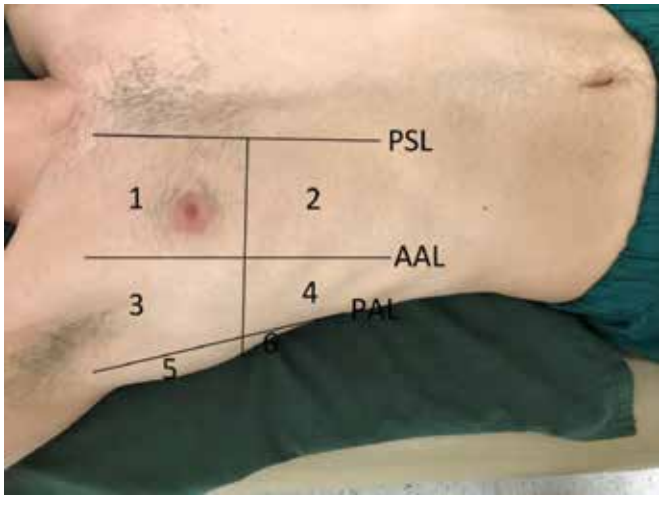


Figure 1. Chest segments in lung ultrasound
AAL: Anterior axillary line, PAL: posterior axillary line, PSL: parasternal line

As in the ultrasound evaluation, we divided each lung into lateral, anterior, and posterior quadrants based on the posterior and anterior axillary lines, and then each quadrant was divided into lower and upper sections. Each quadrant was scored 0-3. Score 0 indicated no parenchymal involvement, score 1 indicated parenchymal involvement rate between 0 and 33%, score 2 indicated parenchymal involvement rate between 33% and 66%, and score 3 indicated parenchymal involvement rate above 66%.

Statistical Analysis

SPSS statistical software package (SPSS, version 17.0 for windows) was used for the statistical analyses and G-power 3 for MacOs program was used for power analysis. Intergroup power analysis between more than two independent groups was performed priori based on the Pearson correlation one tail test, (q: 0.8; power: 0.8; alpha error: 0.05). In order for the total sample size to generate 0.8 power, a total of 46 data [thorax ultrasonography (USG) and thorax CT] of 23 patients were planned to be included in the study, the distribution of parameters is homogeneous or not was checked with the Kolmogorov-Smirnov test. Parametric tests were used for the data with homogeneous distribution, while nonparametric tests were used for the data with non-normally distribution. Pearson's correlation test was used to determine whether there is a significant relationship between CT score and LUS score. Results were given as mean ± standard deviation. We considered A p-value of below 0.05 as statistically significant.

Results

The study included 29 patients with thorax CT and LUS at intensive care admission. The mean age of the patients was 61.93±14.21 years, 37% of them were female. The patients' demographic characteristics are given in Table 1. Of the 29 patients, 13 died in intensive care. There was no significant difference between the mean age of survived and dead patients (57.6±12.8 vs. 67.3±14.4; p=0.065). Regarding the gender distribution, the ratio of males was higher among the survived patients, and the ratio of females was higher among the patients who died (0.018). The two groups showed no difference in terms of length of stay in the ICU, body mass index, and co-morbidities (Table 1).

Of the survived patients, 5 were followed up with high flow nasal oxygen (HFNO), 8 with non-invasive mechanical ventilation (NIMV) and 3 with IMV. Of the patients who died, 3 were followed with HFNO, 8 with NIMV and 2 with IMV. A strong positive correlation was found between thorax CT score and LUS score (r=0.964; p<0.001) (Figure 2). The thorax CT score of the survivors was 15.5±2.7, and the LUS score was 27.3±4.9. The thorax CT score of those who died was 14.1±3.4, and the LUS score was 25.6±5.8. No significant difference was found between the two groups in terms of thorax CT score and LUS score (Table 2).

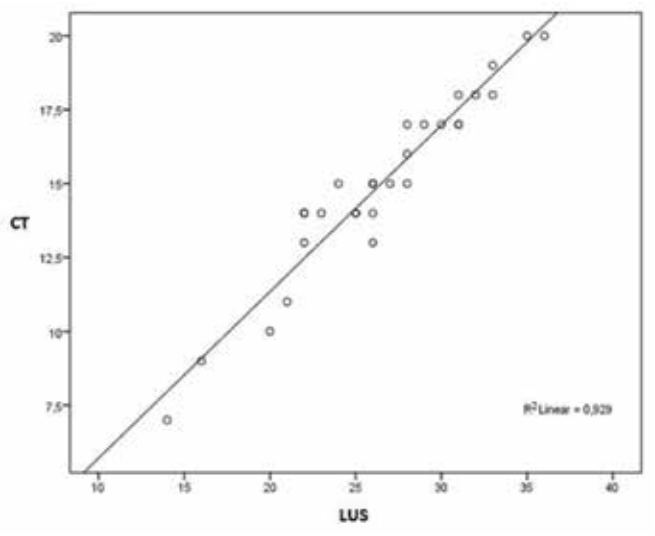


Figure 2. Correlation of thorax CT and LUS scores. There is a strong positive correlation between CT and LUS scorings (r=0.964; p=0.001)
CT: Computed tomography, LUS: lung ultrasound

Discussion

In the study, the correlation of LUS with CT score and its role in determining mortality was evaluated in patients requiring intensive care follow-up due to COVID-19 pneumonia. As a result of the study, a strong positive correlation was found between thorax CT score and LUS score, but it was found that the thorax CT score and LUS score were not effective in determining mortality.

Poggiali et al. (13) reported that there was a strong harmony between thorax CT and simultaneous LUS in COVID-19 patients presenting with flu-like symptoms. The authors of this study suggested the use of LUS as an alternative to thorax CT for early diagnosis of COVID-19 infection. Yin et al. (14) showed that there was a significant correlation between higher LUS score and 28-day increase in mortality in 175 patients admitted to the ICU in their study. In our study, no significant correlation was found between thorax CT score and LUS score and the severe COVID-19 patients' mortality. We thought it might be depending on our less number of patients.

LUS is increasingly used as a reliable tool for evaluating lung diseases, especially in intensive care. Since COVID-19 pneumonia lesions are predominantly peripheral and subpleural, the use of LUS is more appropriate (5). Typical patterns detected by LUS are characterized by both split (Figure 3) and combined B-lines of different shapes (Figure 4), irregular and/or split pleural line, peripheral small consolidations (Figure 5), and large consolidations with dynamic air bronchograms (15,16). These patterns are often interleaved with "protected areas" (A-lines) (17). A large pleural effusion is not a common finding (15). Yasukawa

Table 1. Comparation of demographic and clinical data

	Group 1 (survivors) (n=16)	Group 2 (non-survivors) (n=13)	p-value
Age	57.6±12.8	67.3±14.4	0.065
Gender (M/F)	13/3	5/8	0.018
BMI	29.7±7.3	33.5±6.8	0.164
Duration of ICU stay (days)	13.2±8.5	11.5±8.9	0.602
Co-morbidite (exist/not exist)	12/4	11/2	0.525
Ventilation (n)			
HFNO	5	3	0.689
NIMV	8	8	
IMV	3	2	

HFNO: High flow nasal oxygen, NIMV: Non-invasive mechanical ventilation, IMV: invasive mechanical ventilation, BMI: body mass index, ICU: intensive care unit

Table 2. Comparison of survivors and non-survivors CT and LUS scorings			
	Group 1 (survivors) (n=16)	Group 2 (non-survivors) (n=13)	p-value
CT score	15.5±2.7	14.1±3.4	0.244
LUS score	27.3±4.9	25.6±5.8	0.401
CT: Computed tomography, LUS: lung ultrasound			

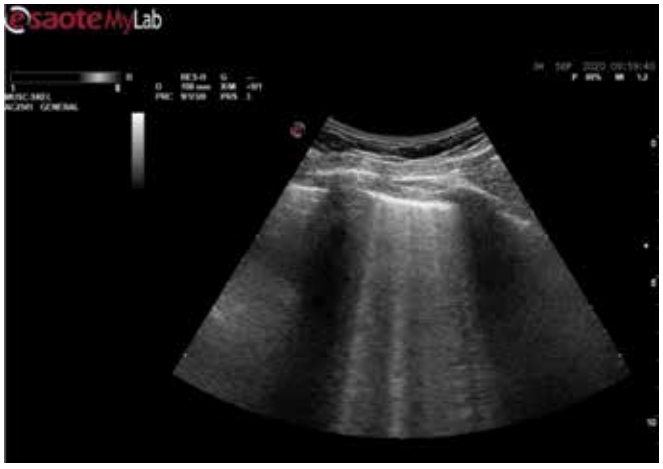


Figure 3. Lung ultrasound shows multiple B-lines

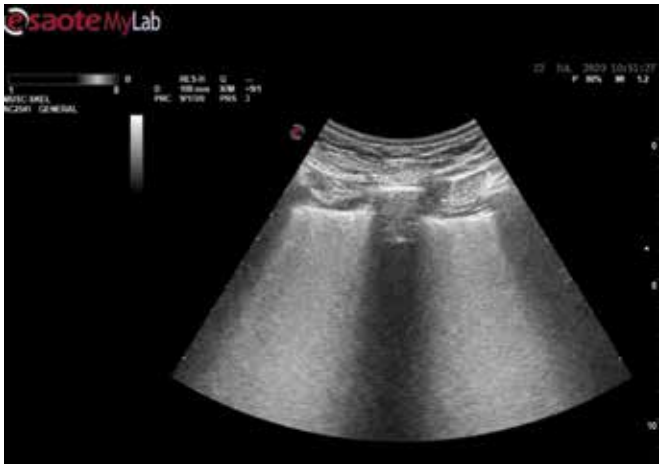


Figure 4. Lung ultrasound shows confluent B-lines

and Minami (8) evaluated the LUS findings of 10 patients who presented to the Internal Medicine Department with COVID-19, and all patients had thick irregular pleural lines and converging B lines. They reported small subpleural consolidations in five of 10 patients. Peng et al. (15) reported the recurrence of A lines following treatment. They recommended the use of ultrasound to assess critical treatment response and prognosis prior to the COVID-19 outbreak, that their recurrence indicates a reduction in interstitial infiltration. In our study, abnormal LUS findings,

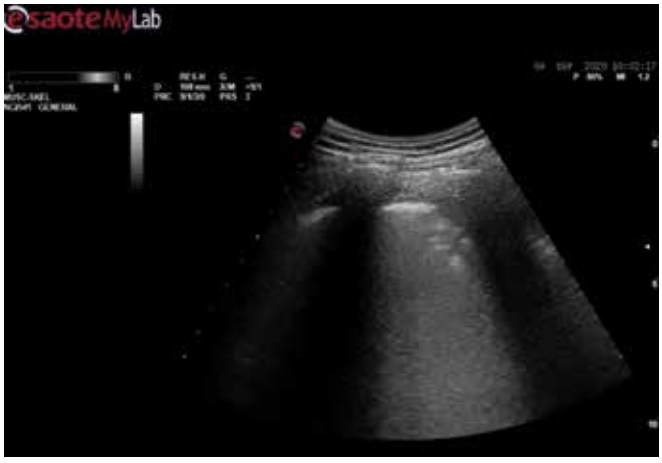


Figure 5. Lung ultrasound shows small subpleural consolidation

pleural line abnormalities, mainly B-lines, and consolidation were found in COVID-19 patients. Bilateral involvement was found with a dominant distribution in the posterior segment of the lungs. The composition of the different B-lines density and areas of consolidation varied in parallel with clinical severity.

NIMV, HFNO, continuous positive airway pressure devices and IMV were used for the intensive care treatment of COVID-19 pneumonia (18,19). In our study, 16 of 29 patients were followed with NIMV, 8 with HFNO and 5 with IMV, daily lung examinations were performed with USG and treatment was planned. LUS is used for PEEP titration, changing ventilation parameters, and extubation planning (12,20). In their study, Schultz et al. (9) stated that the follow-up of COVID-19 patients under IMV could be performed with LUS as an easy bedside tool. Bouhemad et al. (20) demonstrated the significance of LUS in determining ventilator settings by recruitment with PEEP. With the repeated LUS and scoring system, it made it possible to follow up the lung pathology.

The significance of lung imaging in areas affected by the COVID-19 outbreak was reported by Ai et al. (21) stating that 60-93% of patients had positive thorax CT findings consistent with COVID-19 before RT-PCR results turn positive. In a study by Kalafat et al. (22), they found positive LUS findings consistent with COVID-19 pneumonia

in a woman who initially had a negative RT-PCR result. They reported that the patient, whose RT-PCR tests were negative and positive in the repeated follow-up, correlated with the LUS score and CT score. The study by Yasukawa and Minami (8) showed that LUS was a promising additional lung imaging tool in COVID-19 pneumonia, especially in environments with limited resources. LUS was easy to perform in our study, and therefore it guided us in the triage of the patient suspected of having COVID-19 pneumonia.

In their study, Pan et al. (23) followed up lung involvement by performing multiple thorax CT scans at different times (at least three). Ai et al. (21) concluded in their study that multiple RT-PCR assays and serial thorax CT scans had high sensitivity for the diagnosis of COVID-19. CT has been used predominantly for the diagnosis of COVID-19; however, limitations such as radiation exposure, limited mobility, and expensive devices may limit its usefulness, especially during emergencies with insufficient medical resources. Vetrugno et al. (24) stated in their study that they achieved a significant reduction using chest X-rays and CT scans during this pandemic with LUS, which helped them perform the care and management of their patients a little more efficient.

Considering its sensitivity, portability, and safety, LUS is the preferred imaging modality to aid in the early diagnosis and evaluation of COVID-19 pneumonia. In addition, ultrasound is the only imaging technique accessible near patients' beds for timely diagnosis of pulmonary complications and follow-up of disease changes (25).

Considering that approximately 9 to 12% of healthcare workers are infected in light of data from Italy and Spain, the two countries with the highest rate of COVID-19, this is a very important point (1). In our study, the same physician responsible for the patient obtained pulmonary images with with LUS at the bedside, so that the number of healthcare professionals who could be exposed to the virus could be minimized.

Conclusion

Thorax CT is an effective imaging technique used to diagnose and follow up COVID-19 patients. LUS can help diagnose COVID-19 in environments with limited resources where chest X-ray, CT, and RT-PCR are not readily available or have a long turnaround time. The strong correlation between LUS score and CT score in COVID-19 patients shows that LUS can be preferred when CT is required. This may provide early detection and intervention for complications, especially during follow-up. The mortality of COVID-19 patients cannot be predicted with thorax CT score and LUS score. Future studies including more patients will shed light on this issue.

Ethics

Ethics Committee Approval: The study was approved by the Clinical Research Ethics Committee of Gaziosmanpaşa Training and Research Hospital (decision no: 87, date: 28.05.2020).

Informed Consent: Written informed consent was obtained from the patients to be included in the study and/or their relatives.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: A.V., F.Ç., Design: D.G.M., F.Ç., Data Collection and Process: A.V., F.Ç., Analysis or Interpretation: D.G.M., Ü.A.T., Literature Search: D.G.M., Z.Ç., Writing: A.V.

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

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Vieira ALS, Pazeli Júnior JM, Bastos MG. Role of point-of-care ultrasound during the COVID-19 pandemic: our recommendations in the management of dialytic patients. Ultrasound J 2020;12:30.
2. Chua F, Armstrong-James D, Desai SR, Barnett J, Kouranos V, Kon OM, et al. The role of CT in case ascertainment and management of COVID-19 pneumonia in the UK: insights from high-incidence regions. Lancet Respir Med 2020;8:438-40.
3. Yuan M, Yin W, Tao Z, Tan W, Hu Y. Association of radiologic findings with mortality of patients infected with 2019 novel coronavirus in Wuhan, China. PLoS One 2020;15:e0230548.
4. Yoon SH, Lee KH, Kim JY, Lee YK, Ko H, Kim KH, et al. Chest Radiographic and CT Findings of the 2019 Novel Coronavirus Disease (COVID-19): Analysis of Nine Patients Treated in Korea. Korean J Radiol 2020;21:494-500.
5. Ye Z, Zhang Y, Wang Y, Huang Z, Song B. Chest CT manifestations of new coronavirus disease 2019 (COVID-19): a pictorial review. Eur Radiol 2020;30:4381-9.
6. Huang P, Liu T, Huang L, Liu H, Lei M, Xu W, et al. Use of Chest CT in Combination with Negative RT-PCR Assay for the 2019 Novel Coronavirus but High Clinical Suspicion. Radiology 2020;295:22-3.
7. Xie X, Zhong Z, Zhao W, Zheng C, Wang F, Liu J. Chest CT for Typical Coronavirus Disease 2019 (COVID-19) Pneumonia: Relationship to Negative RT-PCR Testing. Radiology 2020;296:E41-5.
8. Yasukawa K, Minami T. Point-of-Care Lung Ultrasound Findings in Patients with COVID-19 Pneumonia. Am J Trop Med Hyg 2020;102:1198-202.
9. Schultz MJ, Sivakorn C, Dondorp AM. Challenges and Opportunities for Lung Ultrasound in Novel Coronavirus Disease (COVID-19). Am J Trop Med Hyg 2020;102:1162-3.
10. Drake DH, De Bonis M, Covella M, Agricola E, Zangrillo A, Zimmerman KG, et al. Echocardiography in Pandemic: Front-Line Perspective, Expanding Role of Ultrasound, and Ethics of Resource Allocation. J Am Soc Echocardiogr 2020;33:683-9.
11. Soldati G, Smargiassi A, Inchingolo R, Buonsenso D, Perrone T, Briganti DF, et al. Is There a Role for Lung Ultrasound During the COVID-19 Pandemic? J Ultrasound Med 2020;39:1459-62.
12. Volpicelli G, Lamorte A, Villén T. What's new in lung ultrasound during the COVID-19 pandemic. Intensive Care Med 2020;46:1445-8.
13. Poggiali E, Dacrema A, Bastoni D, Tinelli V, Demichele E, Mateo Ramos P, et al. Can Lung US Help Critical Care Clinicians in the Early Diagnosis of Novel Coronavirus (COVID-19) Pneumonia? Radiology 2020;295:E6.
14. Yin W, Zou T, Qin Y, Yang J, Li Y, Zeng X, et al. Poor lung ultrasound score in shock patients admitted to the ICU is associated with worse outcome. BMC Pulm Med 2019;19:1.
15. Peng QY, Wang XT, Zhang LN; Chinese Critical Care Ultrasound Study Group (CCUSG). Findings of lung ultrasonography of novel corona virus pneumonia during the 2019-2020 epidemic. Intensive Care Med 2020;46:849-50.
16. Sultan LR, Sehgal CM. A Review of Early Experience in Lung Ultrasound in the Diagnosis and Management of COVID-19. Ultrasound Med Biol 2020;46:2530-45.
17. Volpicelli G, Gargani L. Sonographic signs and patterns of COVID-19 pneumonia. Ultrasound J 2020;12:22.
18. Gürün Kaya A, Öz M, Erol S, Çiftçi F, Çiledağ A, Kaya A. High flow nasal cannula in COVID-19: a literature review. Tuberk Toraks 2020;68:168-74.
19. González-Castro A, Fajardo Campoverde A, Medina A, Alapont VMI. Ventilación mecánica no invasiva y oxigenoterapia de alto flujo en la pandemia COVID-19: El valor de un empate [Non-invasive mechanical ventilation and high-flow oxygen therapy in the COVID-19 pandemic: the value of a draw]. Med Intensiva (Engl Ed) 2021;45:320-1.
20. Bouhemad B, Brisson H, Le-Guen M, Arbelot C, Lu Q, Rouby JJ. Bedside ultrasound assessment of positive end-expiratory pressure-induced lung recruitment. Am J Respir Crit Care Med 2011;183:341-7.
21. Ai T, Yang Z, Hou H, Zhan C, Chen C, Lv W, et al. Correlation of Chest CT and RT-PCR Testing for Coronavirus Disease 2019 (COVID-19) in China: A Report of 1014 Cases. Radiology 2020;296:E32-40.
22. Kalafat E, Yaprak E, Cinar G, Varli B, Ozisik S, Uzun C, et al. Lung ultrasound and computed tomographic findings in pregnant woman with COVID-19. Ultrasound Obstet Gynecol 2020;55:835-7.
23. Pan F, Ye T, Sun P, Gui S, Liang B, Li L, et al. Time Course of Lung Changes at Chest CT during Recovery from Coronavirus Disease 2019 (COVID-19). Radiology 2020;295:715-21.
24. Vetrugno L, Orso D, Deana C, Bassi F, Bove T. COVID-19 Diagnostic Imaging: Caution Need Before the End of the Game. Acad Radiol 2020;27:1331.
25. Ji L, Li Y, Cao C, Lv Q, Xie M. Serial bedside lung ultrasonography in a critically ill COVID-19 patient. QJM 2020;113:491-3.

Turk J Intensive Care 2021;19(Suppl 1):8-32
DOI: 10.4274/tybd.galenos.2021.69885

ORIGINAL RESEARCH / *ÖZGÜN ARAŞTIRMA*

Evren Büyükfırat,
Mustafa Durgun,
Nuri Yorulmaz,
İsmail Koyuncu,
Mahmut Alp Karahan,
Ataman Gönel,
Veli Fahri Pehlivan

Investigation of Interactions Between Sedative, Analgesic and Anaesthetic Drugs with SARS-CoV-2, ACE-2 and SARS-CoV-2- ACE-2 Complex by Molecular Docking Method

Sedatif, Analjezik ve Anestezik İlaçların SARS-CoV-2, ACE-2 ve SARS-CoV-2- ACE-2 Kompleksi ile Etkileşimlerinin Moleküler Yerleştirme Yöntemiyle Araştırılması

Received/Geliş Tarihi : 16.06.2020
Accepted/Kabul Tarihi : 20.01.2021

Evren Büyükfırat, Veli Fahri Pehlivan, Mahmut Alp Karahan
Harran University Faculty of Medicine, Department of Anaesthesiology and Reanimation, Şanlıurfa, Turkey

Mustafa Durgun
Harran University Faculty of Arts and Sciences, Department of Organic Chemistry, Şanlıurfa, Turkey

Nuri Yorulmaz
Harran University Faculty of Arts and Sciences, Department of Physics, Şanlıurfa, Turkey

İsmail Koyuncu, Ataman Gönel
Harran University Faculty of Medicine, Department of Biochemistry, Şanlıurfa, Turkey

Evren Büyükfırat MD, (✉),
Harran University Faculty of Medicine, Department of Anaesthesiology and Reanimation, Şanlıurfa, Turkey

E-mail : evrenbf@gmail.com
Phone : +90 414 318 13 69
ORCID ID : orcid.org/0000-0002-6396-0426

ABSTRACT *Objective:* This study aimed to investigate the inhibitory effects of sedative, analgesic and anaesthetic drugs on severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), human angiotensin converting enzyme-2 (ACE-2) and SARS-CoV-2-ACE-2 complex through molecular docking and their potential use for the treatment of coronavirus disease-2019 (COVID-19).
Materials and Methods: In this study, molecular docking was employed to investigate the molecular interaction between drugs under clinical tests (chloroquine, hydroxychloroquine and nelfinavir) and the most commonly used drugs for sedation, analgesia and anaesthesia, such as inhibitors (desflurane, dexmedetomidine, fentanyl, ketamine, midazolam, propofol, remifentanil and sevoflurane) of three different enzymes (6LU7, 1R4L and 6LZG). Autodock 4.2 Lamarckian Genetic Algorithm was used to analyse the probability of the molecular docking. The evaluation was based on docking points calculated by Biovia Discovery Studio Visualizer 2020. As a result of the molecular docking, interaction types, such as hydrogen-electrostatic and van der Waals between enzymes and drugs, were determined and the results were compared.
Results: Among the drugs included in the study, fentanyl had a low binding energy (-8.75 to -7.64 kcal/mol) for SARS-CoV-2, ACE-2 and SARS-CoV-2-ACE-2 complex and can inhibit these proteins at low concentrations. Apart from fentanyl, midazolam, ketamine, propofol and remifentanil can also inhibit proteins; however, sevoflurane and desflurane were found to be ineffective.
Conclusion: Our findings suggest that fentanyl is preferable for sedation, analgesia and anaesthesia in COVID-19 patients and that total intravenous anaesthesia can be preferred for general anaesthesia. However, experimental and clinical studies are required to determine the efficacy of these substances in treatment.
Keywords: Anaesthesia, COVID-19, sedation, molecular docking

ÖZ *Amaç:* Koronavirüs hastalığı-2019 (COVID-19) tedavisi için moleküler docking (kenetlenme) yöntemi ile sedatif, analjezik ve anestezik ilaçların şiddetli akut solunum sendromu koronavirüs 2 (SARS-CoV-2), insan anjiyotensin dönüştürücü enzim-2 (ACE-2) ve SARS-CoV-2- ACE-2 kompleksi üzerindeki inhibitör etkilerinin ve kullanım potansiyelinin araştırılmasıdır.
Gereç ve Yöntem: Bu çalışmada, COVID-19 tedavisi için klinik testlerde kullanılan ilaçlar (klorokin, hidroksiklorokin ve nelfinavir) ve inhibitör olarak sedasyon, analjezi ve anestezi için en sık kullanılan ilaçlar (desfluran, deksmedetomidin, fentanil, ketamin, midazolam, propofol, remifentanil ve sevofluran) ile üç farklı enzim (6LU7, 1R4L ve 6LZG) arasında moleküler etkileşimi araştırmak için moleküler docking prosedürü uygulanmıştır. Autodock 4.2, Lamarckian Genetik Algoritması, moleküler etkileşim olasılığını analiz etmek için kullanılmıştır. Değerlendirme, Biovia Discovery Studio Visualizer 2020 programı ile yapılmıştır. Moleküler docking sonucunda enzim ile ilaçlar arasında hidrojen-elektrostatik ve van der Waals gibi etkileşim türleri ve şiddetleri tespit edilerek sonuçlar karşılaştırılmıştır.

Bulgular: Çalışmaya dahil edilen ilaçlar arasında fentanil, SARS-CoV-2, ACE-2 ve SARS-CoV-2- ACE-2 Kompleksi üzerinde çok düşük enerjiyle (-8,75 ile -7,64 kcal/mol) bağlandığı ve bu proteinleri düşük konsantrasyonlarda inhibe etme potansiyeline sahip olduğu görülmüştür. Fentanilden sonra sırasıyla midazolam, ketamin, propofol ve remifentanilin de proteinleri inhibe etme potansiyeline sahip olduğu görülmüştür. Ancak sevofluran ve desfluranın etkisiz olduğu görülmüştür.
Sonuç: COVID-19 hastalarında uygulanacak sedasyon, analjezi ve anestezi işlemlerinde fentanilin tercih edilebileceğini ve genel anestezi için ise, total intravenöz anestezisinin tercih edilebileceğini düşünüyoruz. Bununla birlikte, bu maddeleri tedavide kullanmak için deneysel ve klinik çalışmalara ihtiyaç vardır.
Anahtar Kelimeler: Anestezi, COVID-19, sedasyon, moleküler docking

Introduction

Towards the end of 2019, a new coronavirus subtype called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) resulted in an acute respiratory disease outbreak and it caused a pandemic threat for global public health (1). This disease has been named as coronavirus disease-2019 (COVID-19) by the World Health Organization. It has caused a global public health problem due to its mortality potential and rapid international spread and the number of cases and deaths increasing day by day (2). Although most COVID-19 patients have mild symptoms and good prognosis, 15% of patients develop acute respiratory distress syndrome (ARDS), pneumonia, heart damage, kidney damage, or multiorgan failure, 7 to 10 days after hospitalization (3).

In addition to the existing severe respiratory failure, pain and distress occur due to various invasive procedures such as mechanical ventilation (MV) in COVID-19 patients, especially during their treatment in the intensive care unit (4). Sedation and analgesia in critical patients are important in reducing inflammation and stress response (5). A mild sedation for most intensive care unit patients ensures patient comfort, maintaining a safe and effective strategy level, thereby achieving improved clinical results (6). The main organ replacement therapy in ARDS patients is invasive MV. Although mild sedation is recommended for MV, deep sedation is inevitable in COVID-19 patients depending on the severity of pneumonia and ARDS. Deep sedation and high-dose analgesics may be required to achieve lung-protective MV targets, in patients who need to be followed in the prone position, and in invasive procedures such as surgical procedures (4,7).

SARS-CoV-2 is a newly discovered pathogen, researches continues for its treatment and a specific drug for the COVID-19 disease has not yet been identified. In addition, due to the rapid spread of the COVID-19 disease, researches for drugs or drug interactions necessary for treatment are carried out rapidly (8). Among the studies conducted for this purpose, the most up-to-date and promising is the molecular docking method, which is based on genomic sequence information combined with protein structure modeling. In molecular docking method, it is aimed to discover therapeutic agents by enabling the identification of drugs with high target specificity targeting highly conserved proteins associated with SARS-CoV and SARS-CoV-2 (9-11). The molecular docking method can be used to model the interaction between a small molecule and a protein at the atomic level. Thus, it allows us to characterize the behavior of small molecules at the binding site of target proteins and to elucidate fundamental biochemical processes. The purpose of molecular docking is to generate an estimate of the ligand-receptor complex structure using computational methods (12).

In this study; we investigated the binding potentials of the most commonly used drugs for sedation, analgesia and anaesthesia (propofol, midazolam, dexmedetomidine, sevoflurane, desflurane, ketamine, fentanyl, remifentanil) to SARS-CoV-2, ACE-2, SARS-CoV-2- ACE-2 complex proteins with molecular docking method. In this way, we aimed to determine which drugs are more advantageous in patients undergoing invasive mechanic ventilation in intensive care units where sedation is inevitable, or in other procedures that require sedation, analgesia and anaesthesia.

Materials and Methods

Proteins/Macromolecules

In this study, we chose COVID-19 [Protein Data Bank (PDB) ID: 6LU7 chain A] the crystal structure of SARS-CoV-2, human ACE-2 (PDB ID: 1R4L chain A), and SARS-CoV-2- ACE-2 complex (PDB ID: 6LZG chain A and B) novel coronavirus spike receptor-binding domain complexed with its receptor ACE-2. The 6LU7 (13), the 1R4L (14) and the 6LZG (15) structures were obtained from the RCSB PDB

(https://www.rcsb.org/), in.pdb format. The proteins target structures (with ligand and free) were presented in Table 1.

Ligand

In this study, the interaction of compounds used for sedation, analgesia and anaesthesia was investigated. The dimensional structures of the compounds as described in Table 2 were obtained from PubChem database (https://pubchem.ncbi.nlm.nih.gov) in structure-data file format. In this study, desflurane, dexmedetomidine, fentanyl, ketamine, midazolam, propofol, remifentanil and sevoflurane molecules were used. Also, chloroquine, hydroxychloroquine and nelfinavir were used as standards for comparison.

Molecular Docking

Preparation of the ligands (desflurane, dexmedetomidine, fentanyl, ketamine, midazolam, propofol, remifentanil and sevoflurane) and the three different enzymes (6LU7, 1R4L, and 6LZG) for docking were performed by Autodock tools (16). The 3 dimensional structures of the ligands were optimized by MM3 and saved in.mol2 format (17). Autodock 4.2 was supported by Autodock tools, MGL tools. The docking analyses were performed by both Autodock 4.2, and BIOVIA Discovery Studio Visualizer 2020.

Results

The docking analysis results for the drugs under clinical test (chloroquine, hydroxychloroquine and nelfinavir) and the sedatives, analgesics and anaesthetics drugs (desflurane, dexmedetomidine, fentanyl, ketamine, midazolam, propofol, remifentanil and sevoflurane) as inhibitors with the three different enzymes (6LU7, 1R4L, and 6LZG), including binding energy, inhibition constant, intermolecular energy, van der Waals (VDW)-H Bond desolvation energy, electrostatic energy, total internal energy, torsional free energy are presented in Table 3.

Table 3 shows the docking score values for 1R4L, 6LU7 and 6LZG. The binding energies obtained from docking 1R4L with the chloroquine, hydroxychloroquine and nelfinavir were -7.02, -6.41, and -8.77 kcal/mol, respectively. The binding energies of desflurane, dexmedetomidine, fentanyl, ketamine, midazolam, propofol, remifentanil and sevoflurane with 1R4L are in the range of (-1.79 kcal/mol) - (-7.44 kcal/mol), while fentanyl has the highest value. The binding energies obtained from docking 6LU7 with the chloroquine, hydroxychloroquine and nelfinavir were -7.19, -6.93, and -11.13 kcal/mol, respectively. The binding energies of desflurane, dexmedetomidine, fentanyl, ketamine, midazolam, propofol, remifentanil and sevoflurane with 6LU7 are in the range of (-1.75 kcal/mol) - (-7.97 kcal/mol), while fentanyl has the highest value. The binding energies obtained from docking 6LZG with the chloroquine, hydroxychloroquine and nelfinavir were -7.85, -6.56, and -7.97 kcal/mol, respectively. The binding energies of desflurane, dexmedetomidine, fentanyl, ketamine, midazolam, propofol, remifentanil and sevoflurane with 6LZG are in the range of (-2.31 kcal/mol) - (-8.11 kcal/mol), while fentanyl has the highest value.

The molecular structure of the docked drugs and their interactions with 1R4L, 6LU7 and 6LZG are presented in Tables 4, 5 and 6, respectively. Here, we will focus on the structure and interactions of fentanyl with the highest placement score. When the molecular structure and interactions of fentanyl with 1R4L are examined, it is seen that there are conventional hydrogen bond interactions with TYR255. Additionally, fentanyl also exhibited carbon hydrogen bond with ASP615, SER254, Pi-Sigma interaction with TRP610, Pi-Pi T-shaped interaction with TRP610, alkyl interaction with LEU162, pi-alkyl interaction with TYR158 and TYR255. When the molecular structure and interactions of fentanyl with 6LU7 are examined, it is seen that there are pi-sulfur interactions with CYS145, alkyl interactions with MET165, pi-alkyl interaction with MET49 and MET165.

When the interactions of fentanyl with 6LU7 are examined, it appears that there are conventional hydrogen bond interactions with ARG403, carbon hydrogen bond interactions with ARG403, ASN33 and A:GLU37, pi-sigma interactions with PRO389, pi-alkyl interaction with HIS34, TYR495, PHE497, and TYR505. Docking analysis results can be observed in Table 4, 5 and 6, respectively.

Discussion

SARS-CoV-2, a member of the Betacoronavirus family; is an enveloped virus containing a single-stranded RNA genome. The betacoronavirus genome encodes the Spike protein; In this way, it mediates host cell invasion by both SARS-CoV and SARS-CoV-2 by binding to the ACE-2 receptor protein on the surface membrane of host cells (18-20). The interaction between the viral S protein and ACE-2 on the host cell surface is an important consideration as it initiates the infection process. Cryo-EM structure analysis revealed

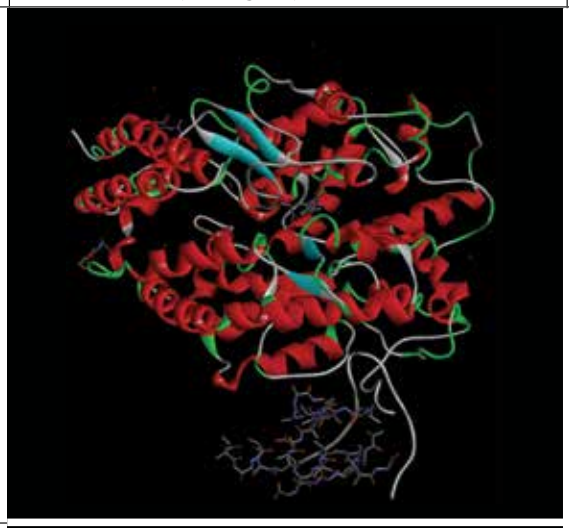
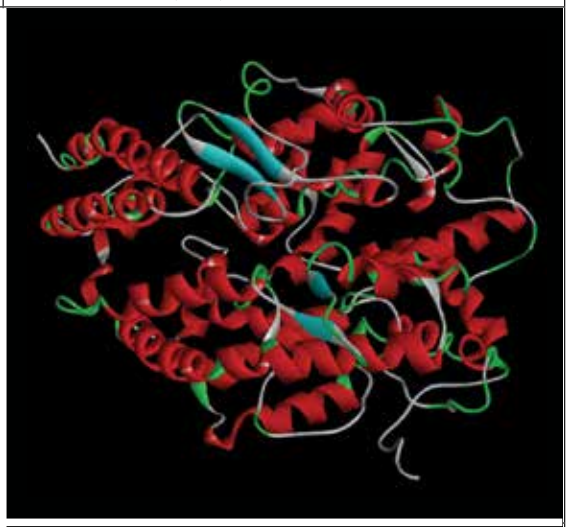
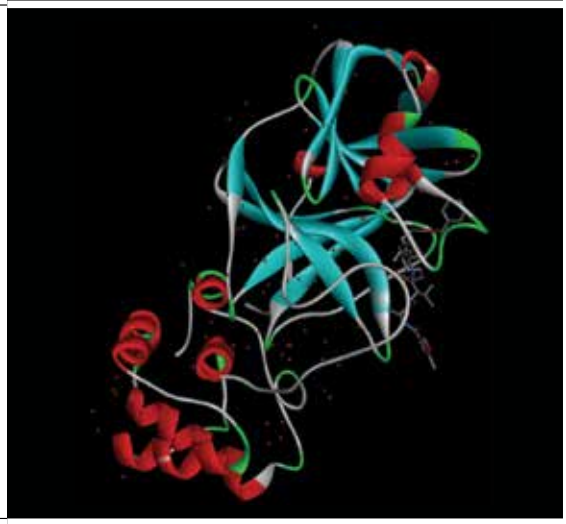
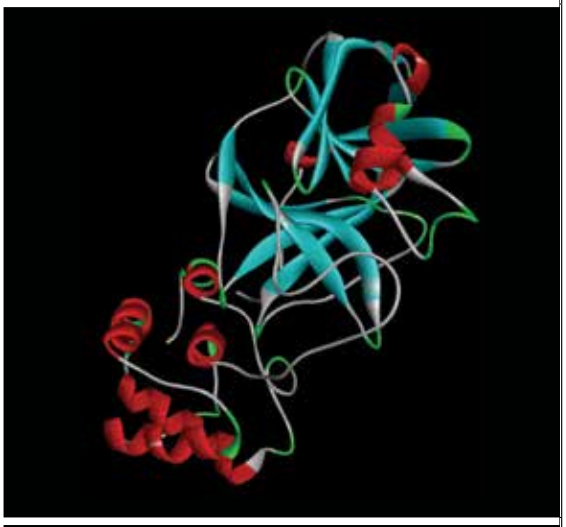
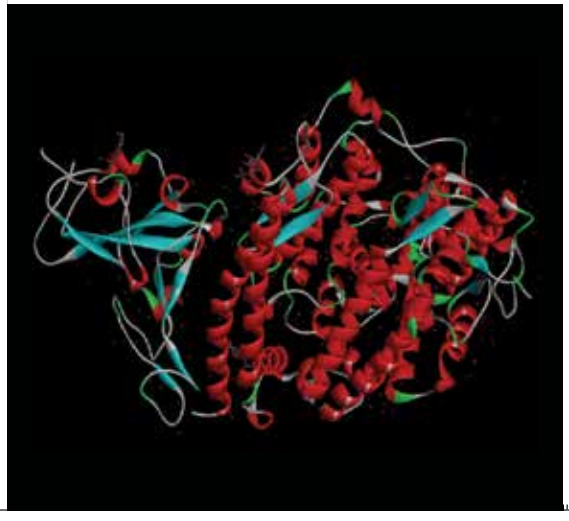
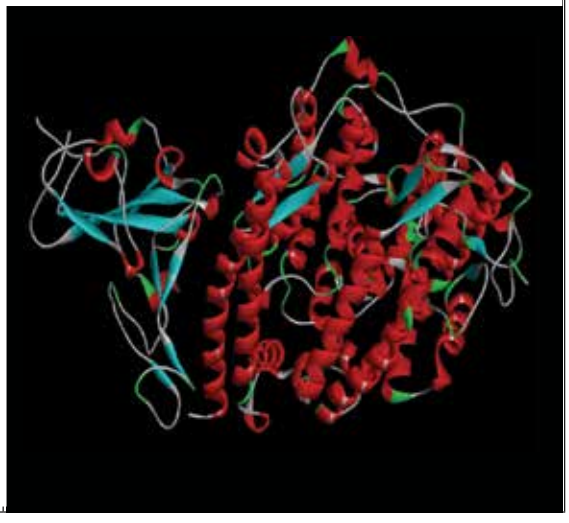
Table 1. Proteins target structures (with ligand and free) (BIOVIA Discovery Studio Visualizer 2020)			
No	**PDB ID**	**Macromolecule (with ligand)**	**Macromolecule (free)**
1	1R4L		
2	6LU7		
3	6LZG		

Table 2. The name and structure of the drugs under clinical tests and the drugs examined in this study

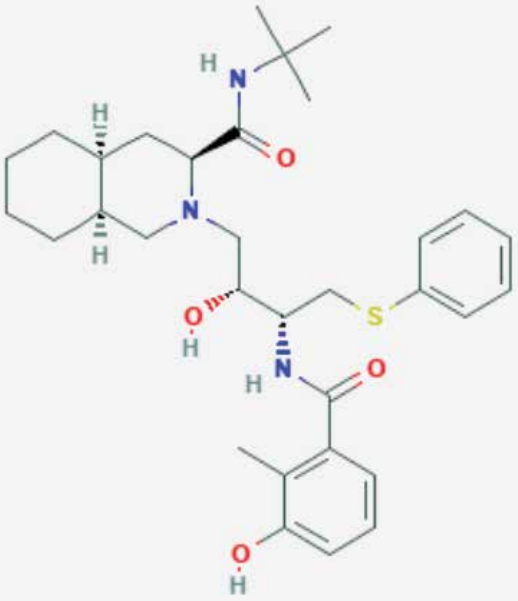
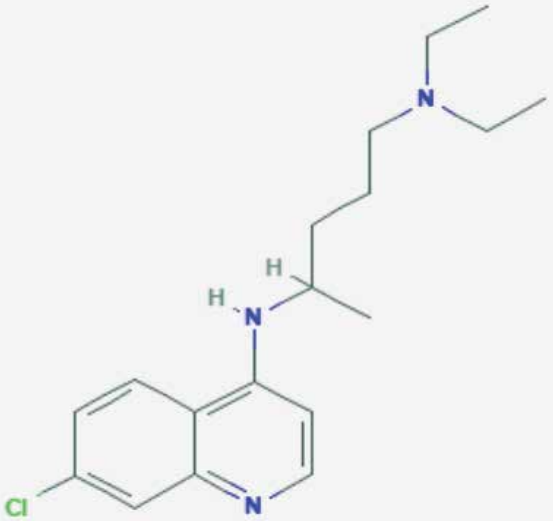
No.	Compound name	PubChem CID	2D structure
1	Nelfinavir	64143	
2	Chloroquine	2719	

Table 2. Continued

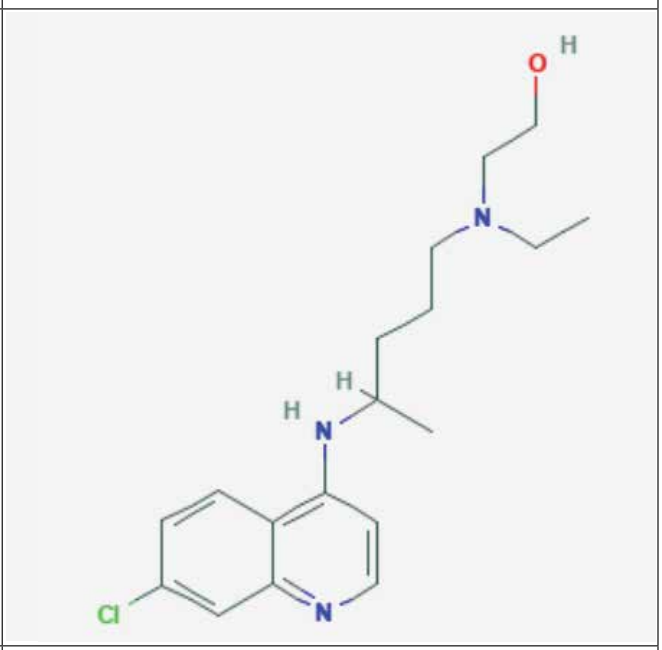
No.	Compound name	PubChem CID	2D structure
3	Hydroxychloroquine	3652	
4	Desflurane	42113	

Table 2. Continued

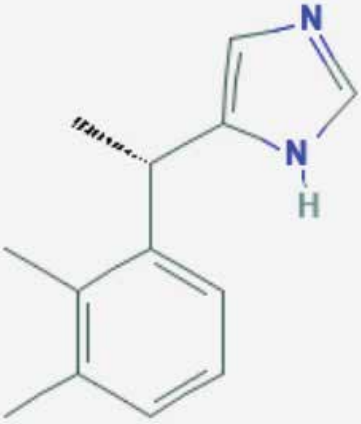
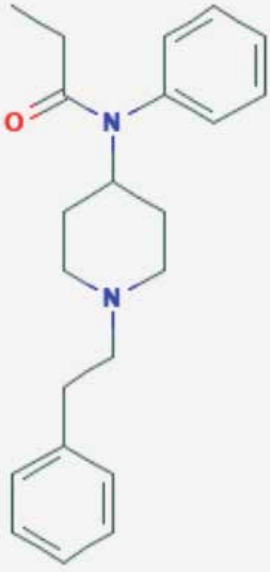
No.	Compound name	PubChem CID	2D structure
5	Dexmedetomidine	5311068	
6	Fentanyl	3345	

Table 2. Continued

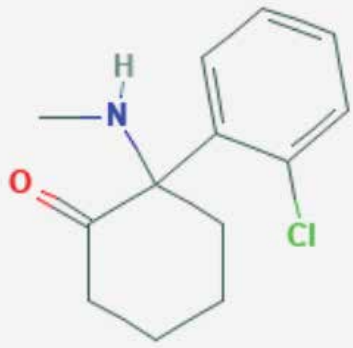
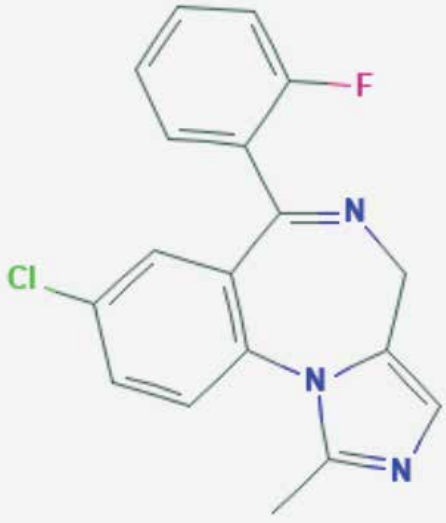
No.	Compound name	PubChem CID	2D structure
7	Ketamine	3821	
8	Midazolam	4192	

Table 2. Continued

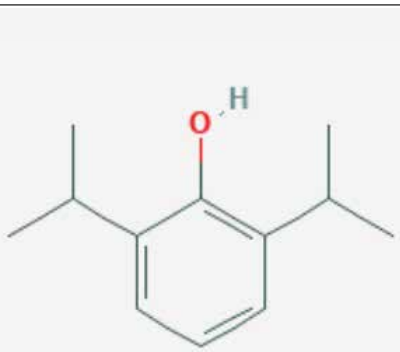
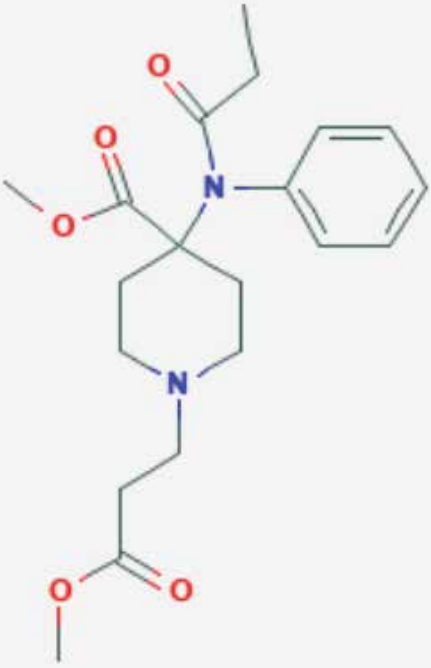
No.	Compound name	PubChem CID	2D structure
9	Propofol	4943	
10	Remifentanil	60815	
11	Sevoflurane	5206	

Table 3. Molecular docking analysis of drugs under clinical tests and the drugs examined in this study as inhibitors against 1R4L, 6LU7 and 6LZG

Protein	Compound	Binding energy (ΔG)	Inhibition constant	Intermolecular energy	VDW-H Bond desolvation energy	Electrostatic energy	Total internal energy	Torsional free energy
1R4L	Chloroquine	-7.02	7.16 μM	-9.41	-7.85	-1.55	-0.73	2.39
	Hydroxychloroquine	-6.41	20.02 μM	-9.39	-7.62	-1.77	-0.79	2.98
	Nelfinavir	-8.77	375.13 nM	-12.35	-10.73	-1.61	-3.00	3.58
	Desflurane	-2.33	19.64 mM	-3.22	-3.04	-0.18	-0.15	0.89
	Dexmedetomidine	-4.97	228.85 μM	-5.56	-5.52	-0.05	-0.46	0.60
	Fentanyl	-7.44	3.54 μM	-9.23	-7.79	-1.43	-1.29	1.79
	Ketamine	-6.43	19.23 μM	-7.03	-5.82	-1.21	-0.02	0.60
	Midazolam	-6.04	37.13 μM	-6.34	-5.98	-0.36	-0.77	0.30
	Propofol	-4.86	272.22 μM	-5.76	-5.71	-0.05	-0.33	0.89
	Remifentanil	-5.73	62.76 μM	-8.42	-6.92	-1.50	-2.30	2.68
	Sevoflurane	-1.79	48.36 mM	-2.99	-2.83	-0.15	-0.18	1.19
6LU7	Chloroquine	-7.19	5.32 μM	-9.38	-9.35	-0.23	-0.94	2.39
	Hydroxychloroquine	-6.93	8.31 μM	-9.91	-9.39	-0.52	-0.61	2.98
	Nelfinavir	-11.13	6.95 nM	-14.71	-14.29	-0.42	-3.68	3.58
	Desflurane	-2.07	30.45 mM	-2.96	-2.95	-0.02	-0.22	0.89
	Dexmedetomidine	-5.91	46.53 μM	-6.51	-6.48	-0.02	-0.42	0.60
	Fentanyl	-7.97	1.43 μM	-9.76	-9.49	-0.27	-1.51	1.79
	Ketamine	-5.74	61.82 μM	-6.34	-4.63	-1.71	-0.08	0.60
	Midazolam	-7.57	2.83 μM	-7.87	-7.82	-0.04	-0.59	0.30
	Propofol	-5.39	112.27 μM	-6.28	-6.25	-0.03	-0.31	0.89
	Remifentanil	-6.15	31.27 μM	-8.83	-8.50	-0.33	-2.14	2.68
	Sevoflurane	-1.75	52.11 mM	-2.94	-2.91	-0.03	-0.19	1.19
6LZG	Chloroquine	-7.85	1.76 μM	-10.24	-8.40	-1.83	-0.53	2.39
	Hydroxychloroquine	-6.56	15.49 μM	-9.55	-8.18	-1.36	-1.12	2.98
	Nelfinavir	-7.97	1.43 μM	-11.55	-10.55	-1.00	-2.69	3.58
	Desflurane	-2.31	20.28 mM	-3.20	-3.10	-0.11	-0.15	0.89
	Dexmedetomidine	-5.91	46.87 μM	-6.50	-6.60	0.10	-0.05	0.60
	Fentanyl	-8.11	1.14 μM	-9.90	-9.23	-0.67	-1.31	1.79
	Ketamine	-6.90	8.72 μM	-7.50	-6.47	-1.03	-0.36	0.60
	Midazolam	-7.15	5.71 μM	-7.45	-7.65	0.20	-0.59	0.30
	Propofol	-5.97	41.74 μM	-6.87	-6.82	-0.05	-0.38	0.89
	Remifentanil	-6.75	11.34 μM	-9.43	-8.01	-1.42	-1.78	2.68
	Sevoflurane	-2.43	16.56 mM	-3.62	-3.43	-0.20	-0.22	1.19

Energy unit: kcal/mol, VDW: van der Waals

Table 4. Molecular structure and interactions of the docked drugs under clinical test and the drugs examined in this study as inhibitors with the 1R4L

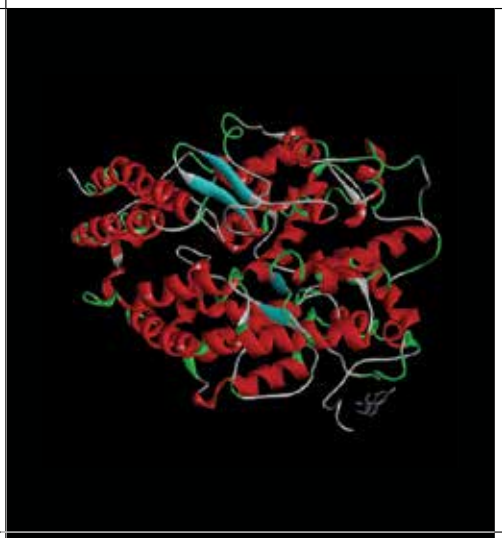
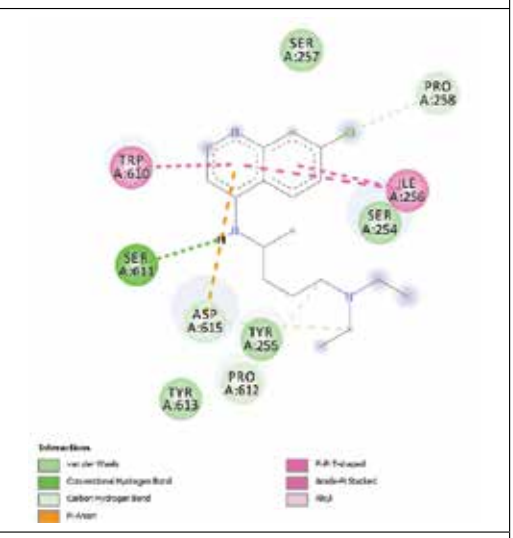
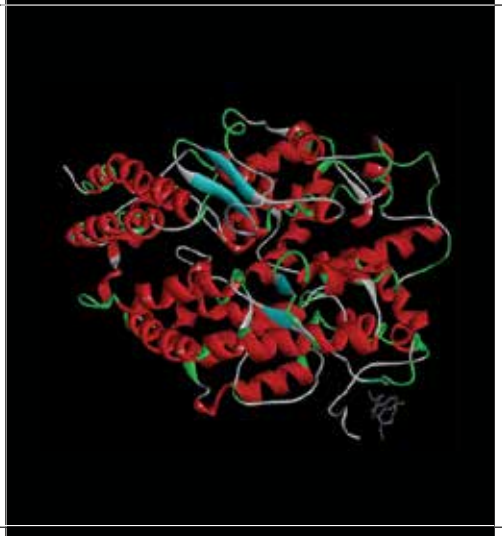
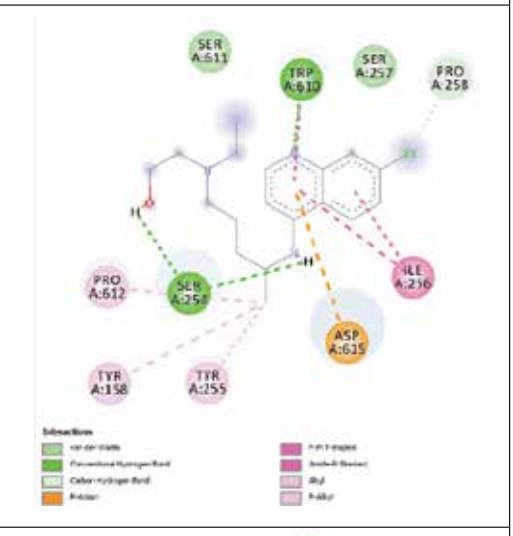
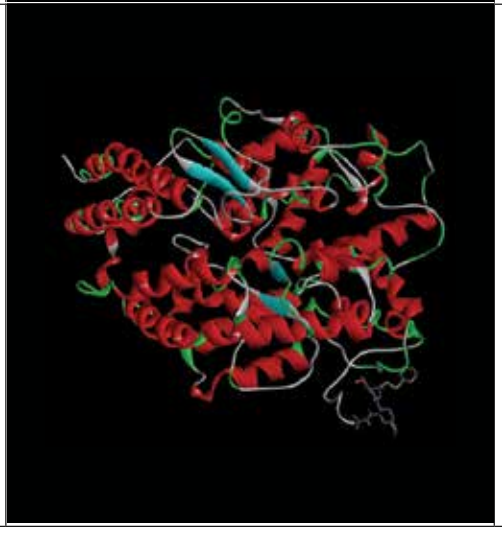
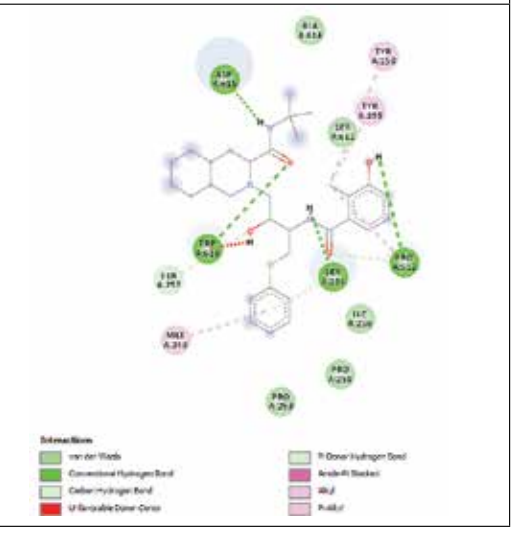
Protein	Compound	Molecular structure and interactions	
1R4L	Chloroquine		
	Hydroxychloroquine		
	Nelfinavir		

Table 4. Continued

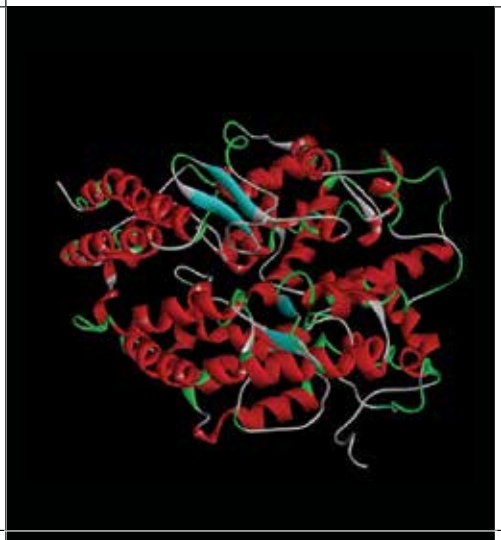
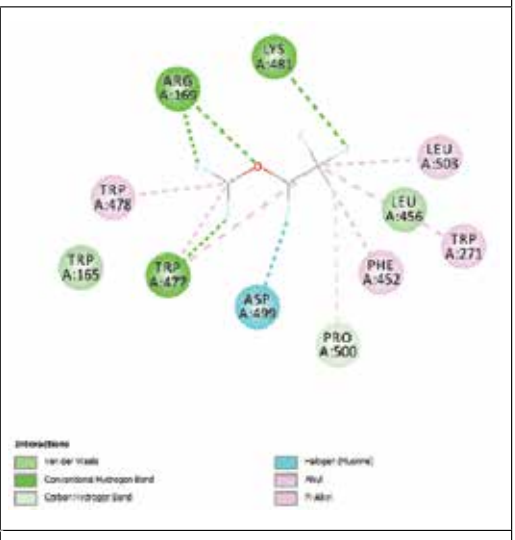
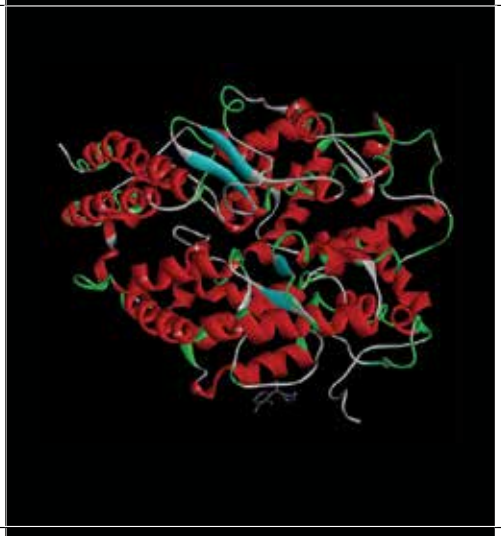
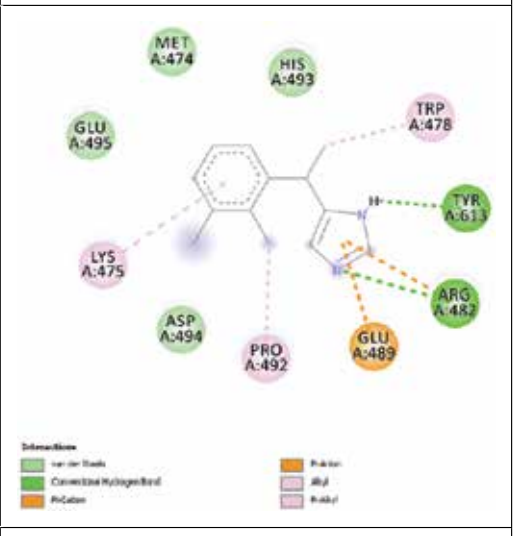
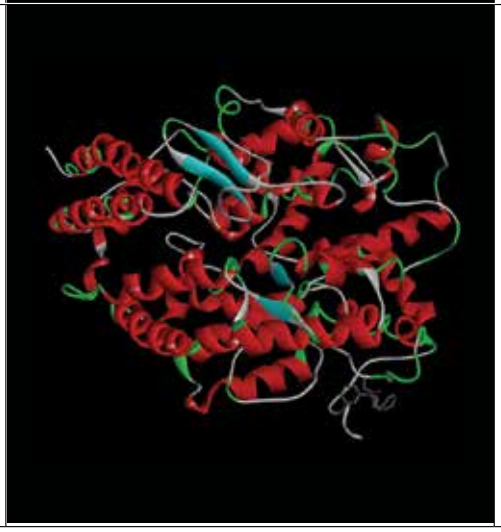
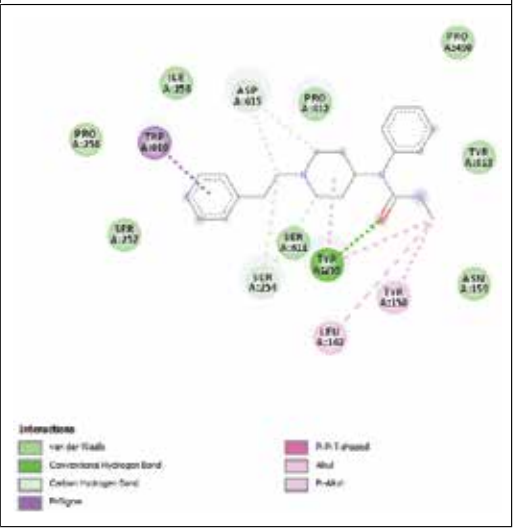
Protein	Compound	Molecular structure and interactions	
1R4L	Desflurane		
	Dexmedetomidine		
	Fentanyl		

Table 4. Continued

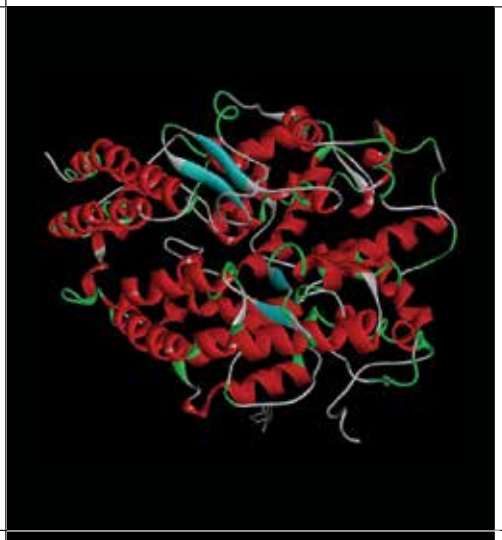
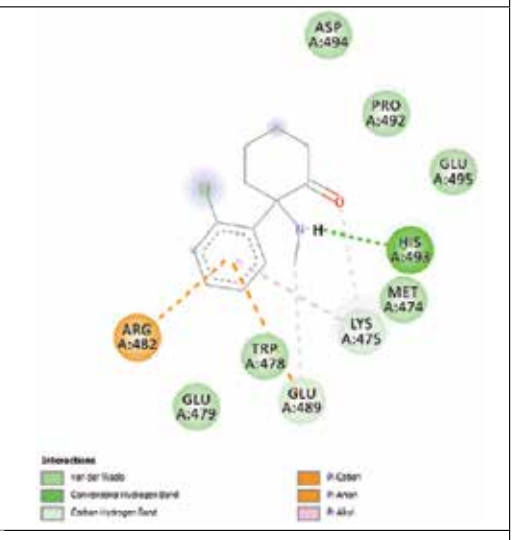
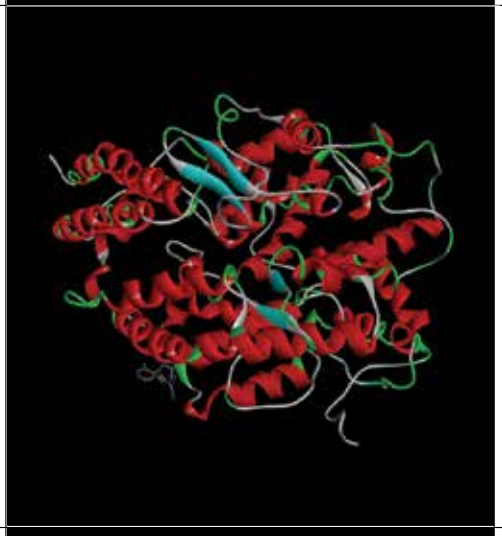
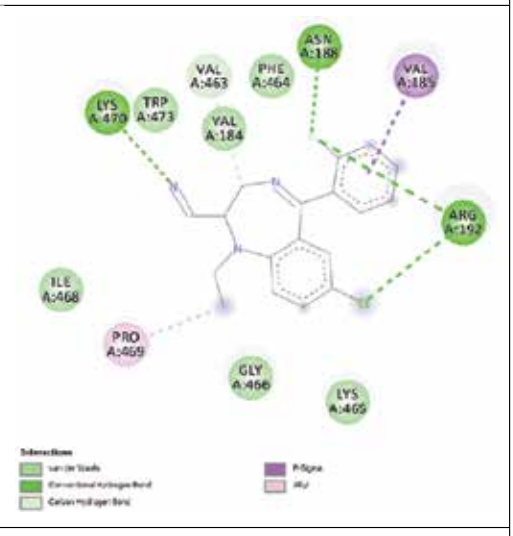
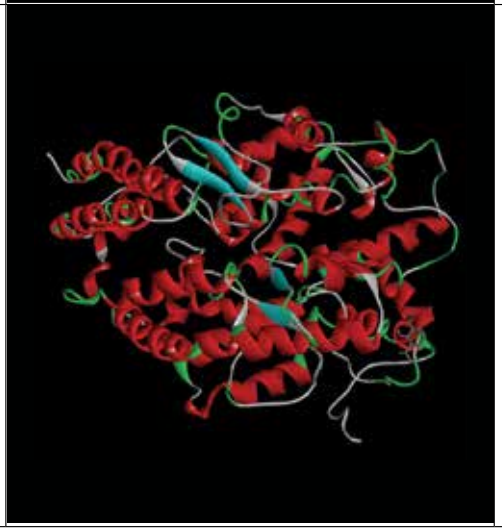
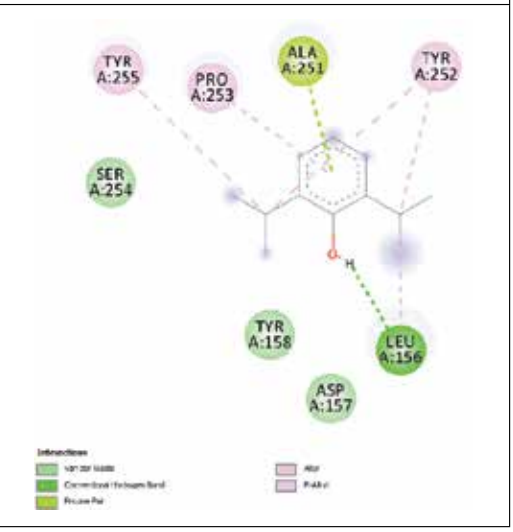
Protein	Compound	Molecular structure and interactions	
1R4L	Ketamine		
	Midazolam		
	Propofol		

Table 4. Continued

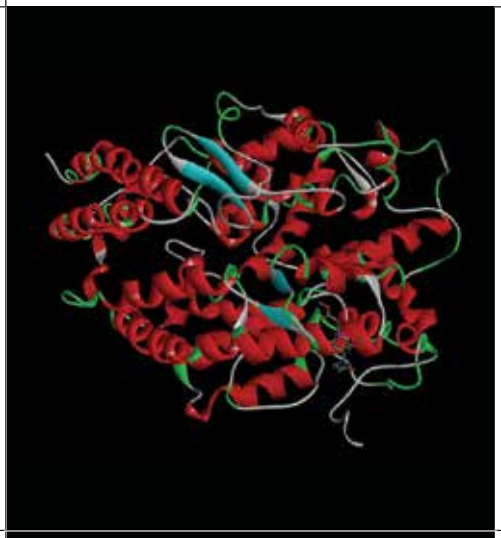
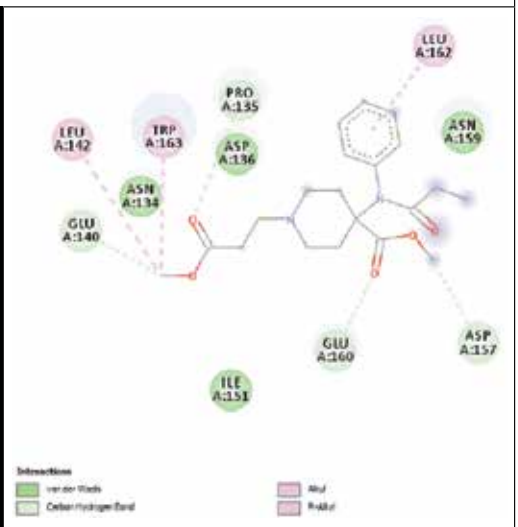
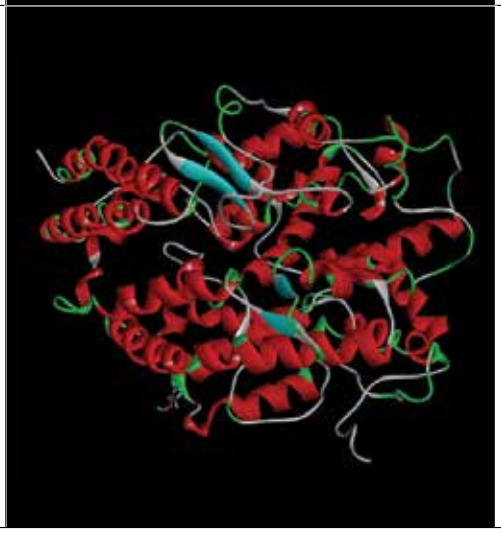
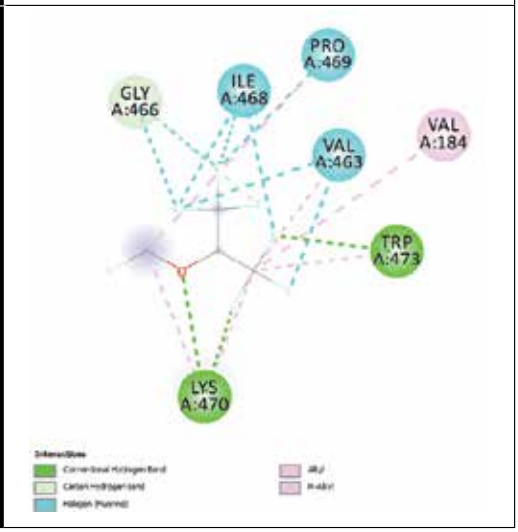
Protein	Compound	Molecular structure and interactions	
1R4L	Remifentanil		
	Sevoflurane		

Table 5. Molecular structure and interactions of the docked drugs under clinical test the drugs examined in this study as inhibitors with the 6LU7

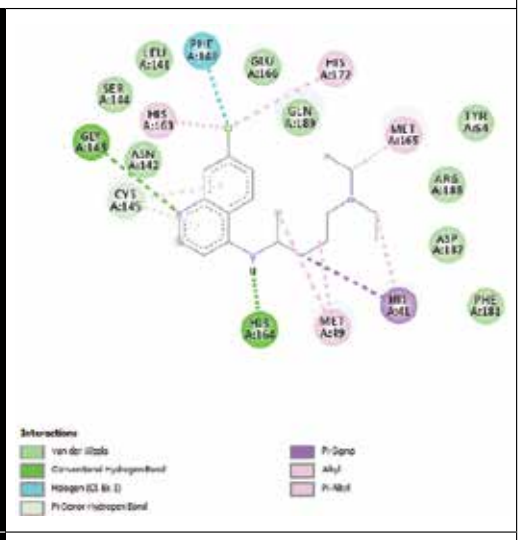
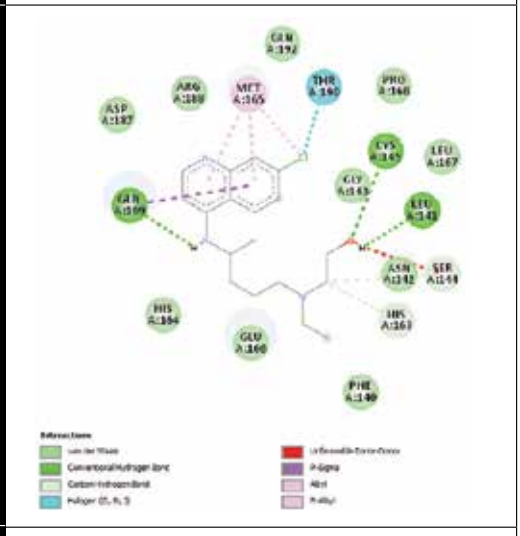
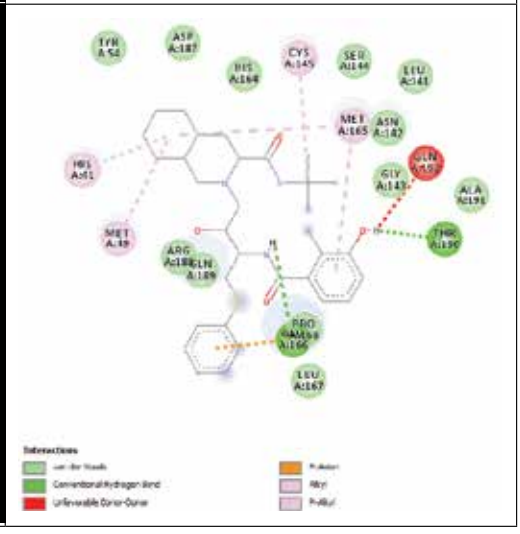
Protein	Compound	Molecular structure and interactions	
6LU7	Chloroquine		
	Hydroxychloroquine		
	Nelfinavir		

Table 5. Continued

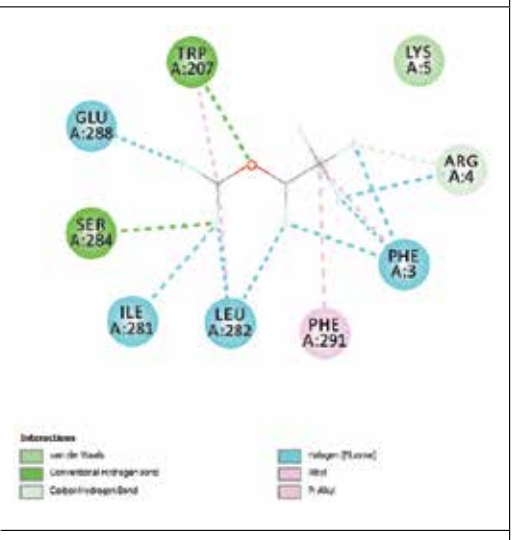
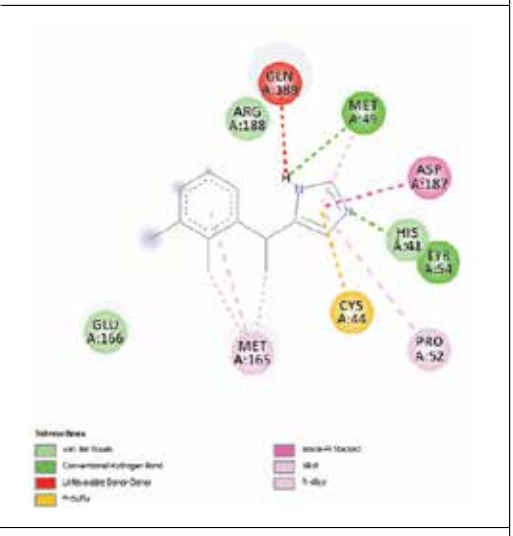
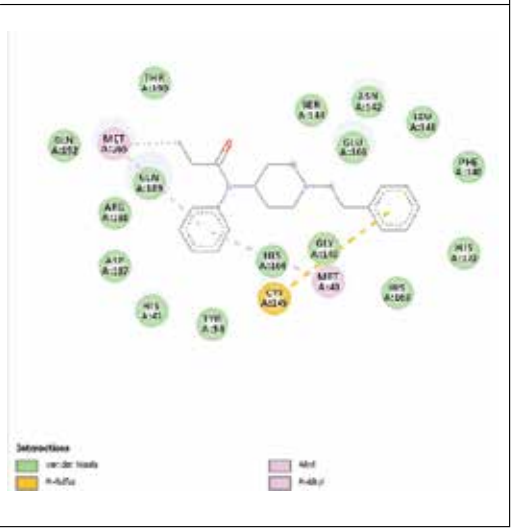
Protein	Compound	Molecular structure and interactions	
6LU7	Desflurane		
	Dexmedetomidine		
	Fentanyl		

Table 5. Continued

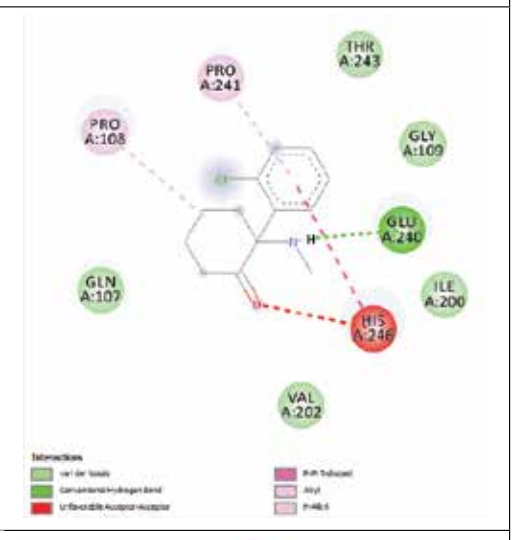
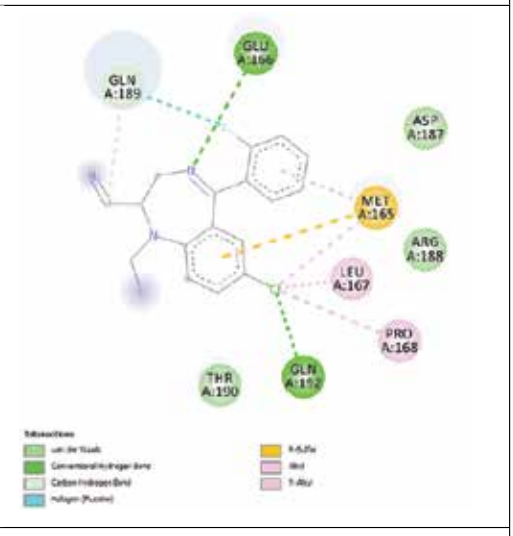
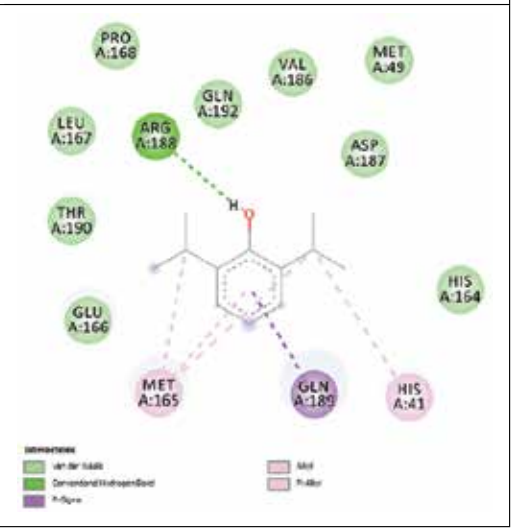
Protein	Compound	Molecular structure and interactions	
6LU7	Ketamine		
	Midazolam		
	Propofol		

Table 5. Continued

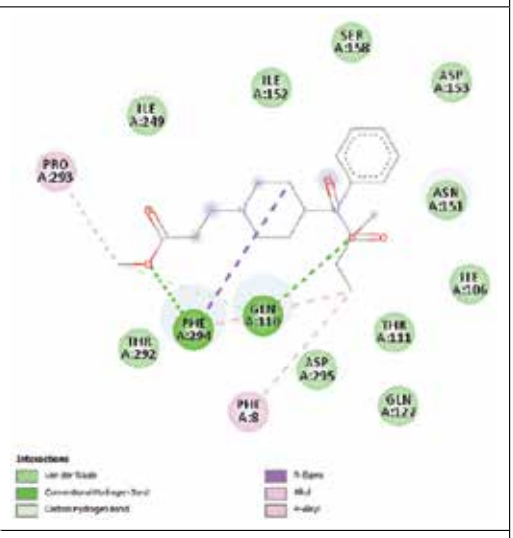
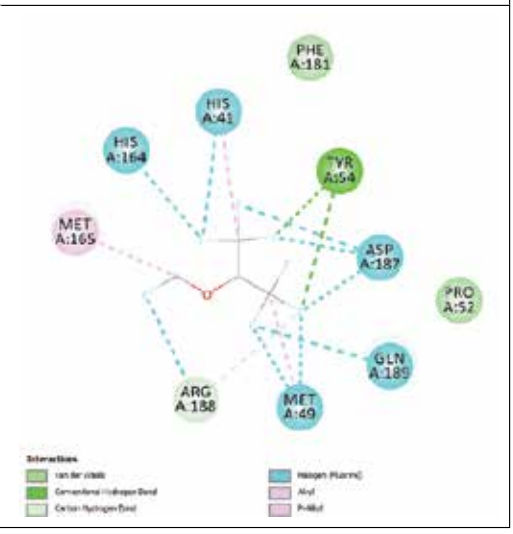
Protein	Compound	Molecular structure and interactions	
6LU7	Remifentanil		
	Sevoflurane		

Table 6. Molecular structure and interactions of the docked drugs under clinical test and the drugs examined in this study as inhibitors with the 6LZG

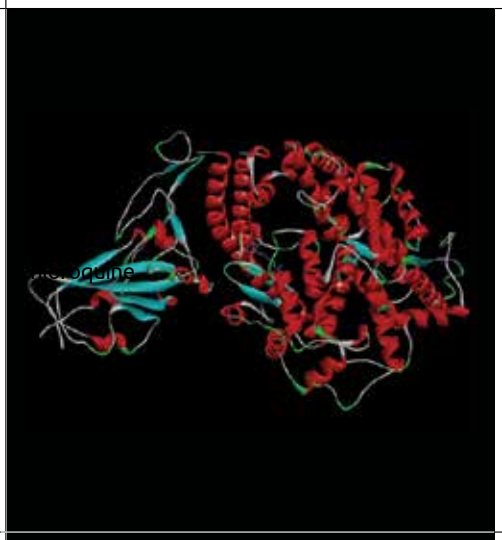
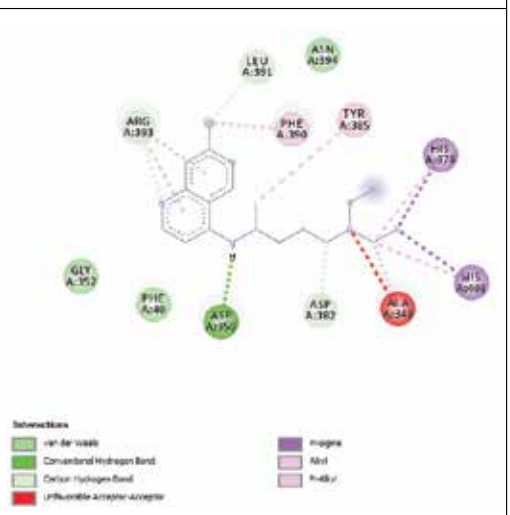
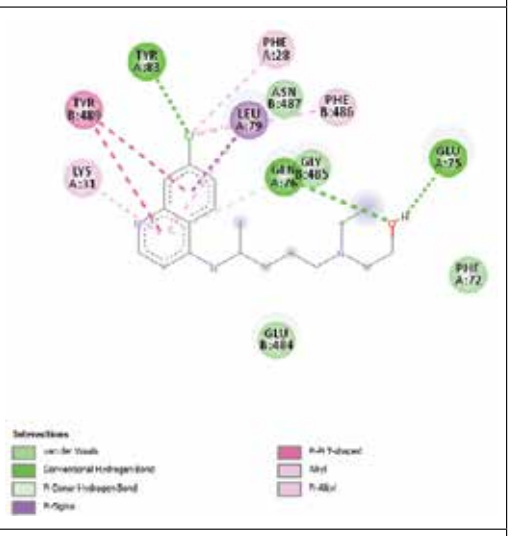
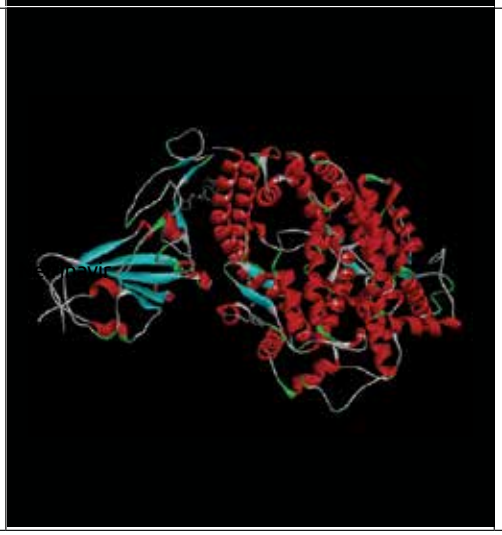
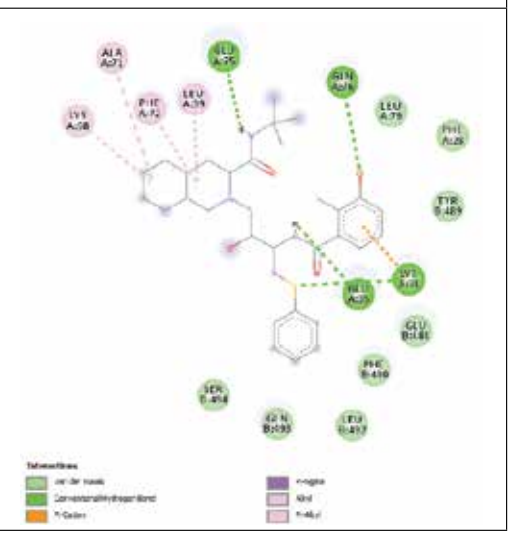
Protein	Compound	Molecular structure and interactions	
6LZG	Chloroquine		
	Hydroxychloroquine		
	Nelfinavir		

Table 6. Continued

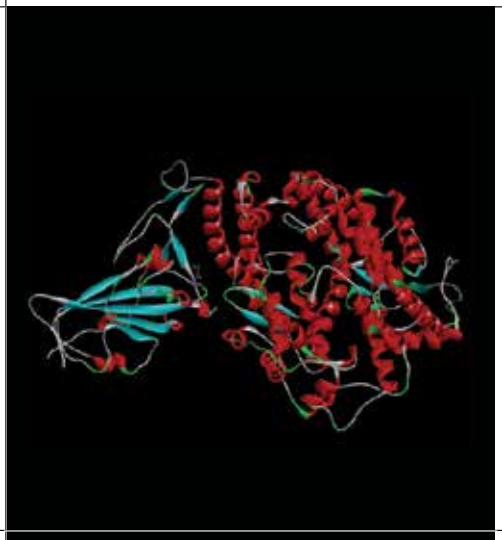
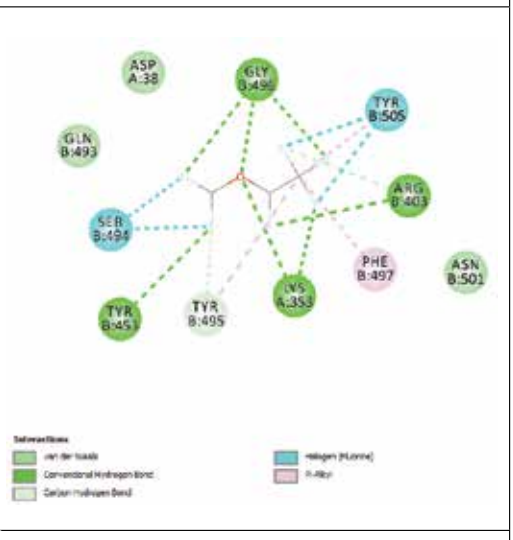
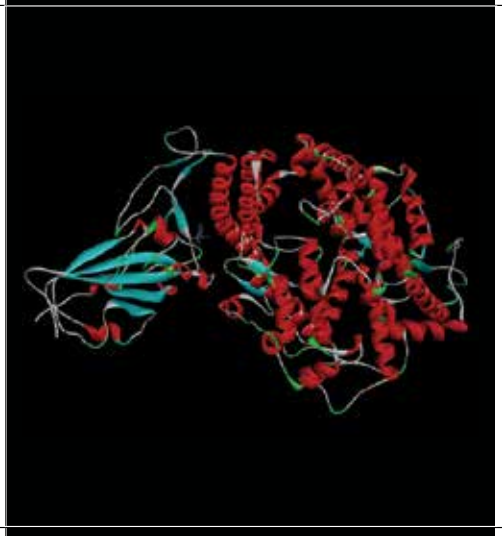
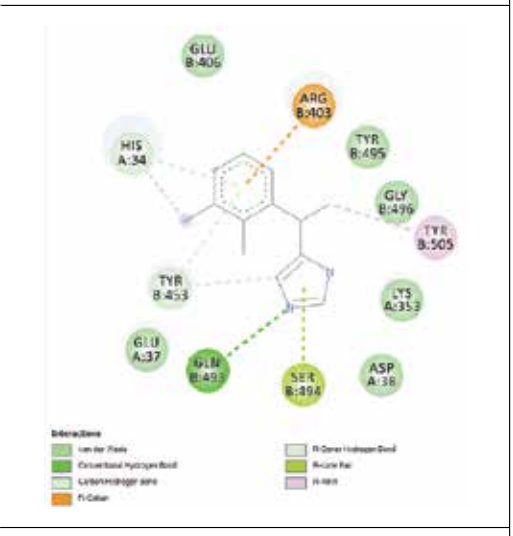
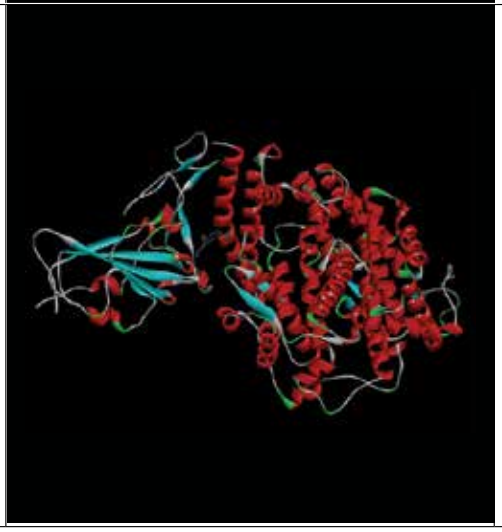
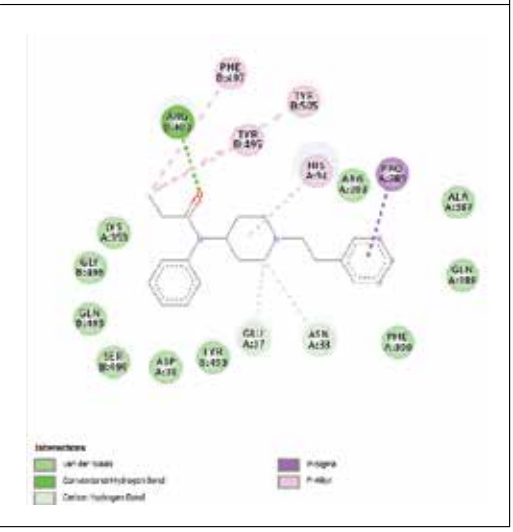
Protein	Compound	Molecular structure and interactions	
6LZG	Desflurane		
	Dexmedetomidine		
	Fentanyl		

Table 6. Continued

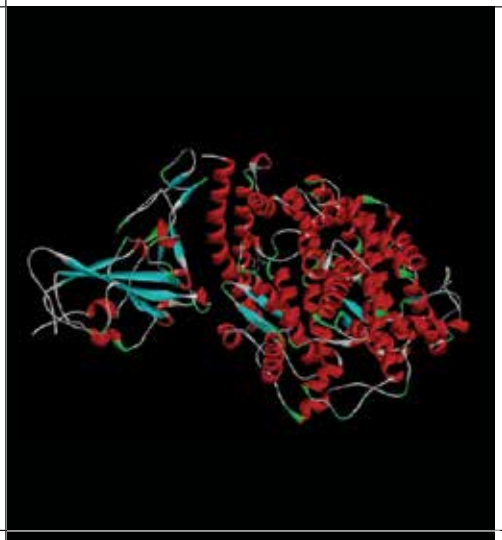
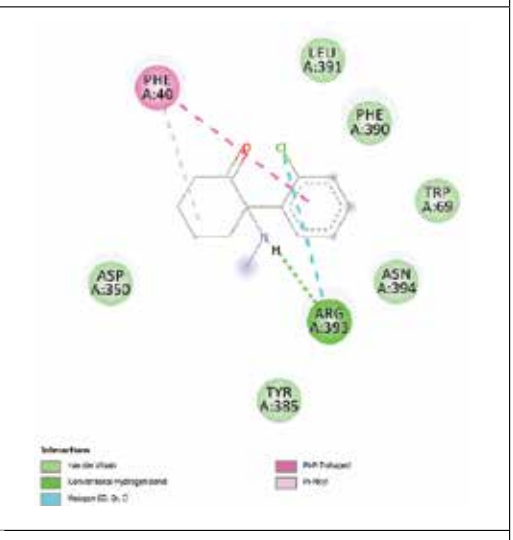
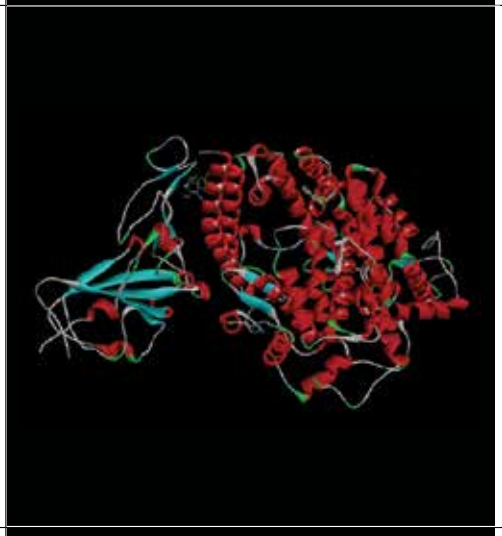
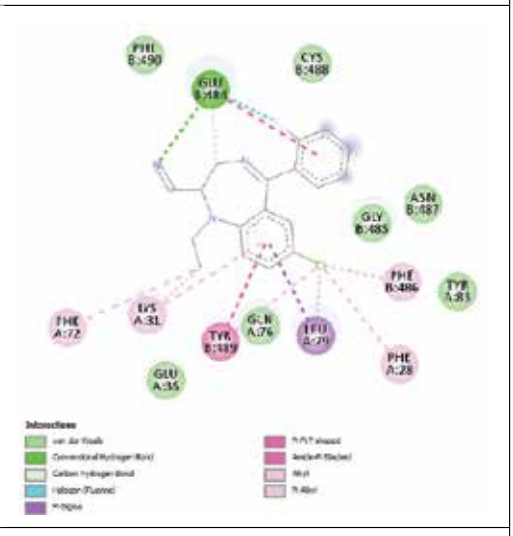
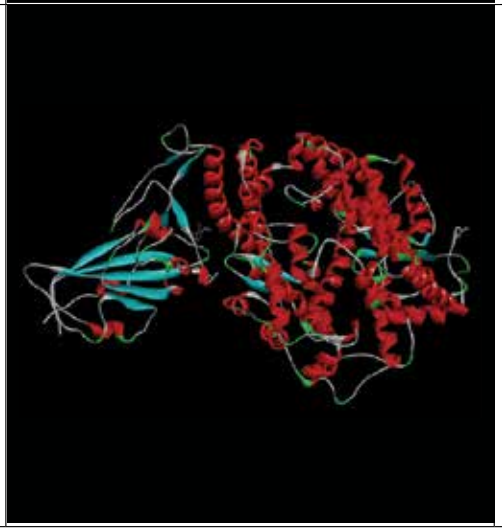
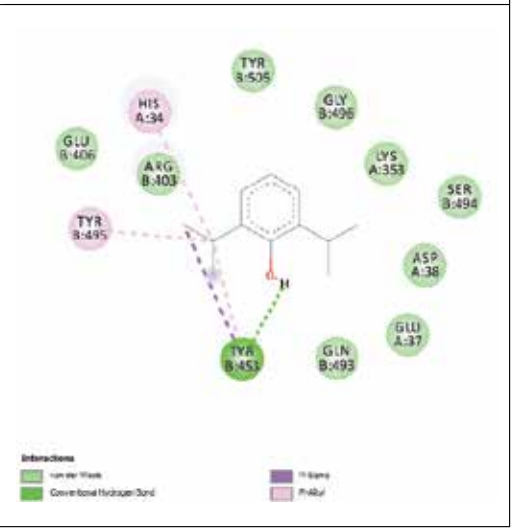
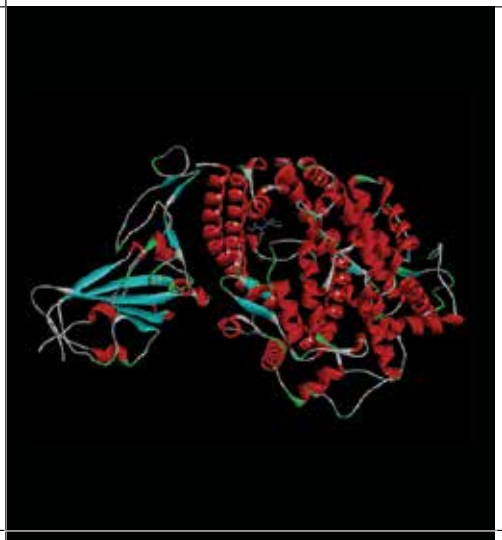
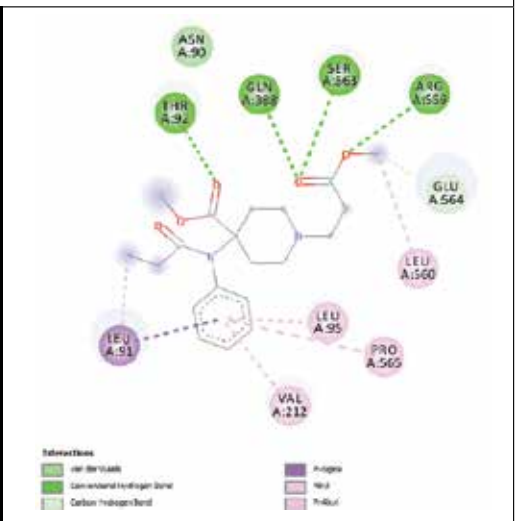
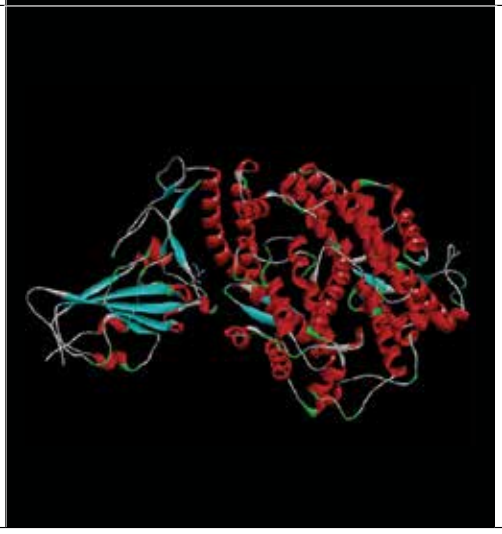
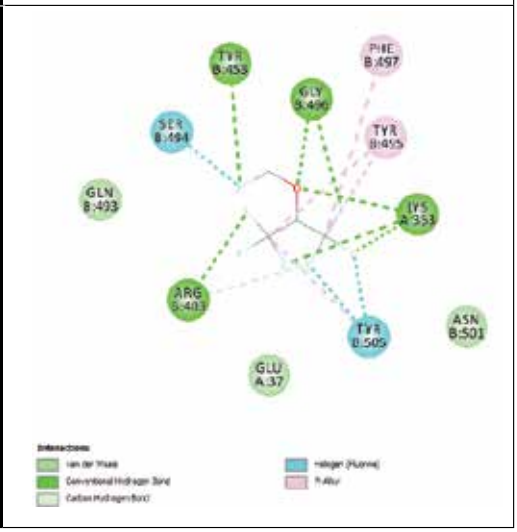
Protein	Compound	Molecular structure and interactions	
6LZG	Ketamine		
	Midazolam		
	Propofol		

Table 6. Continued

Protein	Compound	Molecular structure and interactions	
6LZG	Remifentanil		
	Sevoflurane		

that the SARS-CoV-2 S protein has a binding affinity for ACE-2 approximately 10-20 times higher than that of the SARS-CoV S protein. (9,20). In addition, it is known that SARS-CoV-2 coronaviruses play an important role in the replication/transcription of the main protease (Mpro) enzyme (21). Therefore, these proteins are among the remarkable targets for the development of drugs against COVID-19 disease. It is important to examine ACE-2 to find inhibitors that prevent enzyme activity and virus replication. Molecular docking studies are carried out for the detection of effective drugs (22).

Different and new data were obtained from the researchers conducted with the molecular docking method for the treatment of COVID-19. Positive results obtained by silico screening of various molecules (23) and herbal medicines (24) for the treatment of COVID-19 using calculation methods have been reported. Some clinical studies also support this data. Hung et al. (25) reported that, the anti-viral drugs approved for human therapies such as lopinavir, ribavirin and ritonavir, targeting the Mpro enzyme structure of SARS-CoV-2, have potential effects against COVID-19, and reduced the length of hospital stay by triple combined therapy. Recent studies on viral protease inhibitors have supported the prediction that SARS-CoV-2 Mpro enzyme can be a target for therapeutic agents (8,26,27). In another study it was found that nelfinavir, which is also used as an antiviral drug and protease inhibitor, prevents the membrane fusion by binding to the spike protein complex with low energy (-9.98 kcal/mol) by the molecular docking method. In the same study, it was found that nelfinavir prevented the fusion of SARS-CoV-2 by S protein in Vero cells *in vitro* (28). In addition, the effectiveness of some drugs such as favipiravir, chloroquine and remdesivir has been shown *in vitro* (29). The effectiveness of some drugs is still controversial. In the first clinical studies, it was reported that combination therapy with hydroxychloroquine and azithromycin reduced viral RNA detection compared to control (30). However, the results of ongoing clinical trials brought discussions about the use of Hydroxychloroquine and chloroquine (31). A multicenter, open-label, randomized controlled clinical trial did not show additional benefits in virus elimination of hydroxychloroquine in association with specifically standard of care in patients with mild to moderate COVID-19. It also promoted an increased frequency of adverse events (32).

With the rapid spread of COVID-19 disease, these patients are frequently encountered especially in intensive care units and operating theaters (4). All the possibilities of modern medicine against this global enemy must be used. Until clinical trials are concluded, it may be necessary to modify existing treatments. Being able to choose the most effective agent among drugs frequently used in anaesthesia and intensive care practice will contribute positively to the mortality and morbidity of the patients. The 2018 PADIS guideline provides the most up-to-date recommendations for sedation in critically ill patients, and sedation can be planned according to these recommendations in COVID-19 patients followed in the intensive care unit (4,33). Although there are many studies on the clinical uses of these drugs, our aim in this study is to determine the possible advantageous drug for COVID-19 patients and lead clinical studies.

In our study, A chain for 6LU7, A chain for 1R4L and A and B chain for 6LZG protein were used for macromolecule preparation in docking process. Thus, the interaction between the amino acids and the enzyme, which is involved in the interaction between the functional groups of the drugs specified on the compound molecules, was observed in three dimensions. With the ability to investigate the interaction between hydrogen-electrostatic and VDW reactions in the enzyme active site, molecular docking was performed between compounds and protease, and the results were compared.

According to the results of our study, when the binding score of drugs for 1R4L, 6LU7 and 6LZG was evaluated and binding energies were examined; the binding energies for 1R4L are -1.79 to -7.44 kcal/mol, while fentanyl has the lowest value, sevoflurane has the highest value. The binding energies for 6LU7 were -1.75 to -7.97 kcal/mol, while the lowest value was detected in fentanyl and the highest value in sevoflurane. The binding energies for 6LZG were -2.31 to -8.11 kcal/mol, while the lowest value was detected in fentanyl and the highest value was in desflurane. While fentanyl has the lowest value in binding energies for all three proteins, the highest values were determined in volatile anesthetics, sevoflurane and desflurane. In addition, the drugs we examined in the study were compared with chloroquine, hydroxychloroquine and nelfinavir, which previously detected good binding energy against the SARS-CoV-2 virus using the molecular docking method. In particular, the drug with the closest binding energy to nelfinavir is fentanyl followed by remifentanil, ketamine, midazolam and propofol. As a result, we found that intravenous

agents are superior to volatile agents. This is probably due to structural differences between the drugs. This shows that total intravenous anaesthesia can be preferred in general anaesthesia applications. Fentanyl's potential to bind with the lowest energy can make it a priority choice for sedo-analgesia procedures in COVID-19 patients. We think that the data we obtained in this study, like other our studies conducted with the docking method (34,35), can be helpful in drug development. Our data are not at the level of recommendation for clinical decisions, and they should be supported by clinical studies.

Conclusion

In this study, where we examined the effects of sedative, analgesic and anesthetic drugs on SARS-CoV-2 by molecular docking method, we found that fentanyl and then remifentanil, ketamine, midazolam and propofol inhibits proteins that have important functions in the spread and proliferation of SARS-CoV-2. However, sevoflurane and desflurane are found ineffective in this regard. The data we obtained with the molecular docking method will be a reference for further studies and should be supported by clinical studies.

Ethics

Ethics Committee Approval: Ethics committee approval is not required.

Informed Consent: Patient consent is not required.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: E.B., M.D., N.Y., İ.K., Design: E.B., M.D., N.Y., İ.K., Data Collection and Process: E.B., M.D., N.Y., A.G., V.F.P., Analysis or Interpretation: E.B., M.D., N.Y., İ.K., M.A.K., A.G., V.F.P., Literature Search: E.B., N.Y., İ.K., M.A.K., A.G., V.F.P., Writing: E.B., M.D., N.Y., İ.K., M.A.K., A.G., V.F.P.

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

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020;395:507-13.
2. Sohrabi C, Alsafi Z, O'Neill N, Khan M, Kerwan A, Al-Jabir A, et al. World Health Organization declares global emergency: A review of the 2019 novel coronavirus (COVID-19). Int J Surg 2020;76:71-6.
3. Greenland JR, Michelow MD, Wang L, London MJ. COVID-19 Infection: Implications for Perioperative and Critical Care Physicians. Anesthesiology 2020;132:1346-61.
4. Ammar MA, Sacha GL, Welch SC, Bass SN, Kane-Gill SL, Duggal A, et al. Sedation, Analgesia, and Paralysis in COVID-19 Patients in the Setting of Drug Shortages. J Intensive Care Med 2021;36:157-74.
5. Gommers D, Bakker J. Medications for analgesia and sedation in the intensive care unit: an overview. Crit Care 2008;12 Suppl 3:S4.
6. Barr J, Fraser GL, Puntillo K, Ely EW, Gélinas C, Dasta JF, et al. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. Crit Care Med 2013;41:263-306.
7. Bein T, Grasso S, Moerer O, Quintel M, Guerin C, Deja M, et al. The standard of care of patients with ARDS: ventilatory settings and rescue therapies for refractory hypoxemia. Intensive Care Med 2016;42:699-711.
8. Braz HLB, Silveira JAM, Marinho AD, de Moraes MEA, Moraes Filho MO, Monteiro HSA, et al. In silico study of azithromycin, chloroquine and hydroxychloroquine and their potential mechanisms of action against SARS-CoV-2 infection. Int J Antimicrob Agents 2020;56:106119.
9. Lu R, Zhao X, Li J, Niu P, Yang B, Wu H, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet 2020;395:565-74.
10. Morse JS, Lalonde T, Xu S, Liu WR. Learning from the Past: Possible Urgent Prevention and Treatment Options for Severe Acute Respiratory Infections Caused by 2019-nCoV. Chembiochem 2020;21:730-8.
11. Chan JF, Kok KH, Zhu Z, Chu H, To KK, Yuan S, et al. Genomic characterization of the 2019 novel human-pathogenic coronavirus isolated from a patient with atypical pneumonia after visiting Wuhan. Emerg Microbes Infect 2020;9:221-36.
12. Meng XY, Zhang HX, Mezei M, Cui M. Molecular docking: a powerful approach for structure-based drug discovery. Curr Comput Aided Drug Des 2011;7:146-57.
13. Liu X, Zhang B, Jin Z, Yang H, Rao Z. Crystal structure of COVID-19 main protease in complex with an inhibitor N3. Protein DataBank, 2020.
14. Towler P, Staker B, Prasad SG, Menon S, Tang J, Parsons T, et al. ACE2 X-ray structures reveal a large hinge-bending motion important for inhibitor binding and catalysis. J Biol Chem 2004;279:17996-8007.
15. Wang Q, Zhang Y, Wu L, Niu S, Song C, Zhang Z, et al. Structural and Functional Basis of SARS-CoV-2 Entry by Using Human ACE2. Cell 2020;181:894-904. e9.
16. Morris GM, Huey R, Lindstrom W, Sanner MF, Belew RK, Goodsell DS, et al. AutoDock4 and AutoDockTools4: Automated docking with selective receptor flexibility. J Comput Chem 2009;30:2785-91.

17. Lii JH, Allinger NL. Molecular mechanics. The MM3 force field for hydrocarbons. 3. The van der Waals' potentials and crystal data for aliphatic and aromatic hydrocarbons, J Am Chem Soc 1989;111:8576-82.
18. Su S, Wong G, Shi W, Liu J, Lai ACK, Zhou J, et al. Epidemiology, Genetic Recombination, and Pathogenesis of Coronaviruses. Trends Microbiol 2016;24:490-502.
19. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, et al. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. Cell 2020;181:271-80.e8.
20. Wrapp D, Wang N, Corbett KS, Goldsmith JA, Hsieh CL, Abiona O, et al. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. Science 2020;367:1260-3.
21. Belouzard S, Millet JK, Licitra BN, Whittaker GR. Mechanisms of coronavirus cell entry mediated by the viral spike protein. Viruses 2012;4:1011-33.
22. Kandeel M, Al-Nazawi M. Virtual screening and repurposing of FDA approved drugs against COVID-19 main protease. Life Sci 2020;251:117627.
23. Gurung AB, Ali MA, Lee J, Farah MA, Al-Anazi KM. Unravelling lead antiviral phytochemicals for the inhibition of SARS-CoV-2 Mpro enzyme through in silico approach. Life Sci 2020;255:117831.
24. Zhang DH, Wu KL, Zhang X, Deng SQ, Peng B. In silico screening of Chinese herbal medicines with the potential to directly inhibit 2019 novel coronavirus. J Integr Med 2020;18:152-8.
25. Hung IF, Lung KC, Tso EY, Liu R, Chung TW, Chu MY, et al. Triple combination of interferon beta-1b, lopinavir-ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19: an open-label, randomised, phase 2 trial. Lancet 2020;395:1695-704.
26. Liu C, Zhou Q, Li Y, Garner LV, Watkins SP, Carter LJ, et al. Research and Development on Therapeutic Agents and Vaccines for COVID-19 and Related Human Coronavirus Diseases. ACS Cent Sci 2020;6:315-31.
27. Sheahan TP, Sims AC, Leist SR, Schäfer A, Won J, Brown AJ, et al. Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV. Nat Commun 2020;11:222.
28. Musarrat F, Chouljenko V, Dahal A, Nabi R, Chouljenko T, Jois SD, et al. The anti-HIV drug nelfinavir mesylate (Viracept) is a potent inhibitor of cell fusion caused by the SARSCoV-2 spike (S) glycoprotein warranting further evaluation as an antiviral against COVID-19 infections. J Med Virol 2020;92:2087-95.
29. Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res 2020;30:269-71.
30. Gautret P, Lagier JC, Parola P, Hoang VT, Meddeb L, Mailhe M, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agents 2020;56:105949.
31. Qaseem A, Yost J, Etxeandia-Ikobaltzeta I, Miller MC, Abraham GM, Obley AJ, et al. Should Clinicians Use Chloroquine or Hydroxychloroquine Alone or in Combination With Azithromycin for the Prophylaxis or Treatment of COVID-19 Ann Intern Med. 2020:M20-3862.
32. Tang W, Cao Z, Han M, Wang Z, Chen J, Sun W, et al. Hydroxychloroquine in patients with mainly mild to moderate coronavirus disease 2019: open label, randomised controlled trial. BMJ 2020;369:m1849.
33. Devlin JW, Skrobik Y, Gélinas C, Needham DM, Slooter AJC, Pandharipande PP, et al. Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU. Crit Care Med 2018;46:e825-73.
34. Koyuncu İ, Durgun M, Yorulmaz N, Toprak S, Gonel A, Bayraktar N, et al. Molecular docking demonstration of the liquorice chemical molecules on the protease and ACE2 of COVID-19 virus. Current Enzyme Inhibition 2021;7:98-110.
35. Ozturk H, Yorulmaz N, Durgun M, Basoglu H. *In silico* investigation of Alliin as potential activator for AMPA receptor. Biomed Phys Eng Express 2021;8.

Turk J Intensive Care 2021;19(Suppl 1):33-43
DOI: 10.4274/tybd.galenos.2021.05914

ORIGINAL RESEARCH / *ÖZGÜN ARAŞTIRMA*

Leyla Kazancıoğlu,
Başar Erdivanlı,
Hızır Kazdal,
Abdullah Özdemir,
Tolga Koyuncu,
Ayşe Hızal,
Asiye Özdemir,
İlkay Bahçeci,
Şule Batcık,
Tahir Ersöz

Effectiveness of Laboratory Parameters as Morbidity and Mortality Indicators in Patients with Coronavirus Disease-2019 Admitted to the Intensive Care Unit

Koronavirüs Hastalığı-2019 Tanısıyla Yoğun Bakıma Alınan Hastalarda Morbidite ve Mortalitenin Belirteçleri Olarak Laboratuvar Parametrelerinin Etkinliği

Received/Geliş Tarihi : 08.12.2020
Accepted/Kabul Tarihi : 17.02.2021

Leyla Kazancıoğlu, Başar Erdivanlı, Hızır Kazdal, Abdullah Özdemir, Tolga Koyuncu, Ayşe Hızal, Asiye Özdemir, Şule Batcık, Tahir Ersöz
Recep Tayyip Erdoğan University Faculty of Medicine, Department of Anesthesiology and Reanimation, Rize, Turkey

İlkay Bahçeci
Recep Tayyip Erdoğan University Faculty of Medicine, Department of Medical Microbiology and Clinical Microbiology, Rize, Turkey

Leyla Kazancıoğlu (✉),
Recep Tayyip Erdoğan University Faculty of Medicine, Department of Anesthesiology and Reanimation, Rize, Turkey

E-mail : leyla.kazancioglu@erdogan.edu.tr
Phone : +90 464 212 30 09
ORCID ID : orcid.org/0000-0002-3833-0692

ABSTRACT *Objective:* Laboratory parameters may predict the severity and mortality of coronavirus disease-2019 (COVID-19). We investigated the relationship of laboratory findings obtained at admission and 72nd hour and mortality and morbidity of patients with pneumonia who were treated in two intensive care units.
Materials and Methods: Chart data of 75 patients (March-May 2020) were retrospectively analysed. Patient characteristics and laboratory parameters were compared according to the presence of COVID-19 and mortality. Patients with COVID-19 were compared according to mortality and gender.
Results: The mean patient age was 74.7±11.3 years. COVID-19 positivity was not associated with marked differences in laboratory values. Lung disease, bedridden status, worse renal function scores, and high C-reactive protein level was more often observed in non-survivors ($p<0.05$). A decline in D-dimer level was more apparent in survivors; the increase in ferritin and neutrophil-lymphocyte ratio was more apparent in non-survivors (not significant). Among patients with COVID-19, women had higher mean platelet volume than men ($p=0.033$). The rise in ferritin level was more pronounced in men, whereas the rise in neutrophil-lymphocyte ratio and platelet-lymphocyte ratio was higher in women.
Conclusion: In this geriatric cohort, chronic lung disease and bedridden status were the main determinants of mortality. Moreover, different patterns of inflammatory markers may help predict the severity of COVID-19.
Keywords: COVID-19, pneumonia, intensive care unit, morbidity, mortality, geriatrics

ÖZ *Amaç:* Laboratuvar parametreleri koronavirüs hastalığı-2019'un (COVID-19) şiddet ve mortalitesini ön görebilir. Pnömoni teşhisiyle iki yoğun bakım ünitesinde tedavi edilen hastalarda ilk kabulde ve 72 saat sonra elde edilen laboratuvar bulguları ile mortalite ve morbidite arasındaki ilişkiyi inceledik.
Gereç ve Yöntem: Toplam 75 hastanın kayıtlarından (Mart-Mayıs 2020) gelen bilgiler geriye dönük incelendi. Hasta özellikleri ve laboratuvar parametreleri COVID-19 ve mortalite varlığına göre karşılaştırıldı. COVID-19+ olan hastalar, mortalite ve cinsiyete göre de karşılaştırıldı.
Bulgular: Ortalama yaş 74,7±11,3 yıl idi. COVID-19 pozitifliği laboratuvar değerlerinde belirgin değişikliklerle ikişkili değildi. Akciğer hastalığı, yatağa bağımlılık, kötü böbrek fonksiyon skorları ve yüksek C-reaktif protein eks hastalarda daha yaygın idi ($p<0,05$). D-dimerde azalma sağ kalanlarda daha belirgin idi; ferritin ve nötrofil-lenfosit oranı ölenlerde daha görünür idi (istatistiksel olarak anlamlı değil). COVID-19 hastaları arasında kadınların ortalama trombosit hacmi erkeklerden daha yüksekti ($p=0,033$). Ferritin yüksekliği erkeklerde daha belirgin iken, nötrofil-lenfosit ve trombosit-lenfosit oranları kadınlarda daha yüksek saptandı.
Sonuç: Bu geriatrik kohortta kronik akciğer hastalığı ve yatağa bağımlılık mortalitenin temel belirleyicileri olarak saptandı. Ayrıca enflamatuvar belirteçlerin farklı paternleri de COVID-19'da hastalık şiddetinin ön görülmesine yardımcı olabilir.
Anahtar Kelimeler: COVID-19, pnömoni, yoğun bakım ünitesi, morbidite, mortalite, geriatri

Introduction

An infectious disease caused by coronavirus emerged in Wuhan, China's Hubei province, at the end of December 2019 and spread rapidly around the world. The World Health Organization (WHO) identified coronavirus disease-2019 (COVID-19) disease, which stands for 2019 coronavirus disease, in February 2020 (1). The virus that causes COVID-19 has been identified as severe acute respiratory syndrome coronavirus 2.

In the literature, lymphopenia, increased C-reactive protein, ferritin, alanine and aspartate aminotransaminases and lactate dehydrogenase (LDH), prolonged prothrombin time, and increase in D-dimer, creatine phosphokinase and troponin levels have been reported in these patients (2-4). These changes in laboratory parameters have been associated with a poor prognosis (5-7). The course of COVID-19 disease is very similar to classic acute respiratory distress syndrome disease. However, some differences detected in the laboratory parameters of the patients suggest that the laboratory parameters at the hospitalization stage and after 72 hours can provide prediction about the severity and mortality of the disease (8). In order to test our hypothesis, we planned a retrospective study in which we examined the relationship between hospitalization and 72nd hour laboratory findings of patients who were followed up in our intensive care units with hypoxemia during the COVID-19 pandemic process with mortality and morbidity.

Materials and Methods

Patients

This study was conducted under following permissions of Scientific Research Platform of the Republic of Turkey Ministry of Health (Permit No: Leyla Kazancıoğlu-2020-05-20T12_40_44) and Recep Tayyip Erdogan University Non-invasive Clinical Research Ethics Committee (decision no: 2020/123, date: 01/07/2020). During the COVID-19 pandemic period, the patients we followed up in the intensive care units with the diagnosis of pneumonia between 19 March and 20 May 2020 were diagnosed according to WHO's provisional guide dated 28 January 2020 (9). Because the study we designed as a retrospective cohort study, informed consent from the patients was waived. This study was conducted in accordance with the ethical principles of the Declaration of Helsinki.

Patient characteristics [age, gender, Glasgow coma score (GCS), Acute Physiology and Chronic Health Evaluation-II (APACHE-II) score, arrest history before coming to intensive care unit (ICU), comorbid diseases], pulmonary tomography findings, time from onset of symptoms to hospital admission, referral location, under what conditions intubation was performed, hospitalization time, intubation day and duration, duration of stay in ICU, respiratory parameters (respiratory rate, arterial oxygenation parameters, invasive mechanical ventilation settings), hemodynamic parameters (arterial blood pressure, pulse) and biochemistry, hemogram, coagulometry, arterial blood gas (ABG) parameters, inflammation markers [C-reactive protein (CRP), D-dimer, ferritin, neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio] of hospitalization day and 72nd hour were obtained from the hospital's electronic database.

Biochemistry samples (including inflammatory and coagulation parameters) were evaluated with Beckman Coulter AUS800 (USA) automatic biochemistry analyzer, hemogram samples were evaluated with Mindray BC-6000 (China) automatic hemogram analyzer, and ABG samples were evaluated with Radiometer ABL800 FLEX (USA). The patients were grouped and compared according to the parameters listed below.

Grouping by the Presence of COVID-19 Positivity

Nasopharyngeal swab samples (additionally tracheal aspirate if intubated) were collected from all patients who were taken or planned to be taken to ICUs during the COVID-19 pandemic process. Total RNA was detected with the RNA isolation kit (PCR-Bio-Speedy COVID-19 RT-qPcr, Bioeksen, Turkey). Patients diagnosed with COVID-19 by reverse transcription-polymerase chain reaction were considered COVID-19 positive.

Patients who were found to be positive in the intensive care unit while the swab/aspirate sample taken outside the intensive care unit was negative, was also considered to be COVID-19 positive.

According to the above criteria, patients were divided into 2 groups as the COVID-19 positive pneumonia group (group COVID-19+) and the COVID-19 negative pneumonia group (group COVID-19-).

Grouping by Mortality

All patients were grouped as survivors and non-survivors according to the mortality that occurred during the ICU

hospitalization period. Patients who were discharged from the ICU alive and died in the ward or at home during their follow-up were classified as survivors in grouping.

Grouping of COVID-19 Positive Patients

COVID-19 positive patients were grouped and compared according to mortality. In statistical analysis, COVID-19 positive patients were grouped and compared according to gender, since a significant difference was found only in terms of gender when compared according to the parameters of COVID-19 positive patients.

Statistical Analysis

For statistical analysis, the data were evaluated with SPSS for Windows version 22 (SPSS, IBM, Chicago, IL, USA) software. The conformity of continuous variables to normal distribution was investigated by Kolmogorov-Smirnov test. Data conforming to normal distribution were given as mean ± standard deviation and compared using an independent t-test. Continuous variables not conforming to the normal distribution were given as median (interquartile width) and compared using the Mann-Whitney U test. Categorical data are given as numbers (%) and compared with the Fisher's Exact test. In the analyzes, $p<0.05$ was considered statistically significant.

Results

Data of 75 patients were evaluated (Figure 1). Patient characteristics were given separately in each comparison table. Briefly, the mean age of the COVID-19+ cases was 72.3±10.5 years in the early geriatric group according to the WHO classification, and the mean age of the COVID-19 cases was 76.4±11.6 years in the advanced age group according to the WHO classification, but there was no statistically significant difference (p=0.121) between two groups. The duration between the onset of symptoms and hospital admission was longer in COVID-19+ patients (p=0.01).

Comparison by the Presence of COVID-19 Positivity

Laboratory data taken on the day of hospitalization are given in Table 1. Briefly, no laboratory parameter obtained at the admission was statistically significantly different. However, D-dimer and erythrocyte distribution width were lower and ferritin was higher in COVID-19+ patients (p=0.05, 0.044 and 0.044, respectively).

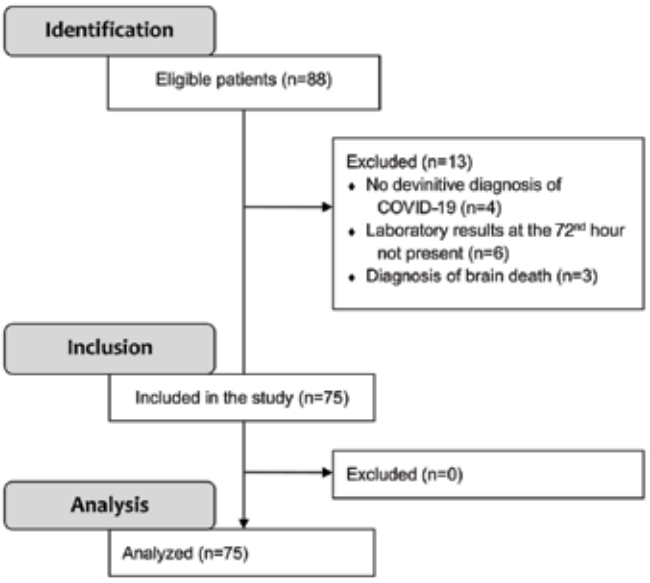


Figure 1. CONSORT flow diagram

Comparison by Mortality

The comparison of laboratory data according to mortality is given in Table 2. Briefly, APACHE-II score was higher in non-survivors (p=0.016). A history of cardiac arrest before reaching the hospital was only seen in non-survivors (p=0.026). Non-survivors had worse renal function scores ($p<0.05$); higher LDH values and white blood cell number (p=0.054 and 0.041, respectively). Among the inflammatory markers, only CRP was significantly different (higher in non-survivors, p=0.022) between groups. To note, the fall in D-dimer was more apparent in survivors; the increase in ferritin and NLR was more apparent in non-survivors, although there was no statistical significance.

Comparison of COVID-19+ Patients by Mortality

There were a total of 31 COVID-19+ patients, including 10 survivors (32.2%) and 21 non-survivors (67.7%). The data of these patients are given in Table 3. Briefly, there was no statistically significant difference. However, the increase in ferritin, NLR and Thrombocyte-lymphocyte ratio (TLR) was more pronounced in non-survivors, but the difference was not statistically significant.

Comparison of COVID-19+ Patients by Gender

Laboratory data of these patients are given in Table 4. In summary, gender distribution was equal. Women had lower GCSs (p=0.056) and higher mean platelet volume (MPV)

Table 1. Patient characteristics and laboratory values according to COVID-19 positivity			
	COVID-19- (n=44)	COVID-19+ (n=31)	p
Patient characteristics			
Age, years	76.4±11.6	72.3±10.5	0.121
Male gender, n (%)	27 (61.4%)	16 (51.6%)	0.546
Exitus, n (%)	30 (68.2%)	20 (64.5%)	0.931
Glasgow coma score	8.5 (3.0-13.2)	9.0 (6.0-15.0)	0.360
APACHE-II score at the day of hospitalization	24.4±10.1	23.1±9.6	0.576
History of cardiac arrest before reaching the hospital, n (%)	10 (22.7%)	3 (9.7%)	0.246
Congestive heart failure, n (%)	12 (27.3%)	7 (22.6%)	0.849
Hypertension, n (%)	32 (72.7%)	21 (67.7%)	0.834
Diabetes mellitus, n (%)	9 (20.5%)	9 (29.0%)	0.561
Chronic obstructive lung disease, n (%)	13 (29.5%)	4 (12.9%)	0.157
Bedridden due to serebrovascular disease, n (%)	10 (22.7%)	4 (12.9%)	0.439
COVID-19 signs present in thorax computerized tomography, n (%)	23 (52.3%)	20 (64.5%)	0.413
Duration between onset of symptoms until admission to hospital, days	2.0 (1.0-2.0)	2.0 (1.0-4.5)	**0.010**
Days in hospital until admission to ICU, days	0.0 (0.0-1.2)	0.0 (0.0-2.0)	0.359
Day of intubation	1.0 (1.0-1.0)	1.0 (1.0-1.0)	0.617
Duration of intubation, days	8.0 (2.8-13.5)	7.0 (2.0-26.0)	0.645
Length of stay in ICU, days	8.5 (3.0-18.2)	7.0 (5.0-26.5)	0.649
FiO_2, %	54.7±13.0	62.7±23.8	0.064
PEEP, cmH_2O	8.2±2.9	9.6±3.8	0.105
Systolic arterial blood pressure, mmHg	130.0 (101.0-170.0)	128.0 (128.0-128.0)	0.932
Diastolic arterial blood pressure, mmHg	80.0 (55.5-90.0)	72.0 (72.0-72.0)	0.924
Pulse, beats/min	106.2±31.5	92.0±32.6	0.678
Biochemistry parameters			
Glucose, mg/dL	150.0 (129.2-201.5)	147.0 (127.2-191.0)	0.972
Urea, mg/dL	78.0 (57.0-126.2)	47.0 (35.0-77.0)	0.019
Creatinine, mg/dL	1.2 (0.9-1.9)	1.0 (0.7-1.4)	0.027
eGFR	44.0 (33.2-72.0)	56.0 (44.0-89.0)	0.077
Albumin, g/dL	32.4±8.5	32.6±4.9	0.927
Total bilirubin, mg/dL	0.8 (0.5-1.3)	0.8 (0.6-1.3)	0.729
Direct bilirubin, mg/dL	0.2 (0.1-0.3)	0.2 (0.1-0.3)	0.613
ALT, U/L	21.5 (14.0-69.8)	25.5 (14.0-42.2)	0.269
AST, U/L	32.0 (24.0-102.0)	40.0 (26.5-69.0)	0.268
GGT, U/L	35.5 (19.2-59.0)	26.5 (20.2-46.5)	0.716
LDH, U/L	344.5 (235.8-567.2)	303.0 (256.5-463.5)	0.596
Creatine kinase, mg/dL	59.5 (54.2-191.2)	85.5 (68.2-113.2)	0.508
Complete blood count parameters			
White blodd cells, 10^3/uL	12.8 (9.0-15.7)	11.5 (6.7 - 13.1)	0.113
Lymphocyte number, 10^3/uL	0.8 (0.5-1.3)	0.9 (0.5 - 1.2)	0.725
Monocyte number, 10^3/uL	0.6 (0.3 - 0.8)	0.4 (0.3 - 0.7)	0.657

Table 1. Continued			
	COVID-19- (n=44)	**COVID-19+ (n=31)**	**p**
Neutrophil number, 10^3/uL	10.6 (7.7-13.3)	9.0 (5.3-11.6)	0.126
Red blood cell mass, 10^3/uL	4.0 (3.6-4.4)	4.1 (3.7- 4.4)	0.628
Hemoglobin, g/dL	11.3±2.1	11.9±2.2	0.310
Hematocrit, %	34.6±6.8	35.5±6.7	0.579
Mean corpuscular volume, fL	88.4±6.1	88.7±4.5	0.833
Platelets, 10^3/uL	225.0 (191.0-269.0)	217.0 (165.8-316.5)	0.986
Mean platelet volume, fL	9.8±1.1	9.9±1.5	0.678
Red cell distribution width (SD), fL	49.1±6.3	45.9±6.5	0.048
Red cell distribution width (CV), %	16.0±2.4	14.8±2.3	0.044
Coagulometry parameters			
Prothrombin time, sec	20.1±8.9	17.5±5.2	0.229
International normalized ratio	1.5±0.7	1.3±0.4	0.219
PT%	68.4±25.4	76.0±23.8	0.273
Fibrinogen, mg/dL	419.3±190.9	476.4±138.8	0.528
Arterial blood gas values			
pH	7.3±0.1	7.3±0.2	0.223
pCO_2, mmHg	52.3±17.5	44.5±15.5	0.123
pO_2, mmHg	70.5 (36.4-86.1)	82.2 (52.1-105.0)	0.241
sO_2, %	75.7±26.9	86.8±14.7	0.108
Lactate, mmol/L	2.0 (1.6-3.5)	1.7 (1.2-3.0)	0.279
Inflammation markers			
C-reactive protein, mg/L			
Day of admission to ICU	87.0 (15.2-163.0)	90.5 (15.0-128.2)	0.991
72nd hour	118.0 (82.0-206.0)	116.5 (85.5-178.2)	0.854
D-dimer, µg FEU/mL			
Day of admission to ICU	3.7 (1.6-4.7)	3.4 (2.2-4.2)	0.824
72nd hour	2.6 (2.0-6.6)	1.5 (0.8-2.3)	0.050
Ferritin, ng/mL			
Day of admission to ICU	67.2 (25.5-219.6)	56.7 (22.3-177.0)	0.684
72nd hour	187.0 (95.9-257.0)	850.0 (319.0-897.5)	0.044
Neutrophil/Lymphocyte ratio			
Day of admission to ICU	10.7 (7.4-20.8)	8.5 (4.5-16.6)	0.176
72nd hour	9.7 (6.7-20.8)	14.8 (9-25.4)	0.305
Platelet/Lymphocyte ratio			
Day of admission to ICU	284.3 (162.7-457.1)	269.6 (118.5-511.6)	0.671
72nd hour	262 (142-451)	315 (269-422)	0.352

ICU: Intensive care unit, FiO_2: fraction of inspired oxygen, PEEP: positive end-expiratory pressure, eGFR: estimated glomerular filtration rate, ALT: alanine aminotransferase, AST: aspartate amino transferase, GGT: gama glutamil transferaz, LDH: lactate dehydrogenase, pCO_2: partial pressure of carbon dioxide, PO_2: partial pressure of oxygen, sO_2: oxygen saturation, APACHE-II: Acute Physiology and Chronic Health Evaluation-II, COVID-19: coronavirus disease-2019, SD: standard deviation, CV: coefficient of variation

Table 2. Patient characteristics and laboratory values according to mortality			
	Survivors (n=22)	**Non- survivors (n=53)**	**p**
Patient characteristics			
Age, years	74.0±12.5	75.0±10.8	0.720
Male gender, n (%)	10 (45.5%)	33 (62.3%)	0.279
COVID-19 positivity, n (%)	10 (45.5%)	21 (39.6%)	0.834
Glasgow coma score	10.5±4.2	8.3±4.8	0.068
APACHE-II score at the day of hospitalization	19.7±8.4	25.6±9.9	0.016
History of cardiac arrest before reaching the hospital, n (%)	-	13 (24.5%)	0.026
Congestive heart failure, n (%)	6 (27.3%)	13 (24.5%)	1.000
Hypertension, n (%)	15 (68.2%)	38 (71.7%)	0.979
Diabetes mellitus, n (%)	7 (31.8%)	11 (20.8%)	0.469
Chronic obstructive lung disease, n (%)	4 (18.2%)	13 (24.5%)	0.768
Bedridden due to serebrovascular disease, n (%)	3 (13.6%)	11 (20.8%)	0.693
COVID-19 signs present in thorax computerized tomography, n (%)	14 (63.6%)	29 (54.7%)	0.649
Duration between onset of symptoms until admission to hospital, days	2.4±1.9	2.5±2.1	0.794
Days in hospital until admission to ICU, days	1.4±2.0	1.1±2.5	0.676
Day of intubation	1.5±2.2	1.4±1.1	0.748
Duration of intubation, days	17.1±23.7	11.4±11.6	0.205
Length of stay in ICU, days	17.7±21.5	13.2±16.1	0.318
FiO_2, %	54.3±17.4	59.5±18.9	0.266
PEEP, cmH_2O	8.6±3.1	8.8±3.5	0.806
Systolic arterial blood pressure, mmHg	130.0±30.0	132.2±46.6	0.941
Diastolic arterial blood pressure, mmHg	73.3±15.3	74.6±25.7	0.941
Pulse, beats/min	87.7±18.6	111.4±32.1	0.267
Biochemistry parameters			
Glucose, mg/dL	156.2±65.0	172.1±61.6	0.332
Urea, mg/dL	61.5±45.4	92.1±52.8	0.024
Creatinine, mg/dL	1.0±0.4	1.7±1.1	0.012
eGFR	69.6±28.6	51.2±27.4	0.013
Albumin, g/dL	32.6±7.6	31.1±5.6	0.393
Total bilirubin, mg/dL	0.9±0.5	1.0±0.7	0.623
Direct bilirubin, mg/dL	0.2±0.2	0.3±0.3	0.148
ALT, U/L	130.3±405.9	107.2±225.8	0.766
AST, U/L	153.7±495.1	161.7±335.7	0.938
GGT, U/L	66.2±107.0	83.3±135.2	0.636
LDH, U/L	308.6±123.6	494.1±376.8	0.054
Creatine kinase, mg/dL	173.4±127.2	157.2±275.4	0.904
Complete blood count parameters			
White blodd cells, 10^3/uL	9.8±4.0	13.0±6.3	0.041
Lymphocyte number, 10^3/uL	0.9±0.5	1.2±1.3	0.347
Monocyte number, 10^3/uL	0.4±0.2	0.7±0.5	0.028

Table 2. Continued			
	Survivors (n=22)	**Non- survivors (n=53)**	**p**
Neutrophil number, 10^3/uL	8.4±3.8	11.0±5.6	0.061
Red blood cell mass, 10^3/uL	4.0±0.6	4.0±0.8	0.953
Hemoglobin, g/dL	11.6±2.0	11.5±2.2	0.882
Hematocrit, %	34.9±6.3	35.0±6.9	0.980
Mean corpuscular volume, fL	88.3±4.6	88.6±5.8	0.862
Platelets, 10^3/uL	238.3±87.7	246.0±106.1	0.779
Mean platelet volume, fL	9.6±1.1	9.9±1.3	0.509
Red cell distribution width (SD), fL	45.8±5.6	48.6±6.7	0.111
Red cell distribution width (CV), %	14.8±2.2	15.7±2.4	0.167
Coagulometry parameters			
Prothrombin time, sec	15.3±2.5	20.6±8.6	0.022
International normalized ratio	1.1±0.2	1.6±0.7	0.024
PT%	86.2±19.1	65.7±24.7	0.005
Fibrinogen, mg/dL	422.8±204.6	476.7±115.8	0.605
Arterial blood gas values			
pH	7.3±0.1	7.3±0.1	0.744
pCO_2, mmHg	56.2±15.2	45.9±16.9	0.069
pO_2, mmHg	72.1±73.4	82.2±42.5	0.568
sO_2, %	74.9±23.6	82.9±22.3	0.300
Lactate, mmol/L	2.4±1.5	3.3±3.3	0.409
Inflammation markers			
C-reactive protein, mg/L			
Day of admission to ICU	52 (9-103)	95.5 (42-194.5)	0.022
72nd hour	107 (82-158)	123 (84-225)	0.205
D-dimer, µg FEU/mL			
Day of admission to ICU	3.9 (2.1-4.9)	3.2 (1.9-3.8)	0.469
72nd hour	2 (1.2-2.3)	2.3 (1.2-7.3)	0.201
Ferritin, ng/mL			
Day of admission to ICU	245 (187-410)	118 (109-177)	0.667
72nd hour	258 (139-996)	418 (160-726)	0.554
Neutrophil/Lymphocyte ratio			
Day of admission to ICU	10.8 (7-17)	9.2 (5.5-19.7)	0.642
72nd hour	7.7 (6-15.2)	16 (9.9-26.9)	0.074
Platelet/Lymphocyte ratio			
Day of admission to ICU	298 (161-500)	255 (148-489)	0.594
72nd hour	209.5 (157.5-282)	185 (144-269)	0.665

ICU: Intensive care unit, FiO_2: fraction of inspired oxygen, PEEP: positive end-expiratory pressure, eGFR: estimated glomerular filtration rate, ALT: alanine aminotransferase, AST: aspartate amino transferase, GGT: gama glutamil transferaz, LDH: lactate dehydrogenase, pCO_2: partial pressure of carbon dioxide, PO_2: partial pressure of oxygen, sO_2: oxygen saturation, APACHE-II: Acute Physiology and Chronic Health Evaluation-II, COVID-19: coronavirus disease-2019, SD: standard deviation, CV: coefficient of variation

(p=0.033). The rise in ferritin was more pronounced in men, whereas the rise in NLR and TLR was higher in women, but the difference was not statistically significant.

Discussion

In this descriptive, retrospective cohort study, in which we examined the effects of clinical and laboratory data of 75 patients with a diagnosis of pneumonia in our ICUs during the COVID-19 pandemic period, on mortality and morbidity, we determined some patient characteristics and laboratory parameters showing morbidity and mortality.

It has been reported that mostly middle-aged and older adults are affected by COVID-19 infection and the mortality rate of older adults is higher (10-13). In a report by the Chinese Center for Disease Control and Prevention, case fatality rates were reported as 8 and 15%, respectively, among those aged 70-79 years and those aged 80 and over (10). In a study conducted in the United Kingdom, the risk of death among patients aged 80 and over was found to be 20 times that of patients aged 50-59 years (13). In the United States, 67% of 2,449 patients diagnosed with COVID-19 during February-March 2020 were over the age of 45; the mortality rate is higher in elderly individuals; It has been reported that 80% of the deaths occur in people aged 65 and over (14). In our study, there was no association between mortality and age. However it is important to note that >80% of our patients are above 65 years of age. Comparison according to mortality showed that comorbidities such as hypertension, congestive heart failure and diabetes mellitus (DM) were as prevalent in survivors as mortal cases. It is interesting to note that mortal cases presented with more frequent chronic obstructive lung disease or bedridden status due to cerebrovascular disease. We are in opinion that in this geriatric patient cohort these two conditions, able to pronounce the severity of oxygenation defect and

Table 3. Comparison of COVID-19+ patients according to mortality

	Survivors (n=10)	Non-survivors (n=21)	p
Age, years	71±13.9	73±8.8	0.637
Male gender, n (%)	4 (25%)	12 (75%)	0.458
Glasgow coma score	10.5 (8-14.8)	9 (6-15)	0.666
APACHE-II score at the day of hospitalization	23 (15-26.8)	26 (13-31)	0.433
Complete blood count parameters			
Mean platelet volume, fL	9 (8.7-10.1)	10.2 (9-11.2)	0.098
Inflammation markers			
C-reactive protein, mg/L			
Day of admission to ICU	112.5 (38-141.8)	87 (11.8-113)	0.441
72nd hour	138 (84-226)	116 (87.5-176.5)	0.749
D-dimer, µg FEU/mL			
Day of admission to ICU	3.7 (2.4-4.4)	3.2 (2.6-3.9)	0.881
72nd hour	2 (0.6-3)	1.2 (0.8-2.2)	0.779
Ferritin, ng/mL			
Day of admission to ICU	150 (38-419.6)	257 (122-277.0)	0.684
72nd hour	418 (220-602)	890.5 (858-1203)	0.100
Neutrophil/Lymphocyte ratio			
Day of admission to ICU	8.4 (5.4-11.7)	8.5 (4.4-18.4)	0.722
72nd hour	8.9 (7.5-10.2)	16.4 (10.6-32.5)	0.266
Platelet/Lymphocyte ratio			
Day of admission to ICU	327 (218-489)	200 (113-512)	0.360
72nd hour	324.5 (316-333)	313 (240-487)	0.874

APACHE-II: Acute Physiology and Chronic Health Evaluation-II, COVID-19: coronavirus disease-2019, ICU: intensive care unit

thrombotic complications, were major determinants of the negative outcome.

COVID-19+ disease can occur in healthy individuals of all ages; however, hospitalization was observed in the elderly group, often accompanied by comorbidities. In a study of 355 patients who died due to COVID-19 infection in Italy, the average number of pre-existing comorbidities was 2.7; there was no concomitant disease in only 3 patients' history (12). In our region, between March and April 2020, mortality rates were higher in patients with COVID-19+ pneumonia in the early geriatric age group. When Table 1 was examined, it was found that the frequency of comorbidity was lower in the COVID-19+ group, but when Table 3 was examined, the frequency of comorbidity was generally higher in patients with a mortal course regardless of the COVID-19 diagnosis. It was striking that the frequency of DM was higher in survivors; we believe that this is due to the non-severity of DM disease in our cohort of patients. We noted that only DM was more prevalent in COVID-19 + patients. The rest were similar, except chronic obstructive lung disease and bedridden status, which were lower. With these results, we thought that the presence of comorbidities in the geriatric age group are not associated with susceptibility to COVID-19 infection. However, given the lower mortality rate among the COVID-19+ patients in our cohort compared to the current literature, we may presume that the lack of comorbidities may decrease the severity of COVID-19 infection.

Among the laboratory parameters studied, D-dimer was found to be higher in patients with COVID-19- on the day of hospitalization. In the follow-up, at the 72nd hour, it was found to be higher in cases with mortality. With these results, we believe that D-dimer is a marker that is not specific to COVID-19 disease and persistently high values may show mortality at the 72nd hour.

In the literature, mortality has been reported to be higher in men compared to women (2,5,15). In a meta-

Table 4. Comparison of COVID-19+ patients according to gender

	Male (n=16)	Female (n=15)	p
Age, years	70±8.9	74.8±11.9	0.210
Exitus, n (%)	12 (75%)	9 (60%)	0.470
Glasgow coma score	11.1±4.9	7.9±4	0.056
APACHE-II score at the day of hospitalization	22.5±10.7	23.8±8.6	0.714
Complete blood count parameters			
Mean platelet volume, fL	9.4±1.4	10.6±1.4	0.033
Inflammation markers			
C-reactive protein, mg/L			
Day of admission to ICU	98 (35.5-119.5)	86 (17.7-127.5)	0.917
72nd hour	104 (86-179)	138 (86.5-176)	0.977
D-dimer, µg FEU/mL			
Day of admission to ICU	5.9 (5.2-6.6)	3.2 (1.8-3.8)	0.127
72nd hour	1.6 (0.5-2.3)	1.5 (1.1-2.5)	0.859
Ferritin, ng/mL			
Day of admission to ICU	118 (32-410)	100 (44-256)	0.698
72nd hour	896 (882-899)	510 (269.5-788)	0.273
Neutrophil/Lymphocyte ratio			
Day of admission to ICU	15.9 (4.9-21.2)	7.4 (4.4-9.8)	0.178
72nd hour	12.9 (10.4-20.3)	19.4 (7.9-32.5)	0.828
Platelet/Lymphocyte ratio			
Day of admission to ICU	382 (117-539)	181 (144.4-318)	0.265
72nd hour	297 (240-333)	454.5 (339-712)	0.104

APACHE-II: Acute Physiology and Chronic Health Evaluation-II, COVID-19: coronavirus disease-2019, ICU: intensive care unit

analysis (including 77,392 patients), COVID-19 patients had significantly higher morbidity, severity and mortality in men compared to women (16). In our study, it was found that the mortality rate was higher in male gender, but there was no statistically significant difference. On the other hand, differences in MPV and NLR values depending on gender were remarkable. MPV and NLR, which are unconventional parameters used in mortality and morbidity monitoring, are also provide information about cardiovascular complications and inflammation (17-20). MPV value was found to be higher than normal in all our patients, and we observed that this elevation was significant only in COVID-19+ female patients. We found that patients with COVID-19 had lower NLR and TLR values on the day of hospitalization, however values at the 72nd hour was higher (albeit not statistically significant). This difference was only seen in women. With these results, we think that the high MPV values, late increase or persistency in high NLR and TLR values may be used as indicators of COVID-19 disease and mortality in women.

In a study comparing severe and moderate COVID-19 patients, red blood cell distribution width-coefficient of variation (RDW-CV), red blood cell distribution width-standard deviation (RDW-SD) values among the morphological parameters were found to be higher in the severe COVID-19 patient group (21). In another study, it was predicted that the increase in RDW value within the first 72 hours after hospitalization in patients with severe sepsis and septic shock may be associated with adverse clinical outcomes (22). In our cohort of patients, RDW-SD and RDW-CV values were higher on the day of hospitalization, similar to D-dimer, in COVID-19-patients and in patients with a mortal course. We believe that the reason for this situation is due to the lower mortality among our COVID-19+ patients.

This retrospective cohort study has many limitations. First of all, the limited number of patients may have affected the statistical significance of the results. Secondly, mortality in COVID-19+ patients was lower than reported in reports published at similar periods, making the markers difficult to interpret. As stated above, it was concluded that parameters such as D-dimer, NLR, and MPV are markers specific to mortality rather than COVID-19. However, it should be kept in mind that all patients admitted to the ICU during the period when patient data are collected were potentially approached as COVID-19+, and all of them were given hydroxychloroquine, favipiravir, azithromycin and similar antibiotics in accordance with the relevant guidelines. In addition, according to the data obtained in this period, the guidelines and treatment scheme were updated frequently. Considering that some patients who started treatment with COVID-19+ were determined to be COVID-19- and the treatments were terminated, it is obvious that it will be difficult to evaluate the effects of empirical antibiotherapy on laboratory parameters in a retrospective study. Finally, the diversity of pneumonia agents in COVID-19- patients and bacterial superinfection agents observed in all COVID-19+ patients may also have caused the difference in biochemical parameters.

Conclusion

As a result, the patient cohort we followed up in the ICU with the diagnosis of pneumonia during the COVID-19 pandemic period consisted of the geriatric age group with comorbidities. In this patient group, we believe that male gender and high D-dimer values measured at 72nd hour are determinative for mortality, and the high MPV value in women and NLR value in men can be used as indicators of COVID-19 disease and mortality.

Ethics

Ethics Committee Approval: Approval for the study (decision no: 2020/123, date: 23.06.2020) was obtained from Recep Tayyip Erdoğan University Faculty of Medicine's Ethics Committee.

Informed Consent: Because the study we designed as a retrospective cohort study, informed consent from the patients was waived.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: L.K., Ş.B., Design: L.K., B.E., A.Ö., T.E., Data Collection and Process: L.K., B.E., H.K., A.Ö., T.K., As.Ö., İ.B., Analysis or Interpretation: L.K., A.Ö., As.Ö., Literature Search: B.E., H.K., A.H., İ.B., Ş.B., T.E., Writing: L.K., A.H.

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

Financial Disclosure: The authors declared that this study received no financial support.

References

1. World Health Organization. Director-General's remarks at the media briefing on 2019-nCoV on 11 February 2020. Available from URL: https://www.who.int/dg/speeches/detail/who-director-general-s-remarks-at-the-media-briefing-on-2019-ncov-on-11-february-2020 (Accessed February 12, 2020).
2. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. JAMA 2020;323:1061-9.
3. Goyal P, Choi JJ, Pinheiro LC, Schenck EJ, Chen R, Jabri A, et al. Clinical Characteristics of Covid-19 in New York City. N Engl J Med 2020;382:2372-4.
4. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med 2020;382:1708-20.
5. Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, et al. Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. JAMA Intern Med 2020;180:934-43.
6. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020;395:1054-62.
7. Shi S, Qin M, Shen B, Cai Y, Liu T, Yang F, et al. Association of Cardiac Injury With Mortality in Hospitalized Patients With COVID-19 in Wuhan, China. JAMA Cardiol 2020;5:802-10.
8. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020;395:507-13.
9. World Health Organization. Clinical management of severe acute respiratory infection when novel coronavirus (nCoV) infection is suspected: interim guidance. Published January 28, 2020. Available from URL: https://www.who.int/publications-detail/clinical-managementof-severe-acute-respiratory-infection-when-novelcoronavirus-(ncov)-infection-is-suspected Accessed January 31, 2020.
10. Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention. JAMA 2020;323:1239–42.
11. Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, et al. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. JAMA 2020;323:2052-9.
12. Onder G, Rezza G, Brusaferro S. Case-Fatality Rate and Characteristics of Patients Dying in Relation to COVID-19 in Italy. JAMA 2020;323:1775-6.
13. Williamson EJ, Walker AJ, Bhaskaran K, Bacon S, Bates C, Morton CE, et al. Factors associated with COVID-19-related death using OpenSAFELY. Nature 2020;584:430-6.
14. CDC COVID-19 Response Team. Severe Outcomes Among Patients with Coronavirus Disease 2019 (COVID-19) - United States, February 12-March 16, 2020. MMWR Morb Mortal Wkly Rep 2020;69:343-6.
15. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395:497-506.
16. Wei X, Xiao YT, Wang J, Chen R, Zhang W, Yang Y, et al. (2020). Sex differences in severity and mortality among patients with COVID-19: evidence from pooled literature analysis and insights from integrated bioinformatic analysis. arXiv 2003.13547v13541.
17. Taskesen T, Sekhon H, Wroblewski I, Goldfarb M, Ahmad MB, Nguyen QT, et al. Usefulness of Mean Platelet Volume to Predict Significant Coronary Artery Disease in Patients With Non-STElevation Acute Coronary Syndromes. Am J Cardiol 2017;119:192-6.
18. Suh B, Shin DW, Kwon HM, Yun JM, Yang HK, Ahn E, et al. Elevated neutrophil to lymphocyte ratio and ischemic stroke risk in generally healthy adults. PLoS One 2017;12:e0183706.
19. Öztürk ZA, Kuyumcu ME, Yesil Y, Savas E, Yıldız H, Kepekçi Y, et al. Is there a link between neutrophil-lymphocyte ratio and microvascular complications in geriatric diabetic patients? J Endocrinol Invest 2013;36:593-9.
20. Bozkurt D, Ozkurt D, Kılavuz A, Caferov N, Köse T, Akcicek F. Non-Traditional mortality predictors for geriatric intensive care unit patients. Turkish Journal of Geriatrics 2018;21:323–32.
21. Wang C, Deng R, Gou L, Fu Z, Zhang X, Shao F, et al. Preliminary study to identify severe from moderate cases of COVID-19 using combined hematology parameters. Ann Transl Med 2020;8:593.
22. Kim CH, Park JT, Kim EJ, Han JH, Han JS, Choi JY, et al. An increase in red blood cell distribution width from baseline predicts mortality in patients with severe sepsis or septic shock Crit Care 2013;17:R282.

Turk J Intensive Care 2021;19(Suppl 1):44-53
DOI: 10.4274/tybd.galenos.2021.30592

ORIGINAL RESEARCH / *ÖZGÜN ARAŞTIRMA*

Döndü Genç Moralar,
Ülkü Aygen Türkmen,
Ayşe Vahapoğlu,
Hüseyin Gökçenoğlu,
Ayfer Kaya Gök

Significance of Lung Ultrasonography in the Follow-up and Treatment of Patients with Coronavirus Disease-2019 Having Respiratory Failure

Solunum Yetersizliği Olan Koronavirüs Hastalığı-2019 Hastalarında Akciğer Ultrasonografisinin Takip ve Tedavideki Yeri

Received/Geliş Tarihi : 06.11.2020
Accepted/Kabul Tarihi : 15.03.2021

Döndü Genç Moralar, Ülkü Aygen Türkmen, Ayşe Vahapoğlu, Hüseyin Gökçenoğlu, Ayfer Kaya Gök
University of Health Sciences Turkey, Gaziosmanpaşa Training and Research Hospital, Clinic of Anesthesiology and Reanimation, İstanbul, Turkey

Döndü Genç Moralar MD, (✉),
University of Health Sciences Turkey, Gaziosmanpaşa Training and Research Hospital, Clinic of Anesthesiology and Reanimation, İstanbul, Turkey

E-mail : dondugencm@gmail.com
Phone : +90 505 373 79 13
ORCID ID : orcid.org/0000-0002-4229-4903

Presented in: Our study was accepted as an oral presentation at the 20th National Intensive Care Congress to be held on 10-15 November 2020. Our study was also decided to participate in the Clinical Study Oral Presentation contest in the congress.

ABSTRACT *Objective:* Lung involvement is commonly seen in patients with coronavirus disease-2019. In such cases, mechanical ventilation support and patient positioning are used to improve oxygenation. This study aimed to evaluate the effect of positioning performed under the guidance of ultrasound-guided patient positioning.

Materials and Methods: Patients were divided into two groups: those who underwent lung ultrasonography and those who did not. Patients who underwent lung ultrasonography were positioned in a way that the region with larger infiltration area was upwards and then the groups were compared.

Results: Arterial blood gas values of 103 patients were evaluated. An increased partial pressure of oxygen (PaO_2) values at 2 and 12 hours after positioning was statistically significant in patients who were positioned under ultrasound guidance. In the group who did not undergo ultrasonography, an increased PaO_2 values was observed at 12 hours. When patients were evaluated according to their positions, an increased PaO_2 values at 2 and 12 hours was statistically significant in the right lateral decubitus position. An increased PaO_2 values was observed in prone position; however, it was not statistically significant.

Conclusion: In our study, an increased oxygenation was observed in a short time, i.e., 2 hours, when patients were positioned under ultrasound guidance.

Keywords: Lung ultrasonography, COVID-19, intensive care, acute respiratory distress syndrome, prone position, intensive care unit

ÖZ *Amaç:* Koronavirüs hastalığı-2019 hastalarında akciğer tutulumu sıklıkla görülmekte, mekanik ventilasyona ihtiyaç duyulmakta, oksijenasyonun artırılmasında pozisyon desteğinden de faydalanılmaktadır. Çalışmamızda ultrasonografi rehberliğinde verilen pozisyon uygulamasının oksijenizasyon üzerine etkisinin değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntem: Hastalar akciğer ultrasonografisi yapılanlar ve yapılmayanlar olmak üzere iki gruba ayrıldı. Akciğer ultrasonografisi yapılan hastalara infiltrasyon alanı fazla olan bölge yukarıda olacak şekilde pozisyon verildi. Gruplar karşılaştırıldı.

Bulgular: Çalışmaya katılan 103 hasta 2. ve 12. saatte arter kan gazı ile değerlendirilerek karşılaştırıldı. Ultrasonografi rehberliğinde pozisyon verilen hastalarda pozisyon verilmesinden sonra 2. saat ve 12. saatte PaO_2 değerlerindeki artışın istatiksel olarak anlamlı olduğu görüldü. Ultrasonografi yapılmayan grupta ise 12. saatte PaO_2 değerlerinde artış görüldü. Hastalar verilen pozisyonlara göre değerlendirildiğinde sağ lateral dekübit pozisyonunda PaO_2 değerinde 2. ve 12. saatteki artış istatiksel olarak anlamlı idi. Pron pozisyonda ise PaO_2 değerinde artış olmakla birlikte istatistiksel olarak anlamlı değildi.

Sonuç: Çalışmamızda hastalara ultrasonografi rehberliğinde pozisyon verildiğinde, 2 saat gibi bir sürede oksijenizasyonda artış olduğu görüldü.

Anahtar Kelimeler: Akciğer ultrasonografisi, COVID-19, yoğun bakım, akut solunum sıkıntısı sendromu, pron pozisyon, yoğun bakım ünitesi

Introduction

Lung involvement is frequently seen in coronavirus disease-2019 (COVID-19) disease, and the incidence of acute respiratory distress syndrome (ARDS) is reported to be 17-42% (1). Computed tomography (CT) is used for diagnosis, but there are risks such as exposure to excessive radiation, problems in the transfer of critical patients, and transmission of infection, and viral contamination (2-4). Therefore, it is not recommended to use CT in disease follow-up. Posteroanterior chest X-ray can often be used to avoid these risks.

However, the use of lung ultrasonography (LU) is becoming gradually more common in the diagnosis and follow-up of pneumonia and ARDS (5,6). LU is also considered to be superior to posteroanterior chest X-ray in the follow-up of COVID-19 patients (7).

Due to reasons such as the pathological progression of COVID-19 pneumonia and the occurrence of peripheral involvement, a surface imaging technique like LU is rather appropriate (4,8). It is also reported that LU has high diagnostic accuracy, is repeatable, noninvasive, ergonomic, and causes less infection, and enables a quick evaluation lung status without using ionizing radiation (8-10). Because of such advantages, LU has readily become a tool for the diagnosis and follow-up of the severity of the lung involvement (3,11).

Besides the mechanical ventilation strategies, the importance of patient positioning is known to improve oxygenation during the treatment of ARDS. Improvements in oxygenation and reduced mortality have been reported in the literature in association with the prone position (12).

Our aim was to investigate the effect of LU-guided appropriate patient positioning on improved oxygenation and ventilation to obtain effective use of lung capacity in COVID-19 patients admitted to the intensive care unit (ICU) due to acute respiratory failure.

The primary aim was to evaluate the effect of LU-guided positioning on oxygenation in patients with hypoxemic respiratory failure due to COVID-19. For this purpose, changes in partial oxygen pressure in arterial blood (PaO_2) levels were examined after patient positioning. The secondary aim of the study was to evaluate the effect of LU-guided patient positioning on ventilation. For this purpose, changes in partial carbon dioxide pressure in arterial blood ($PaCO_2$) levels obtained after patient positioning were examined.

Materials and Methods

This study was approved by the Ministry of Health (dated 05.04.2020, numbered 2020-05-04T00-50-43) and Gaziosmanpaşa Training and Research Hospital's Clinical Research Ethics Committee (decision no: 66, date: 26.05.2020) and written informed consent was obtained from all patients included in the study. The study was registered on clinicaltrials.gov (NCT04432051, date of registration: 06.16.2020). This manuscript adheres to the applicable CONSORT guidelines.

The study was conducted in the ICUs of our hospital between May 26 and July 26, 2020. One hundred ten patients between 18-80 years of age who were diagnosed with moderate and severe ARDS due to COVID-19 were included in the study. All patients included in the study had a partial arterial oxygen pressure:fraction of inspired oxygen (PaO_2:FiO_2) ratio of <200 and received mechanical ventilation support was applied to all patients.

In renal and cardiac failure, the respiratory system and oxygenation can be affected independently of acute respiratory failure due to COVID-19. Therefore, patients with cardiac and renal problems were excluded from the study.

Of the 110 patients included in the study; an intubated patient could not tolerate the prone position and was brought back to the supine position because of a sudden drop in oxygen saturation in arterial blood (SaO_2) and another patient receiving non-invasive mechanical ventilation support was brought back to the supine position because of difficulty adapting to the prone position. When the patients' arterial blood gas (ABG) analyses were evaluated, 5 patients with initial base excess (BE) values of <-3 were considered to have metabolic acidosis and excluded from the study. Thus, 7 patients were excluded from the study, and the data from 103 patients were evaluated.

This study was planned as a prospective randomized-controlled, and double-blinded study. Randomization was performed according to the days of the week. The patients were divided into two parallel groups as patients undergoing LU (group A) and patients without ultrasonography (group B).

All patients included in the study were examined for respiratory system findings and were evaluated by ABG analysis. Mechanical ventilation settings have been adjusted. And during the study, FiO_2 levels and other parameters of mechanical ventilation settings were not changed until ABG was taken at the 12th hour.

The condition of the patients' lungs was scored via LU in group A by an anesthesiologist experienced in LU. Six-zone scanning method was performed on for each hemithorax as recommended in previous studies was used (11,13-15). While performing LU (MyLab™ Seven, Esaote, Genova, Italy), each hemithorax was divided into 6 quadrants for the examination as anterior, lateral, and posterior regions and lower and upper sections within each region, using anterior axillary line and posterior axillary line. Thus, each hemithorax was scanned on six quadrants by using a convex ultrasound (US) probe and scored with lung ultrasound score (LUS) (Table 1) (16).

In LU; A-lines characterized by the horizontal reverberation artifact and mirror images of the pleural line are formed depending on the reflection of the pleura (Figure 1) (2,17,18). A-lines show normally aerated lung. B-lines are hyperechoic, laser-like, vertical reverberation artifacts, which obliterate the A-lines extending from the pleural line to the bottom of the screen (Figure 2) (4,17,19,20). With synchronization of the breath, B-lines move and up to three B-lines appear per lung window (intercostal space) (4,17).

Diagnosis of interstitial lung disease is made in the presence of >3 B-lines, confluent B-lines (white lung), >0.3 mm thick, irregular pleural line, subpleural consolidations per window (Figure 3,4,5) (4,20). Consolidation regions are observed in advanced cases (Figure 6).

Depending on the LUS; patients were brought to the supine, prone, right lateral, or left lateral positions with the side with higher scores kept upside.

Mechanical ventilation adjustments were made to the control patients in group B by taking into account routine respiratory examination and ABG analysis. The patients were positioned as deemed appropriate by the physician.

ABG analysis values of the patients were evaluated in both groups at the beginning (before physical examinations ± ultrasonography) and at the 2nd and 12th hour after physical examinations ± ultrasonography. The researchers who performed ultrasonography and evaluated ABG were different.

PaO_2, $PaCO_2$, SaO_2, BE, lactate and pH values were examined. The changes in the PaO_2 values of the patients were examined and whether there was a change in oxygenation was evaluated. The changes in the $PaCO_2$ values of the patients were examined to check whether there was a change in ventilation.

Demographic data including age, gender, body weight, and concomitant diseases of the patients were recorded. Patients' PaO_2:FiO_2 ratios, Acute Physiology and Chronic Health Evaluation-II (APACHE-II) scores at admission to ICU, length of stay in ICU, and the length of mechanical ventilation, and mortality rates were evaluated.

The primary aim was to evaluate the effect of US-guided positioning on oxygenation in patients with hypoxemic respiratory failure due to COVID-19. For this purpose, changes in PaO_2 values after positioning

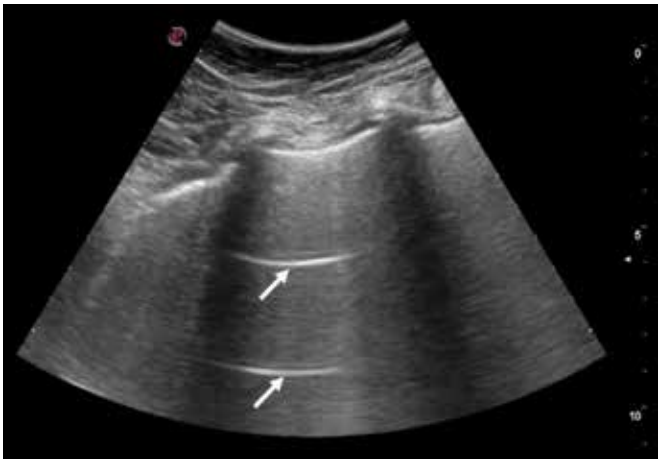


Figure 1. A-Line

Table 1. Original and modified lung ultrasound scores

	Normal aeration	Small loss of aeration	Moderate loss of aeration	Severe loss of aeration
Scoring	0	1	2	3
Original lung ultrasound score	0-2 B-lines	≥3 B-lines	Multiple coalescent B-lines	Consolidation
Modified lung ultrasound	0-2 B-lines	≥3 B-lines or One or multiple small subpleural consolidation, separated by a normal pleural line	Multiple coalescent B-lines or multiple small subpleural consolidations, separated by a thickened or irregular pleural line	Consolidation or Small subpleural consolidation of >1 ×2 cm in diameter

were examined. The secondary aim of the study was to evaluate the effect of US-guided positioning on ventilation. For this, changes in $PaCO_2$ values after positioning were examined.

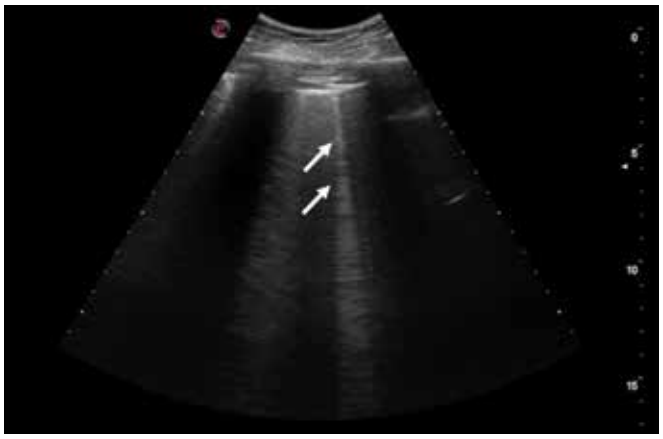


Figure 2. B-Line

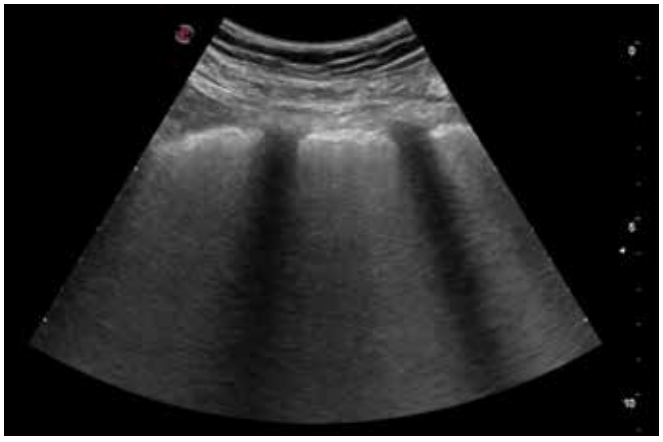


Figure 3. Confluent B-lines (white lung)

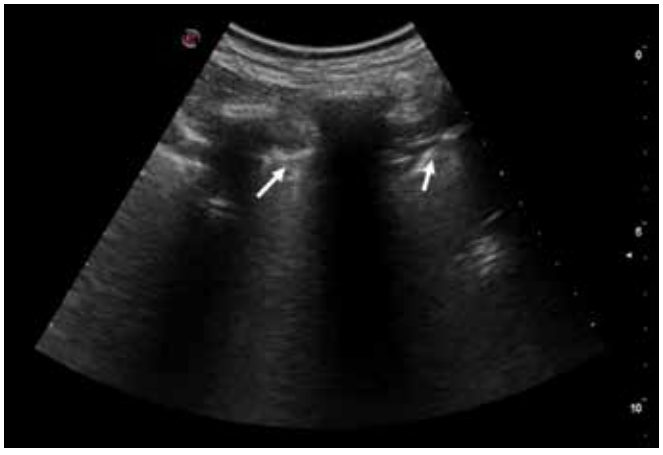


Figure 4. Irregular pleural line

Statistics

Power Analysis

For statistical power analyses, G*power 3 for MacOs was used. Power analysis was performed as priori among independent groups based on t test (Effect size: 0.6; Power: 0.8; alpha error: 0.05). In order for the total sample size to generate 0.8 power; it was calculated that a total of 72 people, 36 people in each group, should be included in the study.

Statistical Analysis

Student's t-test was used to compare continuous demographic variables in independent groups. The chi-square test and Fisher's Exact tests were used to test the distribution of categorical variables between groups.

The repeated measures analysis of variance (repeated measures ANOVA) technique was used to analyze the trend

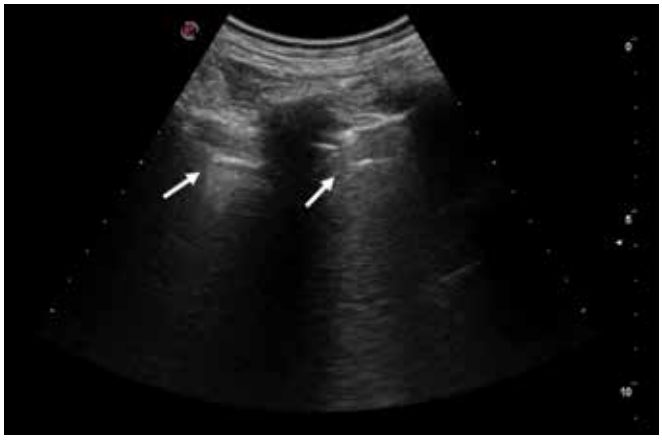


Figure 5. Subpleural consolidation

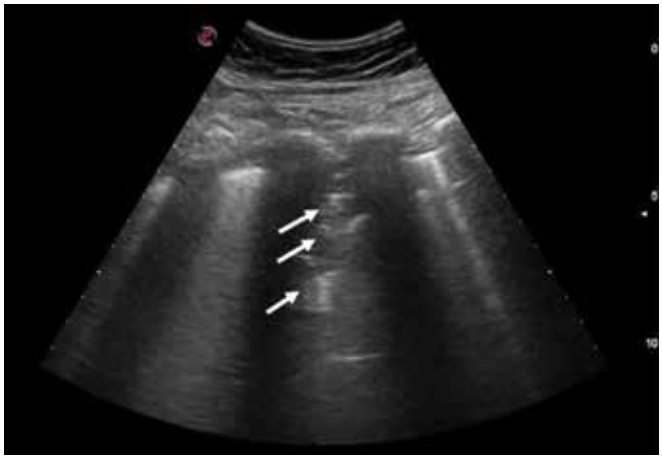


Figure 6. Consolidation

of change in arterial blood gas levels and other parameters along tree different time points as at the beginning and the 2nd and 12th hours after examination ± ultrasonography in 2 different groups (group A and B) and 4 independent groups (according to patient positioning).

With the repeated measures ANOVA technique, the interaction effect test was performed to determine whether the trends differed between groups over time; main effects test was performed to determine whether there was a difference between groups when the change over time was ignored, and the main effect of time test was performed to determine whether there was a difference between time periods when the changes between groups were ignored. In multiple comparison tests, Bonferroni-corrected p-values were used to control the type-I error level. For descriptive statistics, mean ± standard deviation and for categorical variables, frequency distributions and percentages were used. A p-value of <0.05 value was considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics v.23 software package.

Results

A total of 110 patients were included in the study. After excluding 7 patients, the data from 103 patients were evaluated. Mechanical ventilation settings were made for 52 patients according to their initial ABG values, and the patients were positioned under US guidance. 51 patients for whom mechanical ventilation settings were made according to their ABG values, but no evaluation with US, were accepted as the control group.

Demographic data of the patients are shown in Table 2. No significant differences were observed in age, height, body weight, body mass index, and gender variables between the two groups.

APACHE-II scores at admission to the ICU were found to be significantly higher in group A (p=0.036) (Table 3). The PaO_2:FiO_2 ratios of the patients, the length of stay in the ICU, and the length of mechanical ventilation support were similar in both groups (Table 3). Mechanical ventilation support methods used in patients are shown in Table 3. The mean LUS score was found to be 25.19 (Table 4).

No significant difference was found between groups for the variable PaO_2, (p=0.153) (Table 5).

The change over time between PaO_2 values evaluated at the beginning and 12 hours after positioning was found significant (p=0.01) (Table 5).

In group A, the difference between the PaO_2 values evaluated at the beginning and at 2 hours after positioning was statistically significant (p=0.033), and the difference between PaO_2 values evaluated at the beginning and at 12 hours after positioning was statistically significant (p=0.025). In group A, the difference between PaO_2 values evaluated at 2 hours and 12 hours after positioning was statistically insignificant (p=0.0921).

In group B, the change over time between PaO_2 values evaluated at the beginning and at 12 hours after positioning was found significant (p=0.004).

Of the 52 patients; who were positioned under US guidance, 13 patients were followed up in the prone position (25%), 10 in the right upper lateral position (19.2%), 21 in the left upper lateral position (40.3%), and 8 in the supine position (15.3%).

The results of the repeated measures ANOVA for ABG parameters according to the patient position categories, revealed that PaO_2 values were similar across the groups

Table 2. Demographic data and concomitant diseases

		Grup A (mean ± SD) (n, %)	Grup B (mean ± SD) (n,%)	p	Total (mean ± SD)
Age		66.00±11.84	65.64±9.66	0.869	65.82±10.77
Height (cm)		167.32±9.48	168.52±8.56	0.501	167.92±9.01
Body weight (kg)		81.13±15.50	93.23±116.84	0.461	87.12±82.76
Body mass index (kg/m²)		29.11±5.82	33.64±46.04	0.483	31.35±32.58
Gender	Male	27 (46.6)	31 (53.4)	0.365	-
	Female	25 (55.6)	20 (44.4)		-
At least one concomitant disease	Yes	47 (48.0)	51 (52.0)	0.041*	-
	No	4 (100.0)	0 (0.0)		-

*Fisher's Exact test p-value. SD: Standard deviation

Table 3. PaO_2:FiO_2 ratios and APACHE-II scores of patients, the length of stay in intensive care, the length of mechanical ventilation support, and the method of mechanical ventilation

		Group A		Group B		
		Mean ± SD	Median (min-max)	Mean ± SD	Median (min-max)	p
PaO_2:FiO_2		92.36±34.85	80.50 (40.0-200.0)	101.25±40.70	90.0 (46.0-200.0)	0.256
APACHE-II		18.75±8.39	18,0 (7.0-33.0)	15,42±8.96	12.0 (5.0-34.0)	0.036
Length of mechanical ventilation (days)		15.76±9.40	14.50 (3.0-31.0)	16.21±9.40	15.0(4.0-39.0)	0.745
Length of stay in ICU (days)		17.84±9.90	18.0 (3.0-33.0)	18.06±10.02	18.0 (4.0-40.0)	0.907
		n (%)	(%)	n (%)	(%)	
Number of patients undergoing mechanical ventilation	IMV	34 (65.4)	45.3	41 (80.4)	54.7	0.064*
	PSV-CPAP	7 (13.5)	87.5	1 (2.0)	12.5	
	HFNO	11 (21.2)	55.0	9 (17.6)	45.0	

PaO_2:FiO_2: Partial arterial oxygen pressure:Fraction of inspired oxygen, APACHE-II: Acute Physiology and Chronic Health Evaluation, ICU: intensive care unit, IMV: invasive mechanical ventilation, PSV-CPAP: pressure support ventilation- continuous positive airway pressure, HFNO: High-flow nasal oxygenation, *Fisher's Exact p value, SD: standard deviation, min: minimum, max: maximum

Table 4. Lung ultrasound scores

	Group A (mean ± SD)
R total	12.42±2.47
L total	12.73±2.91
Total score	25.19±4.85

SD: Standard deviation

(p=0.94). The change over time in PaO_2 values evaluated at the beginning and 12 hours after positioning was found significant (p=0.032) (Table 6).

The change in PaO_2 levels over time was not significant in the supine, right lateral, and prone position groups. However, in the left lateral position group, the difference between PaO_2 values evaluated at the beginning and 2 hours after positioning and the difference between PaO_2 values evaluated at the beginning and 12 hours after positioning were statistically significant (p=0.009 and 0.038, respectively).

On the other hand, the difference between PaO_2 values evaluated at 2 hours and at 12 hours after positioning was statistically insignificant in the left lateral position group (p=0.710).

In the prone group, the change between PaO_2 levels evaluated at the beginning and 2 hours after positioning was not statistically significant, but the results were close to reaching statistical significance (p=0.074).

As for the change in $PaCO_2$ levels, there was not a significant difference between the groups or by the time (Table 5). Therefore, the $PaCO_2$ variable was not evaluated according to the given position categories.

Also, for the change in the variable SaO_2, no significant difference was found between groups and by the time (Table 5). For the lactate and BE variables, the changes between the groups and by the time were not significant. The 28-day mortality rates were similar in both groups (Table 7).

Discussion

In our study, it was observed that US-guided positioning improved oxygenation in a short time such as 2 hours in COVID-19 patients with acute respiratory failure.

Bedside ultrasonography has an important place in the diagnosis, follow-up and prognosis of patients and can provide guidance for ventilation (10). One of the main limitations of thoracic US is that it cannot be used to examine the deep fields of the lung. However, the use of thoracic US is recommended COVID-19 because the involvement of the distal region is predominant (21,22).

Several studies are available about LU in COVID-19 patients. Characteristic findings of LU in COVID-19 reported by different studies are as follows:

1. Thickening of the pleural line with pleural line irregularities;

2. B-lines in a variety of patterns including focal, multifocal, and confluent;

3. Subpleural small consolidations;

4. Consolidations in a variety of patterns including multifocal small, non-translobar, and translobar patterns with occasional mobile air bronchograms;

5. Appearance of A-lines during the recovery phase;

6. Pleural effusions are uncommon (2,3,9,11,23-25).

Studies in the literature report that bedside LU is an effective way to evaluate the severity of lung involvement and follow up disease progression in COVID-19 patients (2,3,9,23,26). Similar to our study, Vetrugno et al. (14) successfully evaluated their patients using LUS scores, and reported that the use of LU resulted in significant reduction in the number of chest X-rays and tomography scans during the pandemic and helped achieve efficient patient care and management.

The benefits of prone position in addition to the mechanical ventilation strategies to provide oxygenation in the treatment of ARDS are known, and it is reported that, with prone position, oxygen is improved, and mortality is decreased (12,27).

Sztajnbok et al. (28) reported an improvement in oxygenation in their patients who remained in the prone position for 8 to 10 hours. Ghelichkhani and Esmaeili (29) recommended the prone position for at least 12 hours. Özbilen and Altunkan (30) reported that they used the prone position in their patients for 4 hours and reported improvements in oxygenation. In our study, we observed improvements in oxygenation in the 2-hour period after appropriate positioning in the patients under ultrasonography

Table 5. Repeated measures ANOVA results for pH, PaO_2 and $PaCO_2$ variables

	Group A (mean ± SD)	**Group B (mean ± SD)**	**Total (mean ± SD)**	**p (time)**
pH-pre	7.41±0.11	7.43±0.10	7.42±0.10	
pH-2 h	7.32±0.72	7.41±0.11	7.37±0.51	0.396
pH-12 h	7.41±0.11	7.41±0.11	7.41±0.11	
Total	7.38±0.42	7.41±0.10	-	p interaction
p (group)	0.347			0.438
	Group A (mean ± SD)	**Group B (mean ± SD)**	**Total (mean ± SD)**	**p (time)**
PaO_2-pre (mmHg)	86.61±29.78	97.94±40.08	97.22±35.54[a]	
PaO_2-2 h (mmHg)	97.65±40.57	99.93±37.89	98.77±39.09[ab]	0.001
PaO_2-12 h (mmHg)	98.14±44.19	112.89±42.47	105.44±43.77[b]	
Total	94.13±38.18	103.58±40.14		p interaction
p (group)	0.153			0.637
	Group A (mean ± SD)	**Group B (mean ± SD)**	**Total (mean ± SD)**	**p (time)**
$PaCO_2$-pre (mmHg)	50.90±15.35	54.80±22.81	52.60±19.43	
$PaCO_2$-2 h (mmHg)	50.60±15.36	53.23±22.78	51.92±19.38	0.158
$PaCO_2$-12 h (mmHg)	50.92±15.53	57.10±30.47	54.13±24.26	
Total	50.80±15.41	55.04±25.35		p interaction
p (group)	0.334			0.291
	Group A (mean ± SD)	**Group B (mean ± SD)**	**Total (mean ± SD)**	**p (time)**
SaO_2-pre (%)	93.04±8.91	94.08±6.42	93.56±7.75	
SaO_2-2 h (%)	93.30±8.30	94.66±6.15	93.97±7.31	0.636
SaO_2-12 h (%)	91.40±14.13	95.20±7.30	93.28±11.39	
Total	92.58±10.44	94.64±6.62		p interaction
p (group)	0.188		0.092	

Pre: Initial value (before examination ± ultrasonography), 2 h: value at the 2nd hour after examination ± ultrasonography, 12 h: value at the 12th hour after examination ± ultrasonography, SD: standard deviation [a,b,ab]: the mean values denoted by the same letter are the same, the mean values denoted by different letters are different from each other.

guidance. No significant differences occurred between the measurements at 2nd and 12th hours after the positioning.

We found that hypoxia was effectively treated in the left lateral position. In the prone position group, there was an increase in PaO_2 values evaluated 2 hours after positioning, though not statistically significant. The low number of patients may be an important factor in this result.

Studies suggest that the prone position is not preferred by physicians and causes hemodynamic instability (31). In the prone position, accidental removal of the tracheal tube may occur, as well as limited venous access, decubitus ulcer, and bruising around the mouth, edema around the eyes and facial edema due to the presence of endotracheal tube (32). For such reasons, physicians are reluctant to use prone positioning in patients.

We also think that it is not necessary to use prone positioning in every patient. This process is both difficult and risky, in addition to being difficult to tolerate (33). In our study, we had to exclude two of our patients that we applied the prone position because they could not tolerate the position.

In our study, we observed that there was an increase in oxygenation after 2 hours in the patients who were positioned under ultrasonography guidance. The short duration will increase the tolerance of especially noninvasive supported patients, and also complications such as pressure ulcers and edema formation will be prevented.

A study performed during the pandemic reported that; of the 15 patients, who were kept in the prone position for three hours and received non-invasive mechanical ventilation, the respiratory rate decreased, SO_2 increased, and the PaO_2:FiO_2 ratio improved in 73% of the patients during the prone position and in 86.7% of the patients at the end of the prone positioning (34).

A more specific lung scoring technique to evaluate patients with COVID-19 may be better in grading the severity of the disease. For this purpose, we suggest that a new classification should be developed immediately.

Table 6. Repeated measures ANOVA results by patient position categories

	Supin (mean ± SD)	Upper right position (mean ± SD)	Upper left position (mean ± SD)	Prone (mean ± SD)	Total (mean ± SD)	p (time)
PaO_2-pre (mmHg)	80.25±20.80	93.88±36.75	84.20±21.39	88.85±40.68	88.61±29.78[a]	0.032
PaO_2-2 h (mmHg)	86.62±29.35	93.14±37.78	100.72±30.82	102.93±60.77	97.65±40.57[ab]	
PaO_2-12 h (mmHg)	96.18±46.10	95.29±47.70	98.19±33.36	101.47±58.98	98.14±44.19[b]	
Total	87.68±32.08	94.10±40.74	94.37±28.52	97.75±53.47		p (interaction)
p (group)	0.940					0.749
	Supin (mean ± SD)	**Upper right position (mean ± SD)**	**Upper left position (mean ± SD)**	**Prone (mean ± SD)**	**Total (mean ± SD)**	**p (time)**
$PaCO_2$-Pre (mmHg)	51.90±27.58	51.25±11.43	48.63±13.19	54.55±12.09	51.11±15.42	0.838
$PaCO_2$-2 h (mmHg)	49.00±26.08	47.93±11.10	48.66±12.32	56.57±14.11	50.60±15.36	
$PaCO_2$-12 h (mmHg)	48.30±17.13	50.85±16.06	49.56±16.54	55.71±13.46	51.16±15.59	
Total	49.73± 23.59	50.01±12.86	48.95±14.01	55.61±13.22		p (interaction)
p (group)	0.590					0.904

Pre: Initial value (before examination ± ultrasonography), 2 h: value at the 2nd hour after examination ± ultrasonography, 12 h: value at the 12th hour after examination ± ultrasonography, SD: standard deviation

Table 7. Comparison of mortality rates

		Group A		Group B		p
		n, (%)	%	n, (%)	%	
Survival	Survivor	15 (28.8%)	50.0	15 (29.4%)	50.0	1.000
	Non survivor	37 (71.2%)	50.7	36 (70.6%)	49.3	

After positioning our patients for 12 hours, we could have evaluated and scored them again with LU, so that we could have evaluated both the success of the position and the correlation between LUS score and ABG. Finally, the number of patients included in the study could have been higher so that more patients could be evaluated in each position group.

Conclusion

As a result, we found that, if the infiltrative region in the lung is defined with bedside LU in a short time so as to know which positioning to prefer for which region, there is an increase in oxygenation in COVID-19 patients shortly after the application. In our study, we observed that especially the patients in the left lateral position benefited from the position. Instead of bringing all patients to the prone position, we think that customized positioning of the patient according to LU-guided findings can increase oxygenation in a short time like 2 hours. Thus, the potential negative effects of the prone positioning can also be avoided, and proper positioning can be attempted in more patients commonly.

Ethics

Ethics Committee Approval: This study was approved by the Ministry of Health (dated 05.04.2020, numbered 2020-05-04T00-50-43) and Gaziosmanpaşa Training and Research Hospital's Clinical Research Ethics Committee (decision no: 66, date: 26.05.2020).

Informed Consent: Written informed consent was obtained from all patients included in the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: D.G.M., A.V., H.G., A.K.G., Concept: D.G.M., Ü.A.T., A.V., H.G., A.K.G., Design: D.G.M., Ü.A.T., A.V., Data Collection and Process: D.G.M., H.G., A.K.G., Analysis or Interpretation: D.G.M., Ü.A.T., A.V., Literature Search: D.G.M., Ü.A.T., A.V., H.G., A.K.G., Writing: D.G.M., Ü.A.T.

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

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020;395:507-13.
2. Soldati G, Smargiassi A, Inchingolo R, Buonsenso D, Perrone T, Briganti DF, et al. Is There a Role for Lung Ultrasound During the COVID-19 Pandemic? J Ultrasound Med 2020;39:1459-62.
3. Sofia S, Boccatonda A, Montanari M, Spampinato M, D'ardes D, Cocco G, et al. Thoracic ultrasound and SARS-COVID-19: a pictorial essay. J Ultrasound 2020;23:217-21.
4. Moore S, Gardiner E. Point of care and intensive care lung ultrasound: A reference guide for practitioners during COVID-19. Radiography (Lond) 2020;26:e297-e302.
5. Mayo PH, Copetti R, Feller-Kopman D, Mathis G, Maury E, Mongodi S, et al. Thoracic ultrasonography: a narrative review. Intensive Care Med 2019;45:1200-11.
6. Pagano A, Numis FG, Visone G, Pirozzi C, Masarone M, Olibet M, et al. Lung ultrasound for diagnosis of pneumonia in emergency department. Intern Emerg Med 2015;10:851-4.
7. Yasukawa K, Minami T. Point-of-Care Lung Ultrasound Findings in Patients with COVID-19 Pneumonia. Am J Trop Med Hyg 2020;102:1198-202.
8. Poggiali E, Dacrema A, Bastoni D, Tinelli V, Demichele E, Mateo Ramos P, et al. Can Lung US Help Critical Care Clinicians in the Early Diagnosis of Novel Coronavirus (COVID-19) Pneumonia? Radiology 2020;295:E6.
9. Smith MJ, Hayward SA, Innes SM, Miller ASC. Point-of-care lung ultrasound in patients with COVID-19 - a narrative review. Anaesthesia 2020;75:1096-104.
10. Schultz MJ, Sivakorn C, Dondorp AM. Challenges and Opportunities for Lung Ultrasound in Novel Coronavirus Disease (COVID-19). Am J Trop Med Hyg 2020;102:1162-3.
11. Peng QY, Wang XT, Zhang LN; Chinese Critical Care Ultrasound Study Group (CCUSG). Findings of lung ultrasonography of novel corona virus pneumonia during the 2019-2020 epidemic. Intensive Care Med 2020;46:849-50.
12. Mora-Arteaga JA, Bernal-Ramírez OJ, Rodríguez SJ. The effects of prone position ventilation in patients with acute respiratory distress syndrome. A systematic review and metaanalysis. Med Intensiva 2015;39:359-72.
13. Lichtenstein DA, Mezière GA. Relevance of lung ultrasound in the diagnosis of acute respiratory failure: the BLUE protocol. Chest 2008;134:117-25.
14. Vetrugno L, Bove T, Orso D, Barbariol F, Bassi F, Boero E, et al. Our Italian experience using lung ultrasound for identification, grading and serial follow-up of severity of lung involvement for management of patients with COVID-19. Echocardiography 2020;37:625-7.
15. Bouhemad B, Brisson H, Le-Guen M, Arbelot C, Lu Q, Rouby JJ. Bedside ultrasound assessment of positive end-expiratory pressure-induced lung recruitment. Am J Respir Crit Care Med 2011;183:341-7.
16. Monastesse A, Girard F, Massicotte N, Chartrand-Lefebvre C, Girard M. Lung Ultrasonography for the Assessment of Perioperative Atelectasis: A Pilot Feasibility Study. Anesth Analg 2017;124:494-504.
17. Saraogi A. Lung ultrasound: Present and future. Lung India 2015;32:250-7.
18. Doerschug KC, Schmidt GA. Intensive care ultrasound: III. Lung and pleural ultrasound for the intensivist. Ann Am Thorac Soc 2013;10:708-12.
19. Soldati G, Demi M, Smargiassi A, Inchingolo R, Demi L. The role of ultrasound lung artifacts in the diagnosis of respiratory diseases. Expert Rev Respir Med 2019;13:163-72.
20. Lichtenstein D, Mézière G, Biderman P, Gepner A, Barré O. The comet-tail artifact. An ultrasound sign of alveolar-interstitial syndrome. Am J Respir Crit Care Med 1997;156:1640-6.
21. Shi H, Han X, Jiang N, Cao Y, Alwalid O, Gu J, et al. Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: a descriptive study. Lancet Infect Dis 2020;20:425-34.
22. Pan F, Ye T, Sun P, Gui S, Liang B, Li L, et al. Time Course of Lung Changes at Chest CT during Recovery from Coronavirus Disease 2019 (COVID-19). Radiology 2020;295:715-21.
23. Convissar DL, Gibson LE, Berra L, Bittner EA, Chang MG. Application of Lung Ultrasound During the COVID-19 Pandemic: A Narrative Review. Anesth Analg 2020;131:345-50.
24. Xing C, Li Q, Du H, Kang W, Lian J, Yuan L. Lung ultrasound findings in patients with COVID-19 pneumonia. Crit Care 2020;24:174.
25. Duclos G, Lopez A, Leone M, Zieleskiewicz L. "No dose" lung ultrasound correlation with "low dose" CT scan for early diagnosis of SARS-CoV-2 pneumonia. Intensive Care Med 2020;46:1103-4.
26. Jin YH, Cai L, Cheng ZS, Cheng H, Deng T, Fan YP, et al. A rapid advice guideline for the diagnosis and treatment of 2019 novel coronavirus (2019-nCoV) infected pneumonia (standard version). Mil Med Res 2020;7:4.
27. Guérin C, Reignier J, Richard JC, Beuret P, Gacouin A, Boulain T, et al. Prone positioning in severe acute respiratory distress syndrome. N Engl J Med 2013;368:2159-68.
28. Sztajnbok J, Maselli-Schoueri JH, Cunha de Resende Brasil LM, Farias de Sousa L, Cordeiro CM, Sansão Borges LM, et al. Prone positioning to improve oxygenation and relieve respiratory symptoms in awake, spontaneously breathing non-intubated patients with COVID-19 pneumonia. Respir Med Case Rep 2020;30:101096.
29. Ghelichkhani P, Esmaeili M. Prone Position in Management of COVID-19 Patients; a Commentary. Arch Acad Emerg Med 2020;8:e48.
30. Özbilen F, Altunkan AA. COVID-19 and Awake Prone Position. J Turk Soc Intens Care 2020;18:50-6.
31. Guérin C, Beuret P, Constantin JM, Bellani G, Garcia-Olivares P, Roca O, et al. A prospective international observational prevalence study on prone positioning of ARDS patients: the APRONET (ARDS Prone Position Network) study. Intensive Care Med 2018;44:22-37.
32. McCormick J, Blackwood B. Nursing the ARDS patient in the prone position: the experience of qualified ICU nurses. Intensive Crit Care Nurs 2001;17:331-40.
33. Telias I, Katira BH, Brochard L. Is the Prone Position Helpful During Spontaneous Breathing in Patients With COVID-19? JAMA 2020;323:2265-7.
34. Sartini C, Tresoldi M, Scarpellini P, Tettamanti A, Carcò F, Landoni G, et al. Respiratory Parameters in Patients With COVID-19 After Using Noninvasive Ventilation in the Prone Position Outside the Intensive Care Unit. JAMA 2020;323:2338-40.

Turk J Intensive Care 2021;19(Suppl 1):54-61
DOI: 10.4274/tybd.galenos.2021.20082

ORIGINAL RESEARCH / *ÖZGÜN ARAŞTIRMA*

Osman Uzundere,
Cem Kıvılcım Kaçar,
Meral Erdal Erbatur,
Mehmet Salih Gül,
Mesut Akgündüz,
Zeki Korhan,
Ömer Can

Factors Affecting the Mortality of Patients in Critical Condition with Coronavirus Disease-2019 in the Intensive Care Unit

Koronavirüs Hastalığı-2019 Nedeniyle Yoğun Bakım Ünitesinde Yatan Kritik Hastalarda Mortaliteye Etki Eden Faktörler

Received/Geliş Tarihi : 27.01.2021
Accepted/Kabul Tarihi : 23.03.2021

Osman Uzundere, Cem Kıvılcım Kaçar, Meral Erdal Erbatur, Mehmet Salih Gül, Mesut Akgündüz, Zeki Korhan, Ömer Can

University of Health Sciences Turkey, Diyarbakır Gazi Yaşargil Training and Research Hospital, Clinic of Anesthesiology and Reanimation, Diyarbakır, Turkey

Osman Uzundere MD, (✉),
University of Health Sciences Turkey, Diyarbakır Gazi Yaşargil Training and Research Hospital, Clinic of Anesthesiology and Reanimation, Diyarbakır, Turkey

E-mail : osmanuzundere@hotmail.com
Phone : +90 412 258 00 60
ORCID ID : orcid.org/0000-0002-5968-4561

ABSTRACT *Objective:* This study aimed to determine the factors affecting the mortality of patients in critical condition with coronavirus disease-2019 (COVID-19) in the intensive care unit (ICU).
Materials and Methods: We included a total of 445 patients who are admitted in the ICU due to COVID-19. Patients were divided into two groups-those who survived and those who died during the ICU follow-up-and their demographic, clinical and laboratory characteristics were compared. Factors affecting mortality were also determined.
Results: Older age, high Kidney Disease: Improving Global Outcome (KDIGO) stage and Sequential Organ Failure Assessment (SOFA) scores at first admission to the ICU, high neutrophil/lymphocyte ratio, high D-dimer levels, low bicarbonate (HCO_3) values and high lactate dehydrogenase (LDH) and creatinine levels were determined as independent risk factors for mortality in patients in critical condition with COVID-19 admitted in the ICU. Particularly, a substantial relationship was observed between the KDIGO stage and mortality during the ICU admission.
Conclusion: Age, KDIGO stage and SOFA scores at first admission, neutrophil/lymphocyte ratio and D-dimer, HCO_3, LDH and creatinine levels were independent risk factors for mortality in patients in critical condition with COVID-19 admitted in the ICU.
Keywords: Coronavirus disease 2019, ICU, kidney disease: improving global outcome, mortality, sequential organ failure assessment score

ÖZ *Amaç:* Bu çalışmada yoğun bakım ünitesinde (YBÜ) yatan kritik koronavirüs hastalığı-2019 (COVID-19) hastalarını demografik, klinik ve laboratuvar özellikleri açısından karşılaştırıp mortaliteye etkili olan faktörleri saptamayı amaçladık.
Gereç ve Yöntem: Çalışmaya YBÜ'de COVID-19 nedeniyle yatan 445 hasta dahil edildi. Hastalar YBÜ'de takipleri sırasında mortalite gelişmeyenler ve mortalite gelişenler olarak iki gruba ayrılıp demografik, klinik ve laboratuvar özellikleri açısından karşılaştırıldı ve mortaliteye etki eden faktörler saptanmaya çalışıldı.
Bulgular: İleri yaş, YBÜ'ye ilk yatıştaki yüksek Böbrek Hastalıkları: Küresel Sonuçların İyileştirilmesi (KDIGO) evresi ve Sıralı Organ Yetmezliği Değerlendirmesi (SOFA) skorları, yüksek nötrofil lenfosit oranı, yüksek D-dimer düzeyleri düşük bikarbonat (HCO_3) değerleri, yüksek laktat dehidrogenaz (LDH) düzeyleri ve yüksek kreatinin düzeyleri YBÜ'de yatan kritik COVID-19 hastalarında mortalite için bağımsız risk faktörleri olarak saptandı. Özellikle YBÜ'ye başvuru esnasındaki KDIGO evresiyle mortalite arasındaki ilişki dikkat çekiciydi.
Sonuç: YBÜ'de yatan kritik COVID-19 hastalarında yaş, ilk yatıştaki KDIGO ve SOFA skorları, nötrofil lenfosit oranı, D-dimer, HCO_3, LDH ve kreatinin mortalite için bağımsız risk faktörleridir.
Anahtar Kelimeler: Koronavirüs hastalığı-2019, YBÜ, böbrek hastalıkları: küresel sonuçların iyileştirilmesi, mortalite, sıralı organ yetmezliği değerlendirmesi

Introduction

Based on the data published by the World Health Organization (WHO) on December 12, 2020, the coronavirus disease-2019 (COVID-19) pandemic, in which 69.5 million individuals were infected and 1,582,674 individuals have died, continues to be an issue worldwide (1). Although vaccination studies, which have recently accelerated, are a hope, approximately 15% of the patients with COVID-19 develop critical illnesses requiring oxygen support. In approximately 5% of the patients, respiratory failure secondary to acute respiratory distress syndrome (ARDS) as well as numerous complications including sepsis and septic shock, thromboembolism, renal failure, and cardiac damage, may further develop into a critical illness (2). The disease mortality can be extremely high, particularly due to the complications that may develop in the critical patient group. In the initial publications, it was stated that in-hospital mortality due to severe acute respiratory syndrome coronavirus 2 was approximately 28% (3). Moreover, it was emphasized that mortality was higher in critically ill patients (76%) hospitalized in the intensive care unit (ICU) (4).

When the publications on mortality in patients with COVID-19 were examined, there were reportedly numerous factors that could affect the clinical course and patient mortality (3,5-12). Among these factors, patient characteristics, male sex, advanced age, obesity, smoking, and comorbid diseases (particularly diabetes and hypertension) as well as Acute Physiology and Chronic Health Evaluation-II (APACHE-II) and Sequential Organ Failure Assessment (SOFA) score and several laboratory values are reportedly associated with mortality in patients with COVID-19 (4,12-14).

Currently, no effective treatment has been discovered for managing the COVID-19 epidemic, which has affected the world to a substantial extent (15). Determining the factors that affect mortality remains an important concern in terms of decreasing mortality due to the disease. In the current study that was planned with considering this notion, we aimed to perform a comparative assessment of critical patients with COVID-19 who were followed up in ICUs in our region since the beginning of the pandemic in terms of demographic, clinical, and laboratory characteristics and to determine the factors that affect mortality in this patient group.

Materials and Methods

Study Design, Population, and Data

Critical patients hospitalized due to COVID-19 in ICU of the University of Health Sciences Turkey, Diyarbakır Gazi Yaşargil Training and Research of Hospital between March 22 and September 1, 2020, were included in this study. The study was approved by the Clinical Research Ethics Committee of University of Health Sciences Turkey, Gazi Yaşargil Training and Research of Hospital (decision no: 550, date:11.09.2020). The trial was registered with clinicaltrials.gov (NCT04659876). This retrospective cohort study was conducted in accordance with the 2008 Declaration of Helsinki criteria.

Critical patients diagnosed with COVID-19 on the dates specified, followed up in ICU, aged >18 years, in serious need of oxygen support according to WHO (2) and the temporary guidelines of T.C. Science Board of the Ministry of Health [presence of fever, muscle/joint pain, cough, and sore throat; tachypnea (30 breaths/min) or dyspnea; use of extra respiratory muscles; SpO_2 level below of ≤90% in room air; bilateral diffuse pneumonia symptom detected on chest radiography or computerized tomography (CT); and PaO_2/FiO_2 ratio of <300], and developed or had complications including severe pneumonia, ARDS, sepsis/septic shock, and acute renal failure were included in the study (16). Patients with COVID-19 aged <18 years with mild-to-moderate symptoms, no respiratory distress, and no signs of diffuse pneumonia on chest X-ray or CT as well as ICU patients excepted from COVID-19 diagnosis were excluded from the study. In addition, patients whose complete data could not be accessed from the hospital system or the patient file records were excluded. When the patients were admitted to ICU for the first time, their clinical conditions were evaluated with APACHE-II and SOFA scores, and the degree of renal failure was evaluated using the Kidney Disease: Improving Global Outcomes (KDIGO) classification (17).

Age; sex; comorbidity; ABO and Rh blood groups; APACHE-II and SOFA scores and KDIGO stage during admission to ICU; hemogram parameters [white blood cell (WBC), neutrophil, lymphocyte, neutrophil/lymphocyte (N/L) ratio, hemoglobin, hematocrit, and platelet count]; blood gas values [pH, partial oxygen pressure (PO_2), partial carbon dioxide pressure (PCO_2), bicarbonate (HCO_3), and lactate]; coagulation parameters [prothrombin time (PTZ)

and D-dimer]; blood biochemistry results [creatine kinase (CK), lactate dehydrogenase (LDH), C-reactive protein (CRP), urea, creatinine, alanine aminotransferase, aspartate aminotransferase (AST), total bilirubin, direct bilirubin, and indirect bilirubin]; and procalcitonin (PCT) and ferritin levels of the patients were recorded. Moreover, the length of stay in ICU and whether the patient died or survived were recorded. Patient data were rechecked for erroneous information before the last data entry and entered into a computerized database.

Patients were divided into two groups-those who survived (survivors) and those who died (non-survivors) during ICU follow-up. Both groups were compared in terms of clinical characteristics; APACHE-II and SOFA scores and KDIGO stage; and laboratory values at the first admission to ICU. We attempted to determine the factors that affect mortality in critically ill patients hospitalized in ICU with COVID-19 diagnosis.

Statistical Analysis

SPSS 16.0 software for Windows (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Continuous data were expressed as means (SD or minimum-maximum), and categorical data were expressed as frequencies with percentages. Comparison of categorical data in the groups was performed using chi-square and Fisher's Exact test, and the results were presented as n%. Kolmogorov-Smirnov test was used to determine whether the numerical data fit the normality distribution. Data conforming to the normality distribution were evaluated using Student's t-test, and Mann-Whitney U and Kruskal-Wallis tests were employed to compare data that did not fit the normality distribution. Binary logistic regression was performed for the risk factors that were found to be significant in the univariate analysis. Odds ratio (OR) with 95% confidence interval (CI) was used to report the association between mortality and exposure to the risk factors. In all comparisons, p value of <0.05 was considered significant.

Results

Overall, data of 474 patients were accessed in the study. According to the exclusion criteria, 29 patients were excluded, and the study was completed with 445 patients. The mean [standard deviation (SD)] age of the patients was 68.5 (15.1) years; 232 (52.1%) patients were male and 213 (47.9%) were female. Of the patients included in the study, 338 (76%) had at least one comorbid disease. The most common comorbid diseases were hypertension (40.2%) and diabetes (28.5%). Further, 296 patients died during their follow-up period in ICU and mortality was 66.5%. The mean (SD) length of stay of patients in ICU was 11.2 (10.7) days. The demographic, clinical, and laboratory characteristics of patients are detailed in Table 1.

Table 1. Demographic, clinical, and laboratory characteristics of patients hospitalized in the intensive care unit due to COVID-19

Characteristic	All patients (n=445) mean (min-max)	Survivors (n=149) mean (min-max)	Non-survivors (n=296) mean (min-max)	p-value
Age (year)	68.5 (18-100)	62.7 (22-95)	71.4 (18-100)	<0.001
Sex				
Female	213 (47.9%)	83 (55.7%)	130 (43.9%)	0.019
Male	232 (52.1%)	66 (44.3)	166 (56.1%)	
Blood group				
A	225 (50.6%)	74 (49.7%)	151 (51%)	0.48
B	71 (16%)	21 (14.1%)	50 (16.9%)	
AB	33 (7.4%)	9 (6%)	24 (8.1%)	
0	116 (26.1%)	45 (30.2%)	71 (24%)	
Rh factor				
Negative	61 (13.7%)	21 (12.7%)	42 (14.2%)	0.87
Positive	384 (86.3%)	130 (87.3)	254 (85.8%)	

Table 1. Continued				
Characteristic	**All patients (n=445) mean (min-max)**	**Survivors (n=149) mean (min-max)**	**Non-survivors (n=296) mean (min-max)**	**p-value**
Comorbidities				
No	107 (24%)	42 (28.2%)	65 (22%)	0.14
Yes	338 (76%)	107 (71.8%)	231 (78%)	
Diabetes	127 (28.5%)	38 (25.5%)	89 (30.1%)	0.31
Hypertension	179 (40.2%)	64 (43%)	115 (38.3%)	0.53
COPD	45 (10.1)	19 (12.8%)	26 (8.8%)	0.19
CKD	34 (7.6%)	12 (8.1%)	22 (7.4%)	0.81
CVD	66 (14.8%)	19 (12.8%)	47 (15.9%)	0.38
KDIGO score				
0	189 (42.4%)	113 (75.8%)	76 (25.6%)	<0.001
1	83 (18.7%)	17 (11.4%)	66 (22.3%)	
2	79 (17.8%)	12 (8.1)	67 (22.6%)	
3	94 (21.1%)	7 (4.7)	87 (29.4%)	
APACHE-II score	16.61 (2-49)	13.1 (2-33)	18.3 (2-49)	<0.001
SOFA score	4.34 (1-17)	3.3 (1-12)	4.8 (1-17)	<0.001
Laboratory				
White blood cells ($\times 10^3$/uL)	11.33 (1.13-57.4)	10.6 (2.95-42.7)	11.6 (1.13-57.4)	0.032
Neutrophil ($\times 10^3$/uL)	9.51 (0.66-37.5)	8.75 (1.3-37.5)	9.9 (0.66-34.4)	0.004
Lymphocyte ($\times 10^3$/uL)	0.98 (0.14-3.59)	1.1 (0.19-3.59)	0.93 (0.14-3.5)	<0.001
Neutrophil/lymphocyte ratio	12.8 (0.12-87.14)	9.4 (0.33-60.04)	14.5 (0.12-87.14)	<0.001
Hemoglobin (g/dL)	12.8 (5.6-19.2)	13.06 (5.9-17)	12.6 (5.6-19.2)	0.015
Hematocrit (%)	40.61 (17.8-61.6)	41.2 (20.2-55.9)	40.2 (17.8-61.6)	0.039
Platelet ($\times 10^3$/uL)	242.5 (30-671)	253.4 (84-671)	237.03 (30-628)	0.048
Prothrombin time (s)	13.83 (9.7-34.6)	13.3 (9.9-22.5)	14.1 (9.7-54.9)	0.011
D-dimer (ng/mL)	2019.2 (8.4-44498)	954.5 (75-16948)	2564.4 (8.4-44498)	<0.001
pH	7.36 (6.82-7.55)	7.38 (6.91-7.54)	7.36 (6.82-7.55)	0.01
PO_2 (mmHg)	41.37 (13.5-206)	42.14 (17.9-162)	40.3 (13.5-198)	0.76
PCO_2 (mmHg)	38.61 (20-115)	39.1 (16.9-108)	38.2 (20-115)	0.12
HCO_3 (mmol/L)	21.78 (5.3-32.1)	23.02 (5.9-31.5)	21.16 (5.3-32.1)	<0.001
Lactate (mmol/L)	2.76 (0.6-26)	2.2 (0.6-8.2)	3.04 (0.7-26)	<0.001
Lactate dehydrogenase (U/L)	514.9 (99-4500)	406.7 (139-1079)	569.4 (99-4500)	<0.001
Creatine kinase (IU/L)	314.05 (0.32-14952)	204.4 (11-2949)	369.4 (0.32-14952)	<0.001
C-reactive protein (mg/L)	141.2 (2-350)	120.4 (2-350)	151.7 (2-350)	<0.001
Blood urea nitrogen (mg/dL)	64.1 (8-280)	47.6 (8-267)	72.5 (13-280)	<0.001
Creatinine (mg/dL)	1.55 (0.36-21.8)	1.28 (0.44-10.4)	1.68 (0.36-21.8)	<0.001
ALT (U/L)	42.6 (6-1254)	32.2 (6-442)	47.9 (6-1254)	0.13
AST (U/L)	67.9 (7-3444)	40.8 (9-518)	81.5 (7-3444)	<0.001
Total bilirubin (mg/dL)	0.73 (0.12-6.8)	0.68 (0.14-3.69)	0.75 (0.12-6.8)	0.20
Direct bilirubin (mg/dL)	0.38 (0.1-4.7)	0.34 (0.1-2.31)	0.4 (0.1-4.7)	0.02

Table 1. Continued

Characteristic	All patients (n=445) mean (min-max)	Survivors (n=149) mean (min-max)	Non-survivors (n=296) mean (min-max)	p-value
Indirect bilirubin (mg/dL)	0.33 (0.01-2)	0.33 (0.03-1.86)	0.33 (0.01-2)	0.93
Procalcitonin (ng/mL)	3.19 (0.02-100)	1.39 (0.02-62.8)	4.13 (0.03-100)	<0.001
Ferritin (µg/L)	854.8 (5.86-2000)	673.8 (5.86-2000)	951.5 (16.6-2000)	<0.001
Length of stay in the intensive care unit (day)	11.2 (1-91)	13.02 (1-91)	10.3 (1-79)	0.004

COPD: Chronic obstructive pulmonary disease, CKD: chronic kidney disease, CVD: cardiovascular disease, KDIGO: Kidney Disease: Improving Global Outcomes, APACHE-II: Acute Physiology and Chronic Health Evaluation-II, SOFA: Sequential Organ Failure Assessment, PO_2: partial oxygen pressure, PCO_2: partial carbon dioxide pressure, HCO_3: bicarbonate, ALT: alanine aminotransferase, AST: aspartate aminotransferase, min: minimum, max: maximum, COVID-19: coronavirus disease-2019

Univariate Analysis

Patients were divided into two groups-those who survived (survivors =149, 33.5%) and those who died (non-survivors =296, 66.5%) during ICU follow-up-and compared. In terms of demographic and clinical characteristics, the mean patient age of the non-survivor group was higher (71.4 vs. 62.7 years; p<0.001). Mortality was higher than survival in male patients (56.1% vs. 43.9%; p=0.019). Patients with KDIGO stage 1, 2, and 3 showed higher mortality than expected (p<0.001). Further, patients who died were found to have higher APACHE-II and SOFA scores (p<0.001; p<0.001) (Table 1).

On comparing both groups in terms of laboratory values at the first admission to ICU, the non-survivors showed a significant higher N/L ratio, WBC, neutrophil, PTZ, D-dimer, lactate, LDH, CK, CRP, urea, creatinine, AST, direct bilirubin, PCT, and ferritin values and lower lymphocyte, hemoglobin, hematocrit, platelet, pH, and HCO_3 values. Details and significance values of the comparison between both groups are shown in Table 1.

Risk Factors for Mortality in ICU Patients with COVID-19

Results of the binary logistic regression are shown in Table 2. Advanced age (OR: 1.03; 95% CI: 1.008-1.055), KDIGO stage 1 (OR: 5.23; 95% CI: 2.490-10.97), KDIGO stage 2 (OR: 7.07; 95% CI: 2.9-17.24), KDIGO stage 3 (OR: 33.98; 95% CI: 8.860-130.3), high SOFA score (OR: 1.194; 95% CI: 1.007-1.416), high N/L ratio (OR: 1.069; 95% CI: 1.006-1.137), high D-dimer levels (OR: 1.000; 95% CI: 1.0-1.001), low HCO_3 values (OR: 0.888; 95% CI: 0.802-0.983), high LDH levels (OR: 1.004; 95% CI: 1.002-1.006), and elevated creatinine levels (OR: 0.499; 95% CI: 0.368-0.676) were identified as independent risk factors for mortality in critical COVID-19 patients hospitalized in ICU.

Discussion

In the present study that evaluated the factors affecting mortality in critical patients with COVID-19 followed up in ICU, the mortality was determined to be 66.5%. Moreover, advanced age; high KDIGO stage and SOFA scores at the first admission to ICU; N/L ratio; D-dimer, LDH, and creatinine levels; and low HCO_3 value were determined as independent risk factors affecting mortality in this critical patient group.

Most studies conducted on patients with COVID-19 have emphasized that advanced age is an independent risk factor for mortality (6,7,9,11,18-20). With increasing age, compared with young individuals, stronger host innate responses to viral infections, decreased type 1 interferon expression, age-related defects in T and B cell functions, and excessive type 2 cytokine production result in deficient response to viral infections and prolonged proinflammatory responses, which are considered as the causes of increased mortality risk in older aged patients with COVID-19 (3). In the present study, mean patient age of the non-survivors was 71.4 (18-100) years, and similar to previous studies, advanced age was determined as an independent risk factor for COVID-19.

Numerous studies have reported that male patients with COVID-19 exhibit a more severe disease, and the mortality risk in the male sex is higher (9,14,20,21). The high mortality in males has been attributed to higher chronic comorbidities, such as cardiovascular disease, hypertension, and lung disease, and smoking rate (20). In the present study, the patient group with a mortal course of the disease exhibited a predominance of male population, in accordance

with the literature. However, as a result of the logistic regression analysis, it was determined that male gender is not an independent risk factor for critical COVID-19 patients hospitalized in the ICU. This unexpected result contradicts the studies in the literature. This result may be due to the single-center nature of our study and the limited number of patients.

On literature review, another risk factor that can affect the clinical course of the disease in patients with COVID-19 is the presence of comorbidities. In the meta-analysis by Martins-Filho et al. (6), the authors emphasized that the presence of comorbidities in patients with COVID-19 resulted in a 1.6 times increase in the in-hospital mortality. In a study conducted by COVID-ICU Group (7) wherein they examined 4,244 critical patients with COVID-19, the presence of a history of diabetes mellitus led to a 1.51 times increase in the 90-day mortality. By contrast, in the present study, the presence of comorbidities did not affect mortality in critical

Table 2. Risk factors for mortality in critical patients with COVID-19 in the intensive care unit

Characteristic	Mean (SD)	OR	95% CI OR	p-value
Age (year)	68.5 (15.1)	1.03	1.008-1.055	0.009
Male (%)	232 (52.1)	1.13	0.570-2.230	0.7
KDIGO score (%)				
1	83 (18.7%)	5.23	2.490-10.97	<0.001
2	79 (17.8%)	7.07	2.900-17.24	<0.001
3	94 (21.1%)	33.98	8.860-130.3	<0.001
APACHE-II score	16.6 (7.23)	1.023	0.960-1.090	0.49
SOFA score	4.34 (2.59)	1.194	1.007-1.416	0.041
Laboratory				
White blood cells ($\times10^3$/uL)	11.33 (6.42)	0.995	0.918-1.079	0.91
Neutrophil ($\times10^3$/uL)	9.51 (5.19)	0.950	0.831-1.087	0.45
Lymphocyte ($\times10^3$/uL)	0.98 (0.57)	1.284	0.593-2.780	0.52
Neutrophil/lymphocyte ratio	12.8 (11.36)	1.069	1.006-1.137	0.031
Hemoglobin (g/dL)	12.8 (2.05)	0.694	0.373-1.292	0.25
Hematocrit (%)	40.61 (6.12)	1.062	0.867-1.300	0.56
Platelet ($\times10^3$/uL)	242.5 (100.3)	0.998	0.995-1.001	0.27
Prothrombin time (s)	13.83 (2.76)	1.052	0.925-1.198	0.44
D-dimer (ng/mL)	2019.2 (4887.1)	1.000	1.000-1.001	0.007
pH	7.36 (0.1)	5.381	0.052-554.0	0.47
HCO_3 (mmol/L)	21.78 (4.34)	0.888	0.802-0.983	0.02
Lactate (mmol/L)	2.76 (2.35)	1.010	0.813-1.254	0.92
Lactate dehydrogenase (U/L)	514.9 (413.07)	1.004	1.002-1.006	<0.001
Creatine kinase (IU/L)	314.05 (841.9)	1.000	1.000-1.001	0.17
C-reactive protein (mg/L)	141.2 (89.01)	1.003	0.999-1.006	0.10
Blood urea nitrogen (mg/dL)	64.1 (48.2)	1.000	0.991-1.010	0.91
Creatinine (mg/dL)	1.55 (1.76)	0.499	0.368-0.676	<0.001
AST (U/L)	67.9 (214.3)	1.000	0.993-1.007	0.95
Direct bilirubin (mg/dL)	0.38 (0.36)	0.619	0.288-1.332	0.22
Procalcitonin (ng/mL)	3.19 (10.08)	1.026	0.978-1.077	0.29
Ferritin (µg/L)	854.8 (635.2)	1.000	1.000-1.001	0.79

KDIGO: Kidney Disease: Improving Global Outcomes, APACHE-II: Acute Physiology and Chronic Health Evaluation-II, SOFA: Sequential Organ Failure Assessment, HCO_3: bicarbonate, AST: aspartate aminotransferase, SD: standard deviation, OR: odds ratio, CI: Confidence interval

patients with COVID-19 hospitalized in ICU. We believe that this result can be attributed to the patient population of our study. The mean patient age in this study was considerably high [68.5 (15.1) years], and most patients (76%) reported at least one comorbid disease. We believe that these factors led to the result observed.

APACHE-II and SOFA are scoring systems that are frequently used during the follow-up examination of critically ill patients for assessing disease severity and mortality (22). Some studies have stated that these scoring systems can be used to determine the disease course in patients with COVID-19 and that high APACHE-II and SOFA scores are associated with poor prognosis and mortality (4,22,23). In the present study, it was observed that non-survivor patients showed higher APACHE-II and SOFA scores during their first admission to ICU. However, only a high SOFA score was determined as a risk factor for mortality in critical patients with COVID-19 in ICU.

One of the important organs that is affected besides the respiratory system in patients with COVID-19 is the kidneys. Although renal manifestations specific to COVID-19 have not clearly been defined, acute renal damage may reportedly develop in 0.5-29% of the patients with COVID-19 and the incidence of acute renal damage is higher in patients experiencing severe disease or death (11,23-25). In the present study, patients with a mortal course showed higher KDIGO stages on the first day of admission to ICU. In addition, it was found that with the increase in the KDIGO stage of the patient, there was an increase in the mortality risk. These results indicate that a high KDIGO stage at the time of the first admission to ICU is an independent risk factor for mortality. Urgent application of appropriate treatments to patients with high KDIGO stage at admission will contribute to a substantial reduction in mortality risk.

Characteristic laboratory findings observed in critical patients with COVID-19 are reportedly low lymphocyte, albumin, and PaO_2 levels and high WBC, neutrophil, LDH, CRP, urea, creatinine, PTZ, activated partial thromboplastin time, ferritin, and PCT levels (12,26). Linli et al. (27) evaluated 192 critical patients with COVID-19 and stated that abnormal CRP, WBC, AST, and pH values were associated with high mortality and that CRP values should be closely monitored in these patients. Cummings et al. (11), evaluating 257 critically ill patients, stated that high D-dimer levels were an independent risk factor for in-hospital mortality. In the present study, high WBC, neutrophil, N/L ratio, PTZ, D-dimer, lactate, LDH, CK, CRP, urea, creatinine, AST, direct bilirubin, PCT, and ferritin levels as well as low lymphocyte, hemoglobin, hematocrit, platelet, pH, and HCO_3 levels were detected. High N/L ratio, D-dimer, LDH, and creatinine values and low HCO_3 value were identified as independent risk factors for mortality in critical patients with COVID-19. Careful monitoring of these values in critical patients with COVID-19 hospitalized in ICU may act as a caution sign for mortality.

The most important limitation of this study was that it is retrospective and single centered. Conducting studies on critical patients with COVID-19 hospitalized in ICU with multicenter and large patient series across the country or the world will provide more precise information. Another study limitation is that the parameters such as obesity and regional and ethnic differences mentioned in some studies were not included. There was no information about these features in the data we obtained.

Conclusion

As a result of present study, it has been determined that the demographic characteristics of critical COVID-19 patients hospitalized in the ICU, as well as the clinical situation at the first admission to the ICU and some laboratory values are independent risk factors for mortality. In particular, the relationship between high KDIGO stages and mortality at the first admission to the ICU was noteworthy. We believe that monitoring these factors during the follow-up period of critical patients with COVID-19 in ICU can help predict the clinical course of the disease and reduce mortality.

Ethics

Ethics Committee Approval: The study was approved by the Clinical Research Ethics Committee of University of Health Sciences Turkey, Gazi Yaşargil Training and Research of Hospital (decision no: 550, date: 11.09.2020).

Informed Consent: This retrospective cohort study was conducted in accordance with the 2008 Declaration of Helsinki criteria.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: O.U., C.K.K., M.E.E., M.S.G., M.A., Z.K., Ö.C., Concept: O.U., C.K.K., M.E.E., M.S.G., Z.K., Ö.C., Design: O.U., C.K.K., M.E.E., M.A., Data

Collection and Process: O.U., C.K.K., M.E.E., M.S.G., M.A., Z.K., Ö.C., Analysis or Interpretation: O.U., C.K.K., M.E.E., M.A., Ö.C., Literature Search: O.U., C.K.K., M.E.E., M.S.G., M.A., Z.K., Ö.C., Writing: O.U., C.K.K.

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

Financial Disclosure: The authors declared that this study received no financial support.

References

1. WHO Coronavirus Disease (COVID-19) Dashboard. [cited 2020 Dec 12]. Available from URL: https://covid19.who.int/
2. WHO Clinical management of COVID-19 [cited Oct 25 2020]. Available from URL: https://www.who.int/publications/i/item/clinical-management-of-covid-19.
3. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020;395:1054-62.
4. Luo M, Cao S, Wei L, Zhao X, Gao F, Li S, et al. Intubation, mortality, and risk factors in critically ill Covid-19 patients: A pilot study. J Clin Anesth 2020;67:110039.
5. Zhang J, Wang X, Jia X, Li J, Hu K, Chen G, et al. Risk factors for disease severity, unimprovement, and mortality in COVID-19 patients in Wuhan, China. Clin Microbiol Infect 2020;26:767-72.
6. Martins-Filho PR, Tavares CSS, Santos VS. Factors associated with mortality in patients with COVID-19. A quantitative evidence synthesis of clinical and laboratory data. Eur J Intern Med 2020;76:97-9.
7. COVID-ICU Group on behalf of the REVA Network and the COVID-ICU Investigators. Clinical characteristics and day-90 outcomes of 4244 critically ill adults with COVID-19: a prospective cohort study. Intensive Care Med 2021;47:60-73.
8. Du Y, Lv Y, Zha W, Zhou N, Hong X. Association of body mass index (BMI) with critical COVID-19 and in-hospital mortality: A dose-response meta-analysis. Metabolism 2021;117:154373.
9. Yu C, Lei Q, Li W, Wang X, Liu W, Fan X, et al. Clinical Characteristics, Associated Factors, and Predicting COVID-19 Mortality Risk: A Retrospective Study in Wuhan, China. Am J Prev Med 2020;59:168-75.
10. Chen T, Wu D, Chen H, Yan W, Yang D, Chen G, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. BMJ 2020;368:m1091.
11. Cummings MJ, Baldwin MR, Abrams D, Jacobson SD, Meyer BJ, Balough EM, et al. Epidemiology, clinical course, and outcomes of critically ill adults with COVID-19 in New York City: a prospective cohort study. Lancet 2020;395:1763-70.
12. Skevaki C, Fragkou PC, Cheng C, Xie M, Renz H. Laboratory characteristics of patients infected with the novel SARS-CoV-2 virus. J Infect 2020;81:205-12.
13. Mehraeen E, Karimi A, Barzegary A, Vahedi F, Afsahi AM, Dadras O, et al. Predictors of mortality in patients with COVID-19-a systematic review. Eur J Integr Med 2020;40:101226.
14. Parra-Bracamonte GM, Lopez-Villalobos N, Parra-Bracamonte FE. Clinical characteristics and risk factors for mortality of patients with COVID-19 in a large data set from Mexico. Ann Epidemiol 2020;52:93-8.e2.
15. Sanders JM, Monogue ML, Jodlowski TZ, Cutrell JB. Pharmacologic Treatments for Coronavirus Disease 2019 (COVID-19): A Review. JAMA 2020;323:1824-36.
16. T.R. Ministry of Health COVID-19 information page. The management of Severe Pneumonia, ARDS, Sepsis and Septic Shock [cited Dec 30 2020]. Available from: https://covid19.saglik.gov.tr/
17. Kellum JA, Lameire N, Aspelin P, Barsoum RS, Burdmann EA, Goldstein SL, et al. Kidney disease: improving global outcomes (KDIGO) acute kidney injury work group. KDIGO clinical practice guideline for acute kidney injury [Internet]. Nature Publishing Group. Vol. 2. p. 1-138; 2012. Kidney International Supplements [cited Dec 21 2020]. Available from URL: https://experts.umn.edu/en/publications/kidney-disease-improving-global-outcomes-kdigo-acute-kidney-injur.
18. Leung C. Risk factors for predicting mortality in elderly patients with COVID-19: A review of clinical data in China. Mech Ageing Dev 2020;188:111255.
19. Gallo Marin B, Aghagoli G, Lavine K, Yang L, Siff EJ, Chiang SS, et al. Predictors of COVID-19 severity: A literature review. Rev Med Virol 2021;31:1-10.
20. Albitar O, Ballouze R, Ooi JP, Sheikh Ghadzi SM. Risk factors for mortality among COVID-19 patients. Diabetes Res Clin Pract 2020;166:108293.
21. Li X, Xu S, Yu M, Wang K, Tao Y, Zhou Y, et al. Risk factors for severity and mortality in adult COVID-19 inpatients in Wuhan. J Allergy Clin Immunol 2020;146:110-8.
22. Zou X, Li S, Fang M, Hu M, Bian Y, Ling J, et al. Acute Physiology and Chronic Health Evaluation II Score as a Predictor of Hospital Mortality in Patients of Coronavirus Disease 2019. Crit Care Med 2020;48:e657-65.
23. Yao Q, Wang P, Wang X, Qie G, Meng M, Tong X, et al. A retrospective study of risk factors for severe acute respiratory syndrome coronavirus 2 infections in hospitalized adult patients. Pol Arch Intern Med 2020;130:390-9.
24. Kunutsor SK, Laukkanen JA. Renal complications in COVID-19: a systematic review and meta-analysis. Ann Med 2020;52:345-53.
25. Nimkar A, Naaraayan A, Hasan A, Pant S, Durdevic M, Suarez CN, et al. Incidence and Risk Factors for Acute Kidney Injury and Its Effect on Mortality in Patients Hospitalized From COVID-19. Mayo Clin Proc Innov Qual Outcomes 2020;4:687-95.
26. Lu L, Zhong W, Bian Z, Li Z, Zhang K, Liang B, et al. A comparison of mortality-related risk factors of COVID-19, SARS, and MERS: A systematic review and meta-analysis. J Infect 2020;81:e18-e25.
27. Linli Z, Chen Y, Tian G, Guo S, Fei Y. Identifying and quantifying robust risk factors for mortality in critically ill patients with COVID-19 using quantile regression. Am J Emerg Med 2021;45:345-51.

Turk J Intensive Care 2021;19(Suppl 1):62-72
DOI: 10.4274/tybd.galenos.2021.37167

ORIGINAL RESEARCH / *ÖZGÜN ARAŞTIRMA*

Abdullah Gök,
Umut Sabri Kasapoğlu,
Leman Acun Delen,
Ferda Özmen,
Süsen Banazılı

Lactate/Albumin Ratio as a Prognostic Factor for Short-time Mortality in Critically Ill Patients with Coronavirus Disease-2019

Yoğun Bakım Ünitesinde Takip Edilen Koronavirüs Hastalığı-2019 Olgularında Kısa Dönem Mortalitenin Prognostik Belirteci Olarak Laktat/Albümin Oranı

Received/Geliş Tarihi : 31.05.2021
Accepted/Kabul Tarihi : 23.08.2021

Abdullah Gök, Leman Acun Delen, Ferda Özmen, Süsen Banazılı
Malatya Training and Research Hospital, Clinic of Anesthesiology and Reanimation, Malatya, Turkey

Umut Sabri Kasapoğlu
Malatya Training and Research Hospital, Clinic of Pulmonary and Critical Care Medicine, Malatya, Turkey

Umut Sabri Kasapoğlu MD, (✉),
Malatya Training and Research Hospital, Clinic of Pulmonary and Critical Care Medicine, Malatya, Turkey

E-mail : umutkasapoglu@gmail.com
Phone : +90 554 818 19 19
ORCID ID : orcid.org/0000-0003-2869-9872

ABSTRACT *Objective:* The prognostic role of the initial lactate/albumin ratio (LAR) in critically ill patients with coronavirus disease-2019 (COVID-19) remains unknown. This study aimed to evaluate the prognostic value of the initial LAR in predicting 30-day mortality in critically ill patients with COVID-19 and compare the initial level of serum lactate and albumin for mortality prediction.
Materials and Methods: A single-center and observational clinical study between April 2020 and December 2020 were retrospectively performed. Clinical and laboratory variables of patients evaluated in this study were collected within the first 24 hours following the intensive care unit (ICU) admission.
Results: A total of 282 critically ill patients with COVID-19 were included in the study. The mean age of the patients was 66.34±12.08 years, wherein 179 (63.5%) were male. Patients who died within 30 days had higher lactate (p<0.001), lower serum albumin (p<0.001), and higher LAR levels (p<0.001). ROC analysis revealed that LAR (AUC: 0.824) was superior to the serum albumin (AUC: 0.644) and lactate levels (AUC: 0.795) for mortality prediction. Overall ICU mortality rates (75.6% vs. 13.1%, p<0.001) were significantly higher in patients with LAR of >0.60.
Conclusion: LAR is a useful prognostic factor for risk stratification of critically ill patients with COVID-19.
Keywords: COVID-19, lactate/albumin ratio, lactate, albumin, mortality, predictor

ÖZ *Amaç:* Laktat/albümin oranının (LAR) kritik koronavirüs hastalığı-2019 (COVID-19) olgularındaki prognostik rolü bilinmemektedir. Bu çalışmada, kritik COVID-19 olgularında 30 günlük mortaliteyi tahmin etmede ilk LAR'ın prognostik değerini araştırılması ve mortalite tahmininde serum laktat ve albümin düzeyi ile karşılaştırılması amaçlanmıştır.
Gereç ve Yöntem: Tek merkezli retrospektif gözlemsel klinik çalışmaya Nisan 2020 ve Aralık 2020 tarihleri arasında YBÜ'ye kabul edilen olgular dahil edilmiştir. Çalışmada YBÜ'ye kabul edilen kritik COVID-19 hastalarının yatıştan sonraki ilk 24 saat içindeki klinik ve laboratuvar değişkenleri değerlendirilmiştir.
Bulgular: Çalışmaya 282 kritik COVID-19 olgusu dahil edilmiştir. Hastaların yaş ortalaması 66,34±12,08 yıl olup, 179'u (%63,5) erkekti. Otuz gün içinde ölen olguların daha yüksek laktat (p<0,001), daha düşük serum albümin (p<0,001) ve daha yüksek LAR (p<0,001) seviyelerine sahip olduğu saptanmıştır. Mortalite tahmini için yapılan ROC analizinde, LAR'nin (AUC: 0,824) serum albümin (AUC: 0,644) ve serum laktat (AUC: 0,795) düzeylerinden daha üstün olduğu gösterilmiştir. Bununla birlikte yoğun bakım mortalitesinin LAR >0,60 olan olgularda daha yüksek olduğu saptanmıştır (%75,6 vs. %13,1, p<0,001).
Sonuç: LAR kritik COVID-19 olgularının risk sınıflandırması için yararlı bir prognostik faktör olabilir.
Anahtar Kelimeler: COVID-19, laktat/albümin oranı, laktat, albümin, mortalite, prediktör

Introduction

The novel coronavirus disease-2019 (COVID-19) caused by acute respiratory syndrome coronavirus 2 has begun to be seen at the end of 2019, in Wuhan, China. After that, World Health Organization has declared the COVID-19 pandemic, and it isn't still even close to being over (1,2). Due to the COVID-19 is associated with a high risk of mortality and morbidity in critically ill patients, lots of clinical studies have focused on the identification of prognostic factors to reduce COVID-19 associated mortality (3,4).

The level of serum lactate is the most commonly used biomarker for the management of critically ill patients in the emergency department and intensive care unit (ICU) (5). Hyperlactatemia or elevated levels of serum lactate may be caused by different clinical settings including sepsis, liver diseases, shock, and cancer. Many published studies have shown the association between hyperlactatemia and poor survival of critically ill patients (5-7). Also, in a clinical study by Velavan et al. (8), levels of blood lactate were found significantly elevated in hospitalized COVID-19 patients with severe diseases.

Serum albumin that known as one of the major plasma proteins, is a negative acute phase reactant and has anti-oxidant properties. Many clinical statuses can lead to altered in the level of serum albumin (9,10). Especially, hypoalbuminemia is associated with poor prognosis and shorter survival time in many clinical settings such as sepsis, traumatic brain injury, decompensated heart failure, and cancer (9,11-13). Also, recently published studies showed that a lower level of serum albumin is frequently observed in severe and critically ill COVID-19 patients and it is associated with poor survival (14-17).

Clinical studies have reported that the lactate/albumin ratio (LAR) could have been an important prognostic factor for the prediction of mortality in septic shock, heart failure, and cardiac arrest patients. Also, it was shown that an increased initial LAR level was superior to the initial level of serum lactate alone for in-hospital mortality (10,18-22). To the best of our knowledge, the prognostic role of LAR in critically ill COVID-19 patients remains unknown. Therefore, in the present study, we aimed to evaluate the prognostic value of the LAR on the day of ICU admission in predicting 30-day mortality in critically ill COVID-19 patients, and compare with the initial level of serum lactate and albumin for the prediction of mortality.

Materials and Methods

Study Design and Population

The study was approved by the Clinical Ethics Committee of Malatya İnönü University Faculty of Medicine (protocol no: 2020/154, date: 04.11.2020). We performed a single-center retrospective and observational clinical study in a tertiary level ICU of Malatya Training and Research Hospital between April 2020 and December 2020. A total of 282 critically ill COVID-19 patients aged 18 years and older were enrolled in the study. Patients who died within the first 24 hours and were transferred to the other ICU were excluded from the study.

Data Collection and Definitions

We collected and analyzed the following data: all patients' demographic and clinical variables, scores on the Acute Physiology and Chronic Health Evaluation-II (APACHE-II) and Sequential Organ Failure Assessment (SOFA), laboratory variables, respiratory support type within 24 hours, invasive mechanical ventilation requirement, the use of the vasoactive agent, ICU length of stay, and survival status of the patients at the end of day 30. Patients' clinical and laboratory variables that evaluated in this study were collected within the first 24 hours following the ICU admission.

The normal serum concentration of the albumin was 3.5-5.0 g/dL, and hypoalbuminemia was defined as the level of serum albumin <3.5 g/dL (12). Also, hyperlactatemia was defined as the serum lactate level >2 mmol/L (7).

Measurement of Outcome

All patients were followed up during their ICU stay or until death, and we defined the short time mortality as death within 30 days after the ICU admission. All patients' mortality data were collected from the hospital medical record system.

Statistical Analysis

We used SPSS (Statistical Package for Social Sciences) for Windows 22.0 software (SPSS Inc., Chicago, IL, USA) for the statistical analysis of the variables obtained from the hospital medical record system. All results were analyzed with a confidence interval level of 95% and a significance level of $p<0.05$. The homogeneity and distribution of the variables were assessed with using the Skewness-Kurtosis. Frequencies and percentages were used for the categorical data, mean value ± standard deviation was used for the parametric variables while median (minimum-maximum)

values were used for the non-parametric variables. We used chi-squared test for the comparison of the categorical variables. The independent samples t-test was used for the analysis of the two independent groups' parametric variables while Mann-Whitney U test was used for the analysis of non-parametric variables. Pearson correlation analysis was used for the assessment of the relationship between LAR and disease severity scoring systems. We used receiver operating characteristic (ROC) curve for determine the optimal cut-off value of the LAR. We used the Kaplan-Meier method for determining the overall survival rates of the patients at day 30. And, Long-rank test was used to compare the differences between the survival of the groups. After the univariate survival analysis, we used Cox regression analysis for the assessment of the multivariate survival analysis.

Results

Baseline Characteristics of the Overall Study Population

A total of 282 critically ill COVID-19 patients aged 18 years and older were included in the study. The mean age of the patients was 66.34±12.08 years and 179 (63.5%) of patients were male. One hundred thirty-six of the patients (48.2%) was under 65 years of age. Hypertension (68.2%), diabetes mellitus (38.3%), and coronary artery disease (31.2%) were the most common comorbidities. The SOFA and APACHE-II scores on ICU admission were found 4.00 (2-12) and 17.34±3.95 respectively. And, 137 (48.6%) patients died within 30 days after the ICU admission.

Comparison of the Baseline Clinical Characteristics Between Survivors and Non-survivors

There were significant differences between the survivors and the non-survivors patients respectively age, gender, SOFA score, APACHE-II score, lymphocyte, N-terminal prohormone of brain natriuretic peptide (NT-proBNP), lactate dehydrogenase (LDH), urea, creatinine, ferritin, C-reactive protein (CRP), and procalcitonin ($p<0.05$). As we expected, patients who died within 30 days had higher lactate levels (2.77 vs. 1.73 mmol/L, $p<0.001$), lower levels of serum albumin (2.73 vs. 2.95 g/dL, $p<0.001$), and higher levels of LA ratio (0.92 vs. 0.55, $p<0.001$). Comparison of the baseline clinical and laboratory characteristics of the survivors and non-survivors are summarized in Table 1, 2.

Mortality Prediction Performance of Lactate, Albumin and, Lactate/Albumin Ratio

We performed ROC analysis for the prediction of 30-day mortality and also finding the optimal cut-off value of the LAR for determining the 30-day mortality. ROC analysis showed that LAR [area under curve (AUC): 0.824, $p<0.001$] was superior to the serum albumin (AUC: 0.644, $p<0.001$) and lactate levels (AUC: 0.795, $p<0.001$) for the prediction of 30-day mortality. Also, the optimal cut-off value of the LAR was found 0.60 (Figure 1) (Table 3).

Comparison of the baseline clinical characteristics between patients with LAR >0.60 and patients with LAR ≤0.60

After the determination of the cut-off value of the LAR, the overall study population divided into two groups as patients with LAR >0.60 and patients with LAR ≤0.60. Statistically significant differences were found between the groups by age and gender ($p<0.001$). And, patients with LAR >0.60 had higher SOFA and APACHE-II score on ICU admission ($p<0.001$). We found that laboratory findings of the organ dysfunction and inflammatory parameters were significantly elevated in patients with LAR>0.60. Also, serum level of albumin and count of lymphocytes was found significantly lower in patients with LAR>0.60. The use of vasoactive agents (31.8% vs. 24.6%, $p<0.001$) and 30-day overall ICU mortality rates (75.6% vs. 13.1%, $p<0.001$) were significantly higher in patients with LAR >0.60. We also found that LAR on the day of ICU admission was positively correlated with ICU admission SOFA score ($r=0.335$, $p<0.001$) and APACHE-II score ($r=0.298$, $p<0.001$) (Figure 2). Comparison of the baseline clinical and laboratory characteristics of the patients with LAR >0.60 and patients with LAR ≤0.60 are presented in Table 4, 5.

Survival Analysis of the Patients

In the present study, 30-day overall mortality was found 48.6% in the overall study population. And, 30-day overall ICU mortality rates (75.6% vs. 13.1%, $p<0.001$) were significantly higher in patients with LAR >0.60. Also, patients with hypoalbuminemia and hyperlactatemia had a significantly shorter survival time ($p<0.001$). More importantly, we found that LAR >0.60 was associated with shorter survival time ($p<0.001$) (Figure 3). Univariate survival analysis of the patients summarized in Table 6. We performed multivariate Cox regression survival analysis for the assessment of independent prognostic factors. It showed that LAR >0.60 was significant and independent prognostic factor for the

30-day mortality in critically ill COVID-19 patients [hazard ratio (HR): 10.615; confidence interval (CI): 5.673-19.865, p<0.001) (Table 6).

Discussion

In the present study, we investigated the prognostic role of LAR on the day of ICU admission in critically ill COVID-19 patients. The main result of this study has shown that the LAR >0.60 was associated with a shorter survival time, and had a better prognostic performance for predicting 30-day mortality in critically ill COVID-19 patients.

COVID-19 is associated with high risk of mortality and morbidity especially in hospitalized and critically ill patients. For this reason, several factors such as laboratory and clinical

Table 1. Baseline characteristics of the patients; survivors vs. non-survivors

	Overall (n=282)	Survivors (n=145)	Non-survivors (n=137)	p value
Mean age, years (mean ± SD)	66.34±12.08	63.60±12.89	69.25±10.44	<0.001*
Age				
≥65 years	146 (51.8%)	61 (42.1%)	85 (62%)	0.001**
<65 years	136 (48.2%)	84 (57.9%)	52 (38%)	
Gender				
Female	103 (36.5%)	66 (45.5%)	37 (27%)	0.001**
Male	179 (63.5%)	79 (54.5%)	100 (73%)	
Comorbidities				
Malignancy	4 (1.4%)	1 (0.7%)	3 (2.2%)	0.287**
CKD	14 (5%)	5 (3.4%)	9 (6.6%)	0.228**
Alzheimer disease	24 (8.5%)	13 (9.0%)	11 (8.0%)	0.778**
Cerebrovascular disease	7 (8.5%)	6 (4.1%)	1 (0.7%)	0.066**
Diabetes mellitus	108 (38.3%)	54 (37.2%)	54 (39.4%)	0.707**
COPD	62 (22%)	29 (20.0%)	33 (24.1%)	0.407**
Hypertension	192 (68.1%)	98 (67.6%)	94 (68.6%)	0.853**
CHF	37 (13.1%)	16 (11.0%)	21 (15.3%)	0.286**
CAD	88 (31.2%)	38 (26.2%)	50 (36.5%)	0.062**
Arrhythmia	23 (8.2%)	11 (7.6%)	12 (8.8%)	0.719**
SOFA score, (minimum-maximum)	4.00 (2-12)	3.00 (2-8)	5.00 (3-12)	<0.001***
APACHE-II score, (mean ± SD)	17.34±3.95	15.65±3.21	19.13±3.88	<0.001*
Invasive mechanical ventilation support within the first 24 hours				
Yes	41 (14.5%)	18 (12.4%)	23 (16.7%)	0.298
No	241 (85.5%)	127 (87.6%)	114 (83.3%)	
PaO_2/FiO_2 ratio	172.68±27.99	175.35±29.94	169.85±25.57	0.099
Use of vasoactive agent				
Yes	139 (49.3%)	22 (15.2%)	117 (85.4%)	<0.001**
No	143 (50.7%)	123 (84.8%)	20 (14.6%)	
Renal replacement therapy				
Yes	19 (6.7%)	4 (2.8%)	15 (10.9%)	0.006**
No	263 (93.3%)	141 (97.2%)	122 (89.1%)	

*Independent samples t-test,**chi-squared test, ***Mann-Whitney U test, CKD: chronic kidney disease, COPD: chronic obstructive pulmonary disease, CHF: chronic heart failure, CAD: coronary artery disease, SOFA: Sequential Organ Failure Assessment, APACHE-II: Acute Physiology and Chronic Health Evaluation-II, Min: minimum, Max: maximum, SD: standard deviation

variables for the prediction of the disease severity and outcome has been defined in recently published clinical trials (15,16,23). Determination of these prognostic factors of the critically ill patients could help the decision of therapeutic approaches for improving the short and long-term outcome (10,12).

Recently published clinical studies and meta-analysis that evaluate the prognostic factors in patients with COVID-19

Table 2. Baseline laboratory parameters of the patients; survivors vs non-survivors

	Overall (n=282)	Survivors (n=145)	Non-survivors (n=137)	p-value
Biochemical parameters				
Urea, mg/dL (min-max)	56.00 (13-343)	49.00 (13-343)	65.00 (18-290)	<0.001*
Crea, mg/dL (min-max)	0.88 (0.36-12.02)	0.81 (0.36-9.00)	0.99 (0.50-12.02)	<0.001*
AST, U/L (min-max)	46.00 (11-940)	45.00 (12-900)	47.00 (11-940)	0.080*
ALT, U/L (min-max)	34.00 (5-850)	33.00 (5-404)	35.00 (6-850)	0.506*
CK, U/L (min-max)	116.00 (12-1,000)	111.00 (12-1,000)	132.15 (20-1,000)	0.070*
LDH, IU/L (mean ± SD)	654.43±295.82	592.60±283.93	719.87±295.07	<0.001**
Albumin, g/dL (mean ± SD)	2.85±0.44	2.95±0.47	2.73±0.39	<0.001**
Inflammatory parameters				
Ferritin, ng/dL (mean ± SD)	891.00±619.48	745.33±561.99	1045.18±641.82	<0.001**
CRP, mg/dL (min-max)	12.81 (0.13-94.30)	11.70 (0.13-35.04)	13.64 (1.08-94.30)	0.032*
PCT, ng/mL (min-max)	0.25 (0.02-50.56)	0.19 (0.02-4.38)	0.33 (0.05-50.56)	<0.001*
Total blood count				
WBC, 10^3/µL (mean ± SD)	12.48±6.25	11.92±6.29	13.07±6.18	0.123**
Neu, 10^3/µL (mean ± SD)	11.06±5.90	10.44±5.87	11.72±5.88	0.069**
Lmyph, 10^3/µL (mean ± SD)	0.70 (0.11-5.67)	0.75 (0.20-5.67)	0.64 (0.11-2.83)	0.001*
Hgb, g/dL (mean ± SD)	12.93±1.92	12.82±1.79	13.04±2.06	0.325**
Htc, % (mean ± SD)	39.15±5.88	38.93±5.52	39.38±6.25	0.519**
Plt, 10^3/µL (mean ± SD)	266.22±114.37	274.46±112.29	257.50±116.30	0.214**
Cardiac markers				
Trop-I, ng/mL (min-max)	0.10 (0.10-25.00)	0.10 (0.01-25.00)	0.10 (0.01-15.23)	0.160*
NT-proBNP, pg/mL (min-max)	1180 (22-35,000)	792 (22-35,000)	1615 (86-35,000)	<0.001*
Coagulation parameters				
INR, (min-max)	1.23 (0.90-8.04)	1.21 (0.90-3.92)	1.26 (1.00-8.04)	0.005*
Fibrinogen, ng/dL (min-max)	488 (50-1,519)	492 (50-1,477)	485 (144-1,519)	0.824*
D-dimer, µg/mL (min-max)	1.68 (0.01-39.20)	1.53 (0.18-39.20)	1.70 (0.01-35.50)	0.385*
Arterial blood gas analysis				
pH, (min-max)	7.43 (6.91-7.57)	7.44 (6.91-7.57)	7.42 (7.10-7.56)	0.002*
pO_2, mmHg (min-max)	61.75 (35-227)	62.90 (49-227)	60.60 (35-166)	0.009*
pCO_2, mmHg (min-max)	34.75 (15-93)	35.20 (15-93)	34.40 (17-81)	0.742*
HCO_3, mEq/L (min-max)	22.93±4.80	23.74±4.75	22.07±4.72	0.003**
SpO_2, % (mean ± SD)	90.03±6.11	91.59±4.26	88.37±7.25	<0.001**
Lactate, mmol/L (min-max)	2.00 (0.50-12.20)	1.73±0.68	2.77±1.44	<0.001**
Lactate/albumin ratio	0.68 (0.18-4.36)	0.55 (0.18-2.50)	0.92 (0.34-4.36)	<0.001*

*Mann-Whitney U test, **independent samples t-test, SD: standard deviation, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, CK: creatine kinase, PCT: procalcitonin, NT-proBNP: N-terminal prohormone of brain natriuretic peptide, CRP: C-reactive protein, Lymph: lymphocyte, WBC: white blood cell, Neu: neutrophil, Hgb: hemoglobin, Htc: hematocrit, Plt: platelets, INR: international normalized ratio, Trop-I: troponin-I, Crea: creatinin

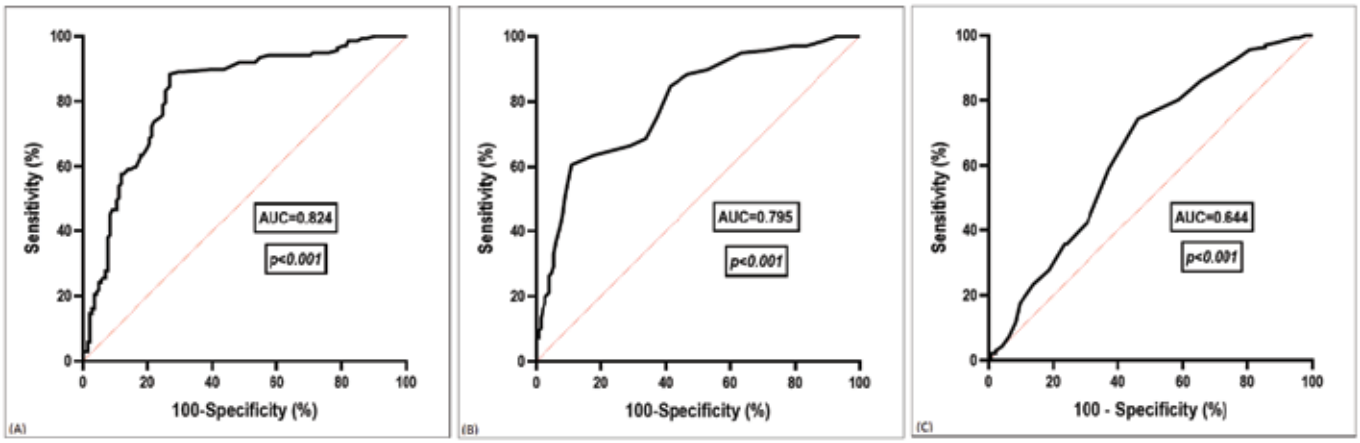


Figure 1. ROC analysis of (A) lactate/albumin ratio (B) serum lactate level (C) serum albumin level for the predicting 30-day mortality
ROC: Receiver operating characteristic, AUC: area under curve

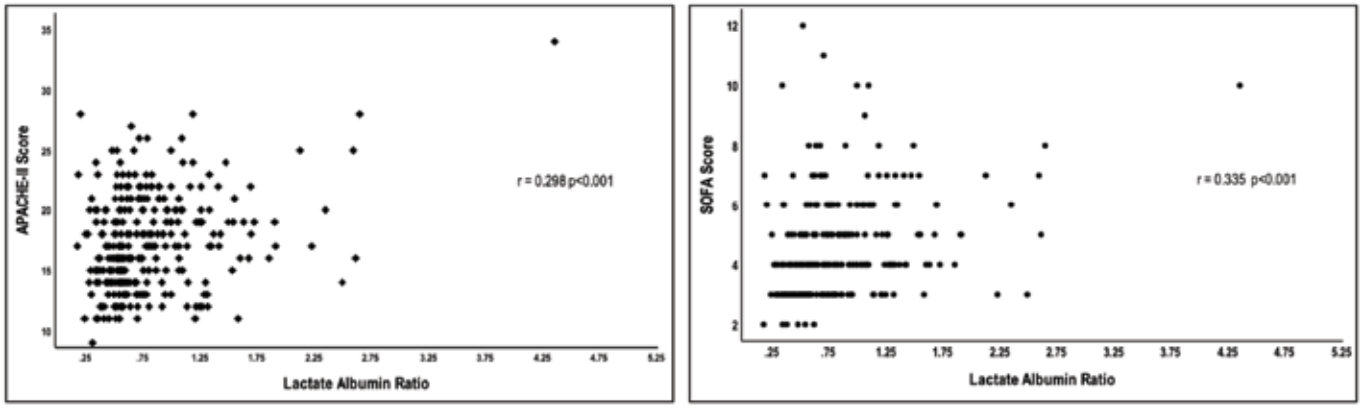


Figure 2. Pearson correlation analysis of LAR with APACHE-II score and SOFA score
APACHE-II: Acute Physiology and Chronic Health Evaluation-II, LAR: lactate/albumin ratio, SOFA: Sequential Organ Failure Assessment

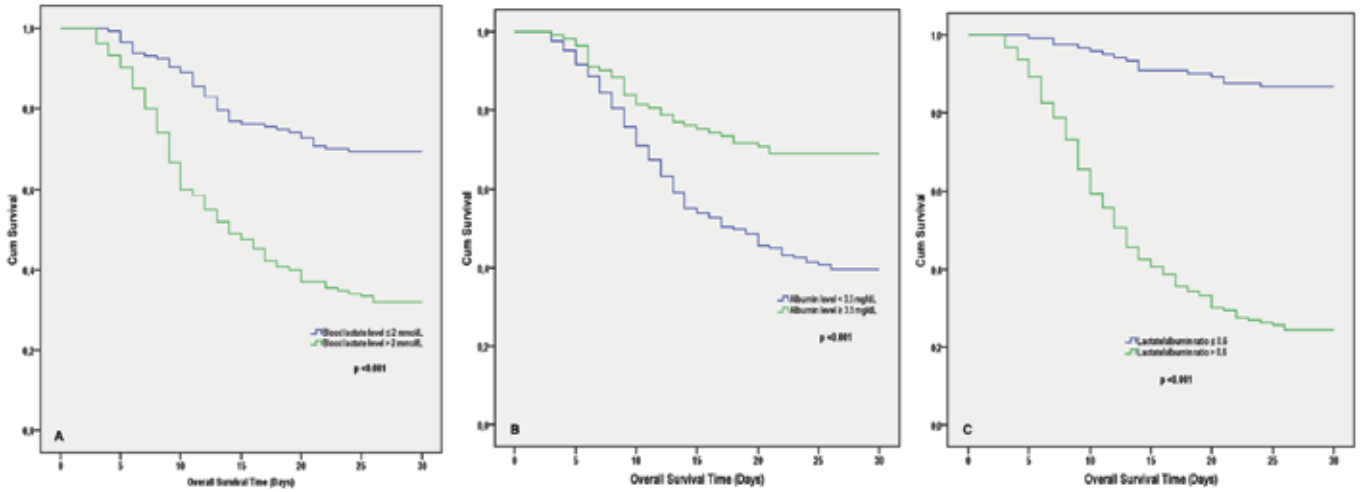


Figure 3. Kaplan-Meier 30-day survival curves for the critically ill COVID-19 patients by A) blood lactate level, B) serum albumin level and C) lactate/albumin ratio. P-values were calculated using the Log-rank test
COVID-19: Coronavirus disease-2019

reported increased level of LDH, CRP, procalcitonin, D-dimer, cardiac biomarkers, and decreased lymphocyte count were associated with severe disease and increased mortality. Also, older age, male sex, comorbidity, and obesity can impact survival in patients with COVID-19 (3,4,24-28). We found significant differences between the survivors and the non-survivors in terms of age, gender, lymphocyte, NT-proBNP, LDH, ferritin, CRP, and procalcitonin, as showed by recently published studies.

Hypoalbuminemia is frequently seen in COVID-19 patients and is associated with disease severity. Although the underlying mechanisms have not been clarified, severe COVID-19 that is characterized by hyperinflammation lead to endothelial damage and increased capillary permeability, and this can lead to the accumulation of albumin in the interstitium. Recently published studies demonstrated that lower level of serum albumin at admission is significantly associated with increased mortality. Also,

Table 3. The values of AUC, sensitivity and specificity of serum lactate level, serum albumin level and lactate albumin ratio for the prediction of 30-days mortality

	AUC	95% CI	Sensitivity	Specificity	p-value
Lactate albumin ratio	0.824	0.774-0.874	89.1%	73.1%	<0.001
Albumin	0.644	0.580-0.709	53.8%	74.5%	<0.001
Lactate	0.795	0.743-0.847	68.6%	66.2%	<0.001

AUC: Area under curve, CI: confidence interval

Table 4. Comparison of the baseline clinical parameters of the patients; LAR ≤0.60 vs LAR >0.60

	Overall (n=282)	LAR ≤0.60 (n=122)	LAR >0.60 (n=160)	p-value
Mean age, years (mean ± SD)	66.34±12.08	63.76±13.09	68.31±10.88	<0.001*
Age				
≥65 years	146 (51.8%)	52 (42.6%)	94 (58.7%)	0.007**
<65 years	136 (48.2%)	70 (57.4%)	66 (41.3%)	
Gender				
Female	103 (36.5%)	60 (49.1%)	43 (26.8%)	<0.001**
Male	179 (63.5%)	62 (50.9%)	117 (73.2%)	
SOFA score, (min-max)	4.00 (2-12)	3.00 (2-12)	5.00 (2-11)	<0.001*
APACHE-II score, (mean ± SD)	17.34±3.95	16.17±3.55	18.23±4.027	<0.001*
Invasive mechanical ventilation support within the first 24 hours				
Yes	41 (14.5%)	17 (13.9%)	24 (15.0%)	0.801
No	241 (85.5%)	105 (86.1%)	136 (85.0%)	
PaO_2/FiO_2 ratio	172.68±27.99	177.32±32.69	169.13±23.29	0.015
Use of vasoactive agent				
Yes	81 (28.8%)	30 (24.6%)	51 (31.8%)	<0.001**
No	201 (71.2%)	92 (75.4%)	109 (68.2%)	
Renal replacement therapy				
Yes	19 (6.7%)	9 (7.3%)	10 (6.2%)	0.708**
No	263 (93.3%)	113 (92.7%)	150 (93.8%)	
Survival status at day 30				
Alive	145 (51.4%)	106 (86.9%)	39 (24.4%)	<0.001
Deceased	137 (48.6%)	16 (13.1%)	121 (75.6%)	

*Independent samples t-test, **chi-squared test, ***Mann-Whitney U test, SOFA: Sequential Organ Failure Assessment, APACHE-II: Acute Physiology and Chronic Health Evaluation-II, min: minimum, max: maximum, SD: standard deviation, LAR: lactate/albumin ratio

hypoalbuminemia has been found as independent prognostic factor for mortality in COVID-19 patients (13,15-17,29,30). Consistent with previous clinical studies and meta-analysis, the present study has confirmed that hypoalbuminemia is associated with a shorter survival time (p<0.001). However, lower level of serum albumin (serum albumin level <3.5 mg/dL) has not found as an independent prognostic factor for the 30-day mortality in critically ill COVID-19 patients (p=0.463). However, the nutrition status of the patient, diseases that cause chronic inflammation,

Table 5. Comparison of the baseline laboratory parameters of the patients; LAR ≤0.60 vs LAR >0.60

	Overall (n=282)	LAR ≤0.60 (n=122)	LAR >0.60 (n=160)	p-value
Blood biochemical parameters				
Urea, mg/dL (min-max)	56.00 (13-343)	51.00 (13-343)	61.50 (18-226)	0.004*
Crea, mg/dL (min-max)	0.88 (0.36-12.02)	0.88 (0.36-12.02)	0.88 (0.42-9.29)	0.137*
AST, U/L (min-max)	46.00 (11-940)	43.50 (14-900)	49.00 (11-940)	0.029*
ALT, U/L (min-max)	34.00 (5-850)	29.00 (5-404)	40.00 (6-850)	0.006*
CK, U/L (min-max)	116.00 (12-1,000)	116.35 (12-1,000)	116.00 (20-1,000)	0.215*
LDH, IU/L (mean ± SD)	654.43±295.82	594.05±279.49	700.47±300.47	0.003**
Albumin, g/dL (mean ± SD)	2.85±0.44	3.06±0.40	2.68±0.41	<0.001**
Inflammatory parameters				
Ferritin, ng/dL (mean ± SD)	891.00±619.48	688.94±553.08	1045.07±624.72	<0.001**
CRP, mg/dL (Min-max)	12.81 (0.13-94.30)	12.37 (0.90-35.04)	13.09 (0.13-94.30)	0.024*
PCT, ng/mL (Min-max)	0.25 (0.02-50.56)	0.19 (0.02-11.67)	0.29 (0.05-50.56)	0.004*
Total blood count				
Wbc, 10^3/µL (mean ± SD)	12.48±6.25	11.01±5.73	13.61±6.24	<0.001**
Neu, 10^3/µL (mean ± SD)	11.06±5.90	9.56±5.30	12.20±6.09	<0.001**
Lmyph, 10^3/µL (Min-max)	0.70 (0.11-5.67)	0.75 (0.20-5.20)	0.65 (0.11-5.67)	0.036*
Hgb, g/dL (mean ± SD)	12.93±1.92	12.59±1.88	13.19±1.92	0.100**
Htc, % (mean ± SD)	39.15±5.88	38.39±6.12	39.73±5.65	0.590**
Plt, 10^3/µL (mean ± SD)	266.22±114.37	260.25±104.79	270.77±121.29	0.445**
Cardiac markers				
Trop-I, ng/mL (min-max)	0.10 (0.10-25.00)	0.10 (0.01-25.00)	0.10 (0.01-15.23)	0.167*
NT-proBNP, pg/mL (min-max)	1180 (22-35,000)	792 (22-35,000)	1411 (32-35,000)	0.001*
Coagulation parameters				
INR, (min-max)	1.23 (0.90-8.04)	1.21 (0.90-11.67)	1.25 (0.98-8.04)	0.006*
Fibrinogen, ng/dL (min-max)	488 (50-1519)	493 (189-1,477)	481 (50-1519)	0.899*
D-Dimer, µg/mL (min-max)	1.68 (0.01-39.20)	1.24 (0.10-39.20)	2.00 (0.01-35.50)	0.001*
Arterial blood gas analysis				
pH, (min-max)	7.43 (6.91-7.57)	7.43 (6.91-7.57)	7.43 (7.10-7.56)	0.375*
pO_2, mmHg (min-max)	61.75 (35-227)	64.60 (49-227)	60.00 (35-166)	0.001*
pCO_2, mmHg (min-max)	34.75 (15-93)	35.00 (15-93)	34.40 (17-81)	0.810*
HCO_3, mEq/L (min-max)	22.93±4.80	23.07±5.47	22.81±4.24	0.395**
SpO_2, % (mean ± SD)	90.03±6.11	91.88±4.19	88.62±6.93	<0.001**
Lactate, mmol/L (min-max)	2.00 (0.50-12.20)	1.50 (0.50-2.20)	2.50 (1.50-12.20)	<0.001*

*Mann-Whitney U test, **independent samples t-test, SD: standard deviation, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, CK: creatine kinase, PCT: procalcitonin, NT-proBNP: N-terminal prohormone of brain natriuretic peptide, CRP: C-reactive protein, Lymph: lymphocyte, WBC: white blood cell, Neu: neutrophil, Hgb: hemoglobin, Htc: hematocrit, Plt: platelets, INR: international normalized ratio, Trop-I: troponin-I, Crea: creatinine, LAR: lactate/albumin ratio

Table 6. Univariate and multivariate survival analysis of lactate, albumin, and lactate albumin ratio on 30-day survival time									
	Number of patients	Univariate survival analysis				Multivariate survival analysis			
		Mean survival time (days ± SE)	95% CI		p-value*	Hazard ratio	95% CI		p-value
			Lower bound	Upper bound			Lower bound	Upper bound	
Blood lactate level									
>2 mmol/L	135 (47.9%)	17.14±0.86	15.46	18.83	<0.001	0.828	0.548	1.252	0.372
≤2 mmol/L	147 (52.1%)	24.57±0.71	23.16	25.97					
Serum albumin level									
<3.5 mg/dL	169 (59.9%)	19.02±0.76	17.52	20.52	<0.001	0.859	0.572	1.289	0.463
≥3.5 mg/dL	113 (40.1%)	24.00±0.88	22.27	25.72					
Lactate albumin ratio									
≤0.6	122 (43.3%)	27.86±0.52	26.83	28.90	<0.001	10.615	5.673	19.865	<0.001
>0.6	160 (56.7%)	15.79±0.74	14.33	17.25					
*P-values were calculated using the Log-rank test. CI: Confidence interval, SE: standard error									

and liver diseases can affect the serum albumin levels in critically ill patients (19).

In addition, several studies have reported that an increased level of blood lactate is associated with severe disease and increased risk of mortality in patients with COVID-19 (8,25,31). Velavan et al. (8), have reported that the level of blood lactate in COVID-19 pneumonia patients is higher compared with non-COVID-19 pneumonia patients. In the recently published study by Vassiliou et al. (32), have emphasized that initial blood lactate is an independent mortality predictor in critically ill COVID-19 patients. The present study has confirmed that hyperlactatemia is associated with a shorter survival time (p<0.001) (Figure 3). However, an increased level of blood lactate (blood lactate level >2 mmol/L) has not found as an independent prognostic factor for the 30-day mortality in critically ill COVID-19 patients (p=0.372). However, several clinical statuses including renal or hepatic dysfunction, medications, and thiamine deficiency can affect the blood lactate levels (10,21,22).

Given these limitations of the single measurement of the lactate and albumin levels, several studies have focused on the mortality prediction performance of the lactate albumin ratio in different clinical settings (10,18-22,33). Studies that evaluate the clinical utility of LAR have shown that increased LAR is significantly associated with increased mortality and organ dysfunction in patients with sepsis and septic shock. In addition, these studies have shown that the mortality prediction performance of the LAR is superior to serum lactate level or albumin level alone in patients with sepsis and septic shock (10,18-20,33). Consistent with previous clinical studies, in the present study, ROC analysis showed that LAR (AUC: 0.824, p<0.001) was superior to the serum albumin (AUC: 0.644, p<0.001) and lactate levels (AUC: 0.795, p<0.001) for the prediction of 30-day mortality.

The clinical trial by Wang et al. (33), have reported that increased LAR correlated with APACHE-II score and PaO_2/FiO_2 ratio in patients with severe sepsis and septic shock. Also, they have emphasized that increased level of LAR on the day of ICU admission was associated with multiple-organ dysfunction syndrome and mortality in patients with severe sepsis and septic shock.

Studies have also investigated the clinical utility of the LAR as a prognostic factor in other clinical settings. In the recently published study by Guo et al. (22), they have emphasized that LAR can be a useful prognostic factor for the short and long-term mortality in critically ill patients with heart failure. Kong et al. (21) found that increased LAR was significantly associated with poor neurologic outcomes in out-of-hospital cardiac arrest patients. Also, the prognostic performance of the LAR was found superior to a single measurement of lactate for predicting neurologic outcomes and survival.

Consistent with previous clinical studies, we found that increased LAR on the day of ICU admission was associated with increased mortality in critically ill COVID-19 patients. Moreover, we found a statistically significant positive correlation between LAR with ICU admission SOFA score

(r=0.335, p<0.001) and APACHE-II score (r=0.298, p<0.001). And, increased level of LAR on the day of ICU admission was associated with hemodynamic instability in critically ill COVID-19 patients. More importantly, with a cut-off value of 0.60, LAR on the day of ICU admission is a significant and independent prognostic factor for the 30-day mortality in critically ill COVID-19 patients (HR: 10.615; CI: 5.673-19.865, p<0.001).

Conclusion

In conclusion, with a cut-off value of 0.60, the LAR on the day of ICU admission is an independent and significant predictor for the 30-days mortality in critically ill COVID-19 patients. Moreover, the mortality prediction performance of the LAR is superior to either serum lactate level or serum albumin level alone. Therefore, LAR can be a useful and easily reachable prognostic factor for early risk stratification of critically ill COVID-19 patients, and can help to manage critically ill COVID-19 patients better.

Acknowledgment: Special thanks to all the physicians, nurses, and caregivers from Malatya Training and Research Hospital.

Ethics

Ethics Committee Approval: The study was approved by the Clinical Ethics Committee of Malatya İnönü University Faculty of Medicine (protocol no: 2020/154, date: 04.11.2020).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.G., U.S.K., F.Ö., S.B., Concept: U.S.K., L.A.D., Design: A.G., U.S.K., Data Collection and Process: A.G., U.S.K., L.A.D., F.Ö., S.B., Analysis or Interpretation: A.G., U.S.K., Literature Search: U.S.K., L.A.D., F.Ö., Writing: A.G., U.S.K., L.A.D., F.Ö., S.B.

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

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020;395:1054-62.
2. Skegg D, Gluckman P, Boulton G, Hackmann H, Karim SSA, Piot P, et al. Future scenarios for the COVID-19 pandemic. Lancet 2021;397:777-8.
3. Gao YD, Ding M, Dong X, Zhang JJ, Kursat Azkur A, Azkur D, et al. Risk factors for severe and critically ill COVID-19 patients: A review. Allergy 2021;76:428-55.
4. Ye L, Chen B, Wang Y, Yang Y, Zeng J, Deng G, et al. Prognostic value of liver biochemical parameters for COVID-19 mortality. Ann Hepatol 2021;21:100279.
5. Gharipour A, Razavi R, Gharipour M, Modarres R, Nezafati P, Mirkheshti N. The incidence and outcome of severe hyperlactatemia in critically ill patients. Intern Emerg Med 2021;16:115-23.
6. Haas SA, Lange T, Saugel B, Petzoldt M, Fuhrmann V, Metschke M, et al. Severe hyperlactatemia, lactate clearance and mortality in unselected critically ill patients. Intensive Care Med 2016;42:202-10.
7. Lee SG, Song J, Park DW, Moon S, Cho HJ, Kim JY, et al. Prognostic value of lactate levels and lactate clearance in sepsis and septic shock with initial hyperlactatemia: A retrospective cohort study according to the Sepsis-3 definitions. Medicine (Baltimore) 2021;100:e24835.
8. Velavan TP, Kieu Linh LT, Kreidenweiss A, Gabor J, Krishna S, Kremsner PG. Longitudinal Monitoring of Lactate in Hospitalized and Ambulatory COVID-19 Patients. Am J Trop Med Hyg 2021;104:1041-4.
9. Kendall H, Abreu E, Cheng AL. Serum Albumin Trend Is a Predictor of Mortality in ICU Patients With Sepsis. Biol Res Nurs 2019;21:237-44.
10. Gharipour A, Razavi R, Gharipour M, Mukasa D. Lactate/albumin ratio: An early prognostic marker in critically ill patients. Am J Emerg Med 2020;38:2088-95.
11. Kasapoglu US, Arinc S, Gungor S, Irmak I, Guney P, Aksoy F, et al. Prognostic factors affecting survival in non-small cell lung carcinoma patients with malignant pleural effusions. Clin Respir J 2016;10:791-9.
12. Akirov A, Masri-Iraqi H, Atamna A, Shimon I. Low Albumin Levels Are Associated with Mortality Risk in Hospitalized Patients. Am J Med 2017;130:1465 e11-e19.
13. Aziz M, Fatima R, Lee-Smith W, Assaly R. The association of low serum albumin level with severe COVID-19: a systematic review and meta-analysis. Crit Care 2020;24:255.
14. Alhazzani W, Moller MH, Arabi YM, Loeb M, Gong MN, Fan E, et al. Surviving Sepsis Campaign: guidelines on the management of critically ill adults with Coronavirus Disease 2019 (COVID-19). Intensive Care Med 2020;46:854-87.
15. Huang J, Cheng A, Kumar R, Fang Y, Chen G, Zhu Y, et al. Hypoalbuminemia predicts the outcome of COVID-19 independent of age and co-morbidity. J Med Virol 2020;92:2152-8.
16. Violi F, Cangemi R, Romiti GF, Ceccarelli G, Oliva A, Alessandri F, et al. Is Albumin Predictor of Mortality in COVID-19? Antioxid Redox Signal 20201;35:139-42.
17. Paliogiannis P, Mangoni AA, Cangemi M, Fois AG, Carru C, Zinellu A. Serum albumin concentrations are associated with disease severity and outcomes in coronavirus 19 disease (COVID-19): a systematic review and meta-analysis. Clin Exp Med 2021;21:343-54.
18. Lichtenauer M, Wernly B, Ohnewein B, Franz M, Kabisch B, Muessig J, et al. The Lactate/Albumin Ratio: A Valuable Tool for Risk Stratification in Septic Patients Admitted to ICU. Int J Mol Sci 2017;18.
19. Shin J, Hwang SY, Jo IJ, Kim WY, Ryoo SM, Kang GH, et al. Prognostic Value of The Lactate/Albumin Ratio for Predicting 28-Day Mortality in Critically ILL Sepsis Patients. Shock 2018;50:545-50.
20. Bou Chebl R, Jamali S, Sabra M, Safa R, Berbari I, Shami A, et al. Lactate/Albumin Ratio as a Predictor of In-Hospital Mortality in Septic Patients Presenting to the Emergency Department. Front Med (Lausanne) 2020;7:550182.
21. Kong T, Chung SP, Lee HS, Kim S, Lee J, Hwang SO, et al. The Prognostic Usefulness of the Lactate/Albumin Ratio for Predicting Clinical Outcomes in Out-of-Hospital Cardiac Arrest: a Prospective, Multicenter Observational Study (koCARC) Study. Shock 2020;53:442-51.
22. Guo W, Zhao L, Zhao H, Zeng F, Peng C, Guo W, et al. The value of lactate/albumin ratio for predicting the clinical outcomes of critically ill patients with heart failure. Ann Transl Med 2021;9:118.
23. Gallo Marin B, Aghagoli G, Lavine K, Yang L, Siff EJ, Chiang SS, et al. Predictors of COVID-19 severity: A literature review. Rev Med Virol 2021;31:1-10.
24. Ji P, Zhu J, Zhong Z, Li H, Pang J, Li B, et al. Association of elevated inflammatory markers and severe COVID-19: A meta-analysis. Medicine (Baltimore) 2020;99:e23315.
25. Ferrando-Vivas P, Doidge J, Thomas K, Gould DW, Mouncey P, Shankar-Hari M, et al. Prognostic Factors for 30-Day Mortality in Critically Ill Patients With Coronavirus Disease 2019: An Observational Cohort Study. Crit Care Med 2021;49:102-11.
26. Gavin W, Campbell E, Zaidi SA, Gavin N, Dbeibo L, Beeler C, et al. Clinical characteristics, outcomes and prognosticators in adult patients hospitalized with COVID-19. Am J Infect Control 2021;49:158-65.
27. Hu J, Wang Y. The Clinical Characteristics and Risk Factors of Severe COVID-19. Gerontology 2021:1-12.
28. Peiro OM, Carrasquer A, Sanchez-Gimenez R, Lal-Trehan N, Del-Moral-Ronda V, Bonet G, et al. Biomarkers and short-term prognosis in COVID-19. Biomarkers 2021;26:119-26.
29. Huang W, Li C, Wang Z, Wang H, Zhou N, Jiang J, et al. Decreased serum albumin level indicates poor prognosis of COVID-19 patients: hepatic injury analysis from 2,623 hospitalized cases. Sci China Life Sci 2020;63:1678-87.
30. Bassoli C, Oreni L, Ballone E, Foschi A, Perotti A, Mainini A, et al. Role of serum albumin and proteinuria in patients with SARS-CoV-2 pneumonia. Int J Clin Pract 2021;75:e13946.
31. Wang Z, Wang Z. Identification of risk factors for in-hospital death of COVID - 19 pneumonia -- lessions from the early outbreak. BMC Infect Dis 2021;21:113.
32. Vassiliou AG, Jahaj E, Ilias I, Markaki V, Malachias S, Vrettou C, et al. Lactate Kinetics Reflect Organ Dysfunction and Are Associated with Adverse Outcomes in Intensive Care Unit Patients with COVID-19 Pneumonia: Preliminary Results from a GREEK Single-Centre Study. Metabolites 2020;10.
33. Wang B, Chen G, Cao Y, Xue J, Li J, Wu Y. Correlation of lactate/albumin ratio level to organ failure and mortality in severe sepsis and septic shock. J Crit Care 2015;30:271-5.

Turk J Intensive Care 2021;19(Suppl 1):73-80
DOI: 10.4274/tybd.galenos.2021.20982

ORIGINAL RESEARCH / *ÖZGÜN ARAŞTIRMA*

Gülçin Hilal Alay,
Perihan Ergin Özcan,
Özlem Polat,
İlkay Anaklı,
Günseli Orhun,
Verda Tuna,
Emre Çeliksoy,
Mehmet Kılıç,
Mutlu Mercan,
Figen Esen

COVID-19 ARDS Patients Successfully Extubated to Extubated to High-Flow Nasal Cannula Oxygen Therapy: A Retrospective Analysis

Yüksek Akışlı Nazal Kanül Oksijen Tedavisine Başarıyla Ekstübe Edilen COVID-19 ARDS Hastalarının Retrospektif Analizi

Received/Geliş Tarihi : 11.07.2021
Accepted/Kabul Tarihi : 04.10.2021

Gülçin Hilal Alay, Perihan Ergin Özcan, Özlem Polat, İlkay Anaklı, Günseli Orhun, Verda Tuna, Emre Çeliksoy, Mehmet Kılıç, Mutlu Mercan, Figen Esen
İstanbul University İstanbul Faculty of Medicine, Department of Anesthesiology and Reanimation, İstanbul, Turkey

Gülçin Hilal Alay MD, (✉),
İstanbul University İstanbul Faculty of Medicine, Department of Anesthesiology and Reanimation, İstanbul, Turkey

E-mail : gulcinhilalalay@gmail.com
Phone : +90 530 067 72 62
ORCID ID : orcid.org/0000-0001-9259-9249

ABSTRACT *Objective:* The acute respiratory distress syndrome (ARDS)-associated coronavirus disease-2019 (COVID-19), caused by the highly contagious severe acute respiratory syndrome coronavirus 2 novel coronavirus, is a major cause of death during the pandemic period. Here, we aim to present a retrospective data analysis of the success of extubation to high-flow nasal oxygen (HFNO) among COVID-19 ARDS patients.

Materials and Methods: The data of 22 COVID-19 ARDS patients who were laboratory confirmed and extubated on HFNO while under intubation in the intensive care unit (ICU) were analyzed. Respiratory variables and demographic characteristics were collected at admission. During the intubation period, mechanical ventilation volumes and pressures and blood gas measurements were recorded. HFNO flow rate, FiO_2, and oxygenation variables were collected for 5 days after extubation. After the planned extubation, the 5-day reintubation rate, length of stay in the ICU, and mortality were recorded.

Results: Sixteen of 22 patients were male (72.7%). The mean age was 69.9±13.2 years and the highest comorbidity was hypertension (59.1%). The time between symptom onset and admission to the ICU was 6.5±7.9 days. Almost all patients were intubated on the same day. Twenty patients were successfully extubated to HFNO. Two patients experienced reintubation. The mean duration of HFNO treatment and length of stay in the ICU were 17.4±6 and 4.8±3.6 days, respectively. The ICU mortality rate of these complete data was 13.6% (3/22).

Conclusion: In high-risk COVID-19 ARDS patients undergoing extubation, HFNO therapy should be considered to prevent respiratory failure after reintubation and post-extubation.

Keywords: Acute respiratory distress syndrome, COVID-19, extubation, high-flow nasal cannula oxygen therapy, weaning

ÖZ *Amaç:* Son derece bulaşıcı şiddetli akut solunum sendromu koronavirüs 2 yeni koronavirüsünün neden olduğu akut respiratuvar distres sendromu (ARDS) ile ilişkili koronavirüs hastalığı-2019 (COVID-19), pandemi döneminde önemli bir ölüm nedenidir. Burada COVID-19 ARDS hastalarında yüksek akımlı nazal oksijen (HFNO) tedavisine ekstübasyon başarısının retrospektif veri analizini sunmayı amaçlıyoruz.

Gereç ve Yöntem: Yoğun bakım ünitesinde (YBÜ) HFNO tedavisine ekstübe edilen, laboratuvarca doğrulanmış 22 COVID-19 ARDS hastasının verileri analiz edildi. Solunumla ilgili değişkenler ve demografik özellikler başvuru sırasında toplandı. Entübasyon süresince mekanik ventilasyon hacimleri ve basınçları ile kan gazı ölçümleri kaydedildi. HFNO akış hızı, FiO_2 ve oksijenasyon değişkenleri ekstübasyondan sonra 5 gün boyunca toplandı. Planlanan ekstübasyonu takip eden 5 gün içinde yeniden entübasyon oranı, YBÜ'de kalış süresi ve mortalite kaydedildi.

Bulgular: Yirmi iki hastanın 16'sı erkekti (%72,7) ve yaş ortalaması 69,9±13,2 yıl olup, en yüksek komorbidite hipertansiyon (%59,1) idi. Semptom başlangıcı ile YBÜ'ye kabul arasındaki süre 6,5±7,9 gündü ve hemen hemen tüm hastalar aynı gün entübe edildi. Yirmi hasta HFNO'ya başarıyla ekstübe edildi ve 2 hasta yeniden entübe edildi. Ortalama yüksek akımlı nazal oksijen tedavisi süresi 4,8±3,6 gün ve yoğun bakımda kalış süresi 17,4±6 gündü. YBÜ mortalite oranı %13,6 (3/22) idi.

Sonuç: Ekstübasyon uygulanan yüksek riskli ARDS COVID-19 hastalarında yeniden entübasyon ve ekstübasyon sonrası solunum yetersizliğini önlemek için HFNO tedavisi düşünülmelidir.

Anahtar Kelimeler: Akut solunum sıkıntısı sendromu, COVID-19, ekstübasyon, yüksek akımlı nazal kanül oksijen tedavisi, weaning

Introduction

High-flow nasal oxygen therapy (HFNO) is one of the newer oxygenation methods commonly used in critical care during acute hypoxemic respiratory failure that can deliver heated and humidified gas up to 100% oxygen at a maximum flow of 60 L min^{-1} nasally. It has also been reported that HFNO can generate flow-dependent, low-level positive airway pressure, reduce airway resistance, and washout nasopharyngeal dead space (1).

Performing HFNO to coronavirus disease-2019 (COVID-19) patients with acute respiratory failure as initial support reduced the intubation rate when compared to non-invasive ventilation (NIV) (2). HFNO has been shown to be superior to conventional oxygen therapy (COT) in reducing extubation failure and reintubation rates when used after extubation, as well as reducing treatment failure when used as a primary support strategy (2). Also, in recently published reviews, it was reported that HFNO treatment has similar reintubation and treatment failure rates when compared to NIV (3,4).

However, there is an important concern that the high gas flow used might cause aerosol dispersion leading to the transmission of the virus into the environment. It was demonstrated that HFNO has a similar risk with standard oxygen masks in terms of the generation and dispersion of bio-aerosols (5). The number of studies regarding the comparison of HFNO and NIV in terms of bioaerosol dispersion are limited. The viral dispersion from different respiratory support devices was quantitatively evaluated with a simulated mannequin model in a negative pressure intensive care unit (ICU) room by Avari et al. (6) and they reported that the HFNO has higher bacteriophage concentrations than invasive mechanical ventilation and non-invasive helmet ventilation with a positive end-expiratory pressure (PEEP). However, investigators reported that surgical masks could reduce dispersion distance and viral load in patients under HFNO treatment (7,8).

Thinking about the advantages of HFNO in reducing the risk of intubation and the need for mechanical ventilation, it is not wise to discard this technique for the support of acute respiratory distress syndrome (ARDS) patients with COVID-19. The aim of this study is to evaluate extubation success to HFNO by reporting the outcome data of COVID-19 ARDS patients.

Materials and Methods

After ethics approval was obtained from the İstanbul Faculty of Medicine Clinical Research Ethics Committee (decision no: 12, date: 29.05.2020), this retrospective study was conducted at a university hospital's ICU. Twenty-two ARDS patients whose COVID-19 infection was confirmed with real-time polymerase chain reaction (PCR) test, (18 years of age or older), and who were extubated to HFNO while under mechanical ventilation support between 18 March 2020 and 30 May 2020 in the hospital's four ICUs were included. The exclusion criteria were as follows: 1) The patients who died under invasive mechanical ventilation before the extubation attempt, 2) who did not need any invasive mechanical ventilation support, 3) pregnant patients. The written informed consent from individual patients was not obtained due to collection of the patients data retrospectively. COVID-19 disease was defined as a positive result of reverse transcriptase-PCR testing of a nasopharyngeal swab collected by the local hospital health authority. Under the guidance of the World Health Organization (WHO), a diagnosis of severe acute respiratory syndrome coronavirus 2 pneumonia was made and patients who needed respiratory support with a standard oxygen mask or whose oxygen saturation was below 90% were taken to the ICU. ARDS is defined according to the Berlin definition (9). Data were collected from available electronic medical records and patient files by officers in charge of the university hospital's intensive care department research facilities.

Demographic and clinical data, including age, gender, admission disease severity scores [Sequential Organ Failure Assessment (SOFA) score and Acute Physiology and Chronic Health Assessment-II (APACHE-II)], underlying comorbidities (hypertension, chronic heart disease, chronic lung disease, diabetes mellitus, chronic renal failure, chronic liver disease, malignancies, cerebrovascular disease, autoimmune disease and immunosuppressive state), the time between symptom onset and admission to the ICU, and intubation time were recorded.

Arterial oxygen partial pressure/fractional inspired oxygen (PaO_2/FiO_2) ratio before intubation, days in mechanical ventilation were recorded. Blood gas analysis and respiratory parameters including inspiratory support pressure, PEEP, respiratory frequency, tidal volume (Vt), and frequency, as well as PaO_2/FiO_2 ratio right before extubation, were added to the data chart. Mechanical ventilation volumes, pressures,

and blood gas analysis results were recorded during the intubation period.

The weaning of the patients was performed according to daily screening for the respiratory and clinical criteria. Patients were extubated when they fulfill the criteria of extubation. The extubation criteria include 1) low PEEP level (5-8 cm H_2O), 2) without electrolyte disturbance, 3) hemodynamic stability, 4) interrupted sedation and followed up in spontaneous breathing in pressure support mode, 5) good state of consciousness, 6) received sufficient Vt (at least 5 mL kg^{-1}), 7) sufficient cough reflex which was evaluated with sputum amount, character and viscosity, 8) aspiration frequency of more than 2 hours, 9) achieved pain control, 10) breath rate less than 30/min, 11) oxygen saturation (SpO_2) > 90%, 12) PaO_2 > 60 mmHg,13) rapid shallow breathing index <105. The patients were directly switched to HFNO treatment from invasive mechanical ventilation according to the abovementioned criteria without trial of COT. Patients were continuously treated with HFNO alone with a flow and FiO_2 adjusted to achieve adequate oxygenation of at least 92% of SpO_2 as measured by pulse oximetry. The temperature of the heated humidifier was set to 37 °C to ensure adequate humidification. When the following respiratory failure criteria were disappeared during HFNO treatment (respiratory rate >35 $minute^{-1}$ more than five minutes, hypoxemia that SpO_2 <90%, tachycardia that heart rate (HR) >140 $minute^{-1}$ or 20% increase, bradycardia that 20% reduction in HR, hypertension that systolic blood pressure >180 mmHg, hypotension that systolic blood pressure <90 mmHg, acidosis that pH <7.32 and >10 mmHg increase in arterial carbon dioxide partial pressure ($PaCO_2$), consciousness changes that agitation, sweating or anxiety symptoms, cyanosis, findings of increased breathing effort that accessory muscle use, stress symptoms on the face, increased breathlessness), oxygen support was switched to standard oxygen therapy from HFNO.

Oxygenation variables [PaO_2, $PaCO_2$, arterial oxygen saturation (SaO_2)], the flow rate of HFNO, and FiO_2 were recorded daily for 5 days after extubation. Reintubation rate, length of stay in the ICU, and mortality within 48 hours and during 5 days following extubation were also recorded. Data collection was stopped in those patients who were either switch to COT or invasive mechanical ventilation.

Statistical Analysis

The SPSS (IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.) program was used for statistical data analysis. Categorical variables were presented with percentages and numbers. One sample Kolmogorov-Smirnov test was performed to evaluate whether the continuous variables have a normal distribution. The continuous variables' mean, standard deviation, minimum and maximum values were also presented. Spearman correlation analysis was performed to evaluate the relationship between clinical features, pre-extubation mechanic ventilation volumes, pressures, and blood gas parameters. The p-value <0.05 was considered statistically significant.

Results

The patients' clinical and demographic data were presented in Table 1. The mean age was 69.9±13.2 years, and 72.7% (16/22) of patients were male. The patients' mean APACHE-II score was 19.5±6.8 and the median SOFA score at the day of ICU admission was 5.4±2.6.

The leading comorbidities among our patients were chronic cardiac failure, hypertension, and diabetes and their frequencies were 36.4% (8/22), 59.1% (13/22), and 50% (11/22), respectively. The duration between symptom initiation and ICU admission was 6.5±7.9 days, and the duration between symptom initiation and intubation was 6.8±8.1 days. Seventy-two percent of patients (16/22) were intubated on the day of ICU admission. The mean duration between mechanical ventilation and extubation to HFNO was 9±5.3 days. Twenty patients were extubated successfully to HFNO, only a patient was reintubated within two days and the other one patient was reintubated within the following three days. Three out of 22 patients died (13.6%).

Table 2 shows mean records of blood gasses and respiratory parameters right before extubation. The slight increase in HCO_3 (30.3±5.1 mmol L^{-1}) and base excess (6.3±5.3 mmol L^{-1}) levels were observed with a mean respiratory rate of 17.3±3.9 $minute^{-1}$. Mean PEEP was 7.1±1.0 cmH_2O and improvement in the PaO_2/FiO_2 ratio (247.6±73.1) was evident compared with the initial values. The mean HFNO treatment after extubation and the length of ICU stay was 4.8±3.6 days and 17.4±6 days, respectively.

Patients' blood gas parameters, HFNO flow, and FiO_2 following 5 days of extubation were depicted in Table 3. On the fifth day following extubation the mean PaO_2/FiO_2 ratio was 180.3±46.1 with a mean FiO_2 and flow rate of 0.46±0.07 and 42.2±8.7% L $minute^{-1}$, respectively. The correlation analysis between the duration of HFNO treatment, clinical

features, pre-extubation ventilator parameters, and blood gas parameters was presented in Table 4. There was a significant correlation with pH level before extubation and HFNO treatment duration (r=0.438; p=0.041). Although it was not statistically significant, higher pressure support levels before extubation were associated with longer HFNO duration. (r=-0.409; p=0.059).

Table 1. Demographic characteristics and clinical features of study population

	Mean ± SD/n	min-max/%
Age (years)	69.9±13.2	46-89
BMI (kg m^{-2})	27.8±3	23-36
Gender (n/%)		
Male	16	72.7%
Female	6	27.3%
Chronic disease (n/%)		
Cardiac disease	8	36.4%
Hypertension	13	59.1%
Diabetes mellitus	11	50%
Pulmonary disease	5	22.7%
Cerebrovascular disease	2	9.1%
Malignancy	1	4.5%
Renal disease	1	4.5%
Liver disease	1	4.5%
Symptom initiation to ICU admission (days)	6.5±7.9	1-36
Symptom initiation to intubation (days)	6.8±8.1	1-37
APACHE-II score at ICU admission	19.5±6.8	8-34
SOFA score at ICU admission	5.4±2.6	3-13
Maximum SOFA score	7,8±2.3	4-15
PaO_2/FiO_2 before intubation	111.4±31.9	65-185
Duration of mechanical ventilation (days)	9±5.3	2-21
ICU hospitalization (days)	17.4±6	6-28
HFNO treatment (days)	4.8±3.6	1-15
Successful weaning (n/%)	20	90%
Reintubation in 48 h (n/%)	1	4.5%
Reintubation in 5 days (n/%)	1	4.5%
Death (n/%)	3	13.6%

BMI: Body mass index, ICU: intensive care unit, APACHE-II: Acute Physiology and Chronic Health Evaluation-II, SOFA: Sequential Organ Failure Assessment, HFNO: high-flow nasal oxygen, PaO_2/FiO_2: arterial oxygen partial pressure/fractional inspired oxygen, SD: standard deviation

Discussion

The primary finding of this retrospective study is that high-risk ARDS COVID-19 patients can be successfully extubated to HFNO. Among the non-invasive modalities, high flow oxygen therapy offers many physiological benefits which include decreased anatomical dead space, improved oxygenation, decreased production of carbon dioxide, decreased metabolic demand of breathing (10). Most importantly this technique serves up to superior comfort and improved work of breathing (10). In a small group of patients, delivery of humidified and heated oxygen with high-flow nasal cannula has been shown to be superior to high-flow oxygen via a non-rebreathing mask. Inspiratory effort and respiratory frequency were reduced with HFNO compared with the non-rebreathing mask. HFNO therapy reduces work of breathing and neuroventilatory drive after extubation in patients with chronic obstructive pulmonary disease (11). We did not measure electrical diaphragmatic activity, but we think that HFNO treatment reduces the possibility of reintubation due to high ventilatory impulse and respiratory work in patients with extubated COVID-19 ARDS.

Many other studies showed that performing HFNO as an initial oxygen support system was superior to COT in reducing extubation failure rates (12). Several studies reported that, although HFNO reduced the intubation rates when used as

Table 2. Respiratory parameters and blood gas analysis values before extubation

	Mean ± SD
pH	7.45±0.04
PO_2 (mmHg)	93.2±23.7
PCO_2 (mmHg)	43.2±7.1
HCO_3 (mmol L-1)	30.3±5.1
Base excess	6.3±5.3
SaO_2 (%)	96.7±1.7
Respiratory rate (breathe $minute^{-1}$)	17.3±3.9 (median: 15.5)
Tidal volume (mL)	583.1±150.8
RR/Vt	31.1±11.2
PEEP (cm H_2O)	7.1±1.0
Inspiration support (cm H_2O)	11.7±3.3
FiO_2	0.38±0.04
PaO_2/FiO_2	247.6±73.1

PaO_2/FiO_2: Arterial oxygen partial pressure/fractional inspired oxygen, RR: respiratory rate, Vt: tidal volume, SaO_2: arterial oxygen saturation, PEEP: positive end-expiratory pressure, SD: standard deviation

initial oxygen support, showed no superiority when used after extubation in comparison to NIV. Post-extubation respiratory failure and reintubation rates were compared between HFNO and NIV in a group of high-risk patients. In this multicentric randomized clinical trial, HFNO offered many clinical advantages and proved that it is not inferior to NIV in preventing respiratory failure after reintubation and extubation. A higher reintubation rate was reported (19%) with NIV most probably due to switching to COT after 24 hours (13,14). Other data suggest that more prolonged HFNO may improve outcomes in critically ill patients after extubation (15). Maggiore et al. (16) randomized critically ill patients of the general population either receiving HFNO or COT and observed that the HFNO group has more improvement in oxygenation and lower reintubation rate (3.8%) than COT. Thille et al. (17) reported that the reintubation rate was 18.2% within 48 hours of HFNO treatment with high-risk extubation failure patients. The reintubation rate was 10% (2/20) in our retrospective data which was similar to previous trials. We continued HFNO treatment for at least 48 hours after planned extubation. Considering the high risk of COVID-19 ARDS patients for extubation failure, HFNO can be used in COVID-19 ARDS patients after extubation. The benefits provided in this regard; contributing to patient comfort with heating and humidification, maintaining normal physiology, improving the increased ventilatory drive, and being a more sustainable treatment compared to NIV.

Several reports discussed if endotracheal intubation could be prevented by HFNO treatment in COVID-19 patients who presented with moderate ARDS. Twelve randomized controlled trials provided low-certainty evidence that HFNO may reduce invasive ventilation in patients without COVID-19 patients (2). The results did not provide support for differences in mortality or length of stay in ICU. HFNO appears to have been rarely used during the COVID-19 pandemic in the western countries. This is most probably due to the fear of risk of aerosolization and viral dispersion which might lead to infection transmission. However, the WHO and other scientific communities rank HFNO among possible options for ventilator support (18). Three studies evaluating aerosol generations and dispersion and four studies evaluating droplet dispersion provided very low certainty evidence. A crossover study and two simulation studies showed confusing results about the effect of HFNO on droplet dispersion. Two of these simulation studies reported no increase in aerosol dispersion with HFNO, but one reported that higher flow rates were associated with increased regions of aerosol density (19-27). However, *in vitro* and clinical studies have shown that placing a simple surgical mask on patients significantly reduces dispersion

Table 3. The gas flow, FiO_2, and blood gas value results of five days follow-up of patients under HFNO treatment after extubation

	1st day Mean ± SD (min-max) (n=22)	2nd day Mean ± SD (min-max) (n=20)	3rd day Mean ± SD (min-max) (n=16)	4th day Mean ± SD (min-max) (n=11)	5th day Mean ± SD (min-max) (n=9)
pH	7.44±0.7 7.27-7.55	7.44±0.5 (7.29-7.55)	7.44±0.7 (7.21-7.53)	7.46±0.05 (7.32-7.55)	7.42±0.08 (7.30-7.54)
PaO_2 (mmHg)	102.1±27.2 58-146	90.2±27.9 (61-146)	78.8±13.3 (62-109)	83.9±12.2 (65-101)	80.8±15.7 (60-108)
$PaCO_2$ (mmHg)	41.7±7.8 32-64	42.4±9.8 25-66	40.5±7.7 (31-58)	40±5.5 (34-53)	38.4±4.2 (33-45)
SaO_2 (%)	96.6±2.1 91.3-99.6	96.1±2.7 90-99	96±1.9 (92-98)	96.3±2 (93-99)	94.8±2.5 (90-97)
PaO_2/FiO_2	190.5±61.5 96-335	189.2±64 82-315	171.4±48.8 (121-311)	171.3±51.8 (67-254)	180.3±46.1 (125-270)
HFNO flow (L minute-1)	51.3±4.9 40-60	46.7±8.3 20-60	45.9±4.1 (40-50)	43.6±5 (35-50)	42.2±8.7 (30-60)
FiO_2	0.5±0.1 0.4-1	0.4±0.1 (0.3-0.8)	0.4±0.1 (0.3-0.7)	0.49±0.08 (0.3-0.6)	0.46±0.07 (0.3-0.6)

PaO_2: Arterial oxygen partial pressure, $PaCO_2$: arterial carbon dioxide partial pressure, FiO_2: fractional inspired oxygen, SaO_2: arterial oxygen saturation, HFNO: high-flow nasal oxygen, SD: standard deviation, min: minimum, max: maximum

Table 4. Correlation between clinical features and pre-extubation respiratory parameters				
	HFNO duration after extubation (days)		ICU hospitalization (days)	
	r	p	r	p
Age (years)	-0.214	0.339	0.006	0.980
BMI (kg m^{-2})	-0.199	0.381	-0.140	0.536
Duration between semptom initiation and ICU admission (days)	-0.149	0.509	0.384	0.077
Duration between semptom initiation and intubation (days)	-0.158	0.483	0.374	0.086
APACHE-II score at ICU admission	0.117	0.603	0.381	0.080
SOFA score at ICU admission	0.384	0.078	0.186	0.408
Maximum SOFA score	0.352	0.109	0.346	0.114
PaO_2/FiO_2 before intubation	0.312	0.157	0.169	0.452
Duration of mechanic ventilation (days)	-0.334	0.129	0.476	0.025*
pH before extubation	0.438	0.041*	0.119	0.597
PO_2 before extubation (mmHg)	-0.254	0.253	-0.054	0.813
PCO_2 before extubation (mmHg)	-0.055	0.808	0.007	0.975
HCO_3 before extubation (mmol L^{-1})	0.109	0.628	0.138	0.541
Bas excess before extubation	0.137	0.542	0.117	0.605
SaO_2 before extubation (%)	-0.140	0.533	0.037	0.871
Respiratory rate before extubation	-0.069	0.762	0.196	0.382
Tidal volume before extubation (mL)	-0.017	0.941	-0.186	0.408
RR/Vt before extubation	-0.076	0.736	0.198	0.378
PEEP before extubation	0.094	0.678	-0.481	0.023*
Inspiration support before extubation	-0.409	0.059	0.284	0.200
FiO_2 before extubation	0.044	0.846	-0.434	0.043*
PaO_2/FiO_2 before extubation	-0.211	0.345	0.188	0.401

BMI: Body mass index, ICU: intensive care unit, APACHE-II: Acute Physiology And Chronic Health Evaluation-II, SOFA: Sequential Organ Failure Assessment, HFNO: high-flow nasal oxygen, PaO_2: arterial oxygen partial pressure, FiO_2: fractional inspired oxygen, RR: respiratory rate, Vt: tidal volume, SaO_2: arterial oxygen saturation, PEEP: positive end-expiratory pressure, *Statistically significant

distance (7). Smoke simulation studies also demonstrated that dispersion with 60 L $minute^{-1}$ flow rate was similar to with a simple oxygen mask at 15 L $minute^{-1}$ flow rate (19,28). We followed the same rule that all patients wore a facial mask during HFNO treatment and the mean flow rates were lower than 50 L $minute^{-1}$ in 5 days' follow-up after extubation which we believed that sustained minimum dispersion.

The first limitation of this study is its retrospective nature. Second, we did not have a control group so that we were not able to compare the data with other oxygen support systems. We haven't used any fixed protocol in terms of time period after extubation. However, patients were switched to a standard oxygen mask when they fulfill the necessary clinical and respiratory criteria. Third, the number of patients might not be enough to come to any strong conclusion however we think that the rate of extubation success in our data of high risk of COVID-19 patients worth considering.

Conclusion

In extubated high-risk COVID-19-associated ARDS patients, HFNO therapy should be considered to prevent respiratory failure after post-extubation and reintubation.

Ethics

Ethics Committee Approval: After ethics approval was obtained from the İstanbul Faculty of Medicine Clinical Research Ethics Committee (decision no: 12, date: 29.05.2020).

Informed Consent: The written informed consent from individual patients was not obtained due to collection of the patients data retrospectively.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: Ö.P., F.E., Design: P.E.Ö., Data Collection and Process: Ö.P., İ.A., G.O., V.T., E.Ç., M.K., M.M., Analysis or Interpretation: P.E.Ö., F.E., Literature Search: G.H.A., Writing: G.H.A.

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

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Dysart K, Miller TL, Wolfson MR, Shaffer TH. Research in high flow therapy: mechanisms of action. Respir Med 2009;103:1400-5.
2. Agarwal A, Basmaji J, Muttalib F, Granton D, Chaudhuri D, Chetan D, et al. High-flow nasal cannula for acute hypoxemic respiratory failure in patients with COVID-19: systematic reviews of effectiveness and its risks of aerosolization, dispersion, and infection transmission. Can J Anaesth 2020;67:1217-48.
3. Guo K, Liu G, Wang W, Guo G, Liu Q. Effects of high-flow nasal oxygen cannula versus other noninvasive ventilation in extubated patients: a systematic review and meta-analysis of randomized controlled trials. Expert Rev Respir Med 2021:1-11.
4. Liang S, Liu Z, Qin Y, Wu Y. The effect of high flow nasal oxygen therapy in intensive care units: a systematic review and meta-analysis. Expert Rev Respir Med 2021;15:1335-45.
5. Li J, Fink JB, Ehrmann S. High-flow nasal cannula for COVID-19 patients: low risk of bio-aerosol dispersion. Eur Respir J 2020;55:2000892.
6. Avari H, Hiebert RJ, Ryzynski AA, Levy A, Nardi J, Kanji-Jaffer H, et al. Quantitative Assessment of Viral Dispersion Associated with Respiratory Support Devices in a Simulated Critical Care Environment. Am J Respir Crit Care Med 2021;203:1112-8.
7. Hui DS, Chow BK, Chu L, Ng SS, Lee N, Gin T, et al. Exhaled air dispersion during coughing with and without wearing a surgical or N95 mask. PLoS One 2012;7:e50845.
8. Johnson DF, Druce JD, Birch C, Grayson ML. A quantitative assessment of the efficacy of surgical and N95 masks to filter influenza virus in patients with acute influenza infection. Clin Infect Dis 2009;49:275-7.
9. ARDS Definition Task Force, Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, et al. Acute respiratory distress syndrome: the Berlin Definition. JAMA 2012;307:2526-33.
10. Mauri T, Turrini C, Eronia N, Grasselli G, Volta CA, Bellani G, et al. Physiologic Effects of High-Flow Nasal Cannula in Acute Hypoxemic Respiratory Failure. Am J Respir Crit Care Med 2017;195:1207-15.
11. Di Mussi R, Spadaro S, Stripoli T, Volta CA, Trerotoli P, Pierucci P, et al. High-flow nasal cannula oxygen therapy decreases postextubation neuroventilatory drive and work of breathing in patients with chronic obstructive pulmonary disease. Crit Care 2018;22:180.
12. Xu Z, Li Y, Zhou J, Li X, Huang Y, Liu X, et al. High-flow nasal cannula in adults with acute respiratory failure and after extubation: a systematic review and meta-analysis. Respir Res 2018;19:202.
13. Nava S, Gregoretti C, Fanfulla F, Squadrone E, Grassi M, Carlucci A, et al. Noninvasive ventilation to prevent respiratory failure after extubation in high-risk patients. Crit Care Med 2005;33:2465-70.
14. Hernández G, Vaquero C, Colinas L, Cuena R, González P, Canabal A, et al. Effect of Postextubation High-Flow Nasal Cannula vs Noninvasive Ventilation on Reintubation and Postextubation Respiratory Failure in High-Risk Patients: A Randomized Clinical Trial. JAMA 2016;316:1565-74.
15. Hernández G, Roca O, Colinas L. High-flow nasal cannula support therapy: new insights and improving performance. Crit Care 2017;21:62.
16. Maggiore SM, Idone FA, Vaschetto R, Festa R, Cataldo A, Antonicelli F, et al. Nasal high-flow versus Venturi mask oxygen therapy after extubation. Effects on oxygenation, comfort, and clinical outcome. Am J Respir Crit Care Med 2014;190:282-8.
17. Thille AW, Muller G, Gacouin A, Coudroy R, Decavèle M, Sonneville R, et al. Effect of Postextubation High-Flow Nasal Oxygen With Noninvasive Ventilation vs High-Flow Nasal Oxygen Alone on Reintubation Among Patients at High Risk of Extubation Failure: A Randomized Clinical Trial. JAMA 2019;322:1465-75.
18. World Health Organization. Rolling updates on coronavirus disease (COVID-19). Available from URL: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/events-as-they-happen (accessed May 2020).
19. Hui DS, Chow BK, Lo T, Tsang OTY, Ko FW, Ng SS, et al. Exhaled air dispersion during high-flow nasal cannula therapy versus CPAP via different masks. Eur Respir J 2019;53:1802339.
20. Loh NW, Tan Y, Taculod J, Gorospe B, Teope AS, Somani J, et al. The impact of high-flow nasal cannula (HFNC) on coughing distance: implications on its use during the novel coronavirus disease outbreak. Can J Anaesth 2020;67:893-4.
21. Kotoda M, Hishiyama S, Mitsui K, Tanikawa T, Morikawa S, Takamino A, et al. Assessment of the potential for pathogen dispersal during high-flow nasal therapy. J Hosp Infect 2020;104:534-7.
22. Leung CCH, Joynt GM, Gomersall CD, Wong WT, Lee A, Ling L, et al. Comparison of high-flow nasal cannula versus oxygen face mask for environmental bacterial contamination in critically ill pneumonia patients: a randomized controlled crossover trial. J Hosp Infect 2019;101:84-7.
23. Leonard S, Atwood CW Jr, Walsh BK, DeBellis RJ, Dungan GC, Strasser W, et al. Preliminary Findings on Control of Dispersion of Aerosols and Droplets During High-Velocity Nasal Insufflation Therapy Using a Simple Surgical Mask: Implications for the High-Flow Nasal Cannula. Chest 2020;158:1046-9.
24. Iwashyna TJ, Boehman A, Capelcelatro J, Cohn AM, Cooke JM, Costa DK, et al. Variation in aerosol production across oxygen delivery devices in

spontaneously breathing human subjects. medRxiv - 2020. doi: 10.1101/2020.04.15.20066688
25. Roberts S, Kabaliuk N, Spence C, O'Donnell JN. Nasal high flow therapy and dispersion of nasal aerosols in an experimental setting. J Crit Care 2015;30:842.
26. van Doremalen N, Bushmaker T, Morris DH, Holbrook MG, Gamble A, Williamson BN, et al. Aerosol and Surface Stability of SARS-CoV-2 as Compared with SARS-CoV-1. N Engl J Med 2020;382:1564-7.
27. Bischoff WE, Swett K, Leng I, Peters TR. Exposure to influenza virus aerosols during routine patient care. J Infect Dis 2013;207:1037-46.
28. Ip M, Tang JW, Hui DS, Wong AL, Chan MT, Joynt GM, et al. Airflow and droplet spreading around oxygen masks: a simulation model for infection control research. Am J Infect Control 2007;35:684-9.

Turk J Intensive Care 2021;19(Suppl 1):81-6
DOI: 10.4274/tybd.galenos.2021.44227

ORIGINAL RESEARCH / *ÖZGÜN ARAŞTIRMA*

Lerzan Doğan,
Nazire Afşar,
Dilaver Kaya,
Zeynep Tuğçe Sarıkaya,
Orkhan Mammadov,
Canan Akıncı,
Şahika Bolsoy Deveci,
Filiz Tüzüner,
Fatma Elif Gülek,
Simten Demirel Kaya,
Bülent Güçyetmez,
Alp Dinçer,
Sesin Kocagöz,
İbrahim Özkan Akıncı

Potential Prognostic Predictors for Coronavirus Disease-2019-related Impaired Consciousness in Patients with Critical Illnesses

Kritik Hastalarda Koronavirüs Hastalığı-2019 İlişkili Bilinç Bozukluğunun Potansiyel Prognostik Faktörlerinin Belirlenmesi

Received/Geliş Tarihi : 17.06.2021
Accepted/Kabul Tarihi : 27.10.2021

Lerzan Doğan, Orkhan Mammadov, Simten Demirel Kaya
Acıbadem Altunizade Hospital, Clinic of Intensive Care, İstanbul, Turkey

Nazire Afşar, Dilaver Kaya,
Acıbadem Mehmet Ali Aydınlar University Faculty of Medicine, Department of Neurology, İstanbul, Turkey

Zeynep Tuğçe Sarıkaya, Bülent Güçyetmez
Acıbadem Mehmet Ali Aydınlar University Faculty of Medicine, Department of Anesthesiology and Reanimation, İstanbul, Turkey

Canan Akıncı
Acıbadem Fulya Hospital, Clinic of Intensive Care, İstanbul, Turkey

Şahika Bolsoy Deveci
Acıbadem Maslak Hospital, Clinic of Intensive Care, İstanbul, Turkey

Filiz Tüzüner, Fatma Elif Gülek
Acıbadem Taksim Hospital, Clinic of Anesthesiology and Reanimation, İstanbul, Turkey

Fatma Elif Gülek
Acıbadem Kozyatağı Hospital, Clinic of Anesthesiology and Reanimation, İstanbul, Turkey

Alp Dinçer
Acıbadem Mehmet Ali Aydınlar University Faculty of Medicine, Department of Radiology, İstanbul, Turkey

Sesin Kocagöz
Acıbadem Mehmet Ali Aydınlar University Faculty of Medicine, Department of Infectious Disease and Clinical Microbiology, İstanbul, Turkey

İbrahim Özkan Akıncı
Acıbadem Healthcare Group, Intensive Care Coordinator, İstanbul Turkey

Lerzan Doğan MD, (✉),
Acıbadem Altunizade Hospital, Clinic of Intensive Care, İstanbul, Turkey

E-mail : lredzheb@gmail.com
Phone : +90 216 649 44 44
ORCID ID : orcid.org/0000-0002-1456-4072

ABSTRACT *Objective:* Central nervous system involvement in patients with coronavirus disease-2019 (COVID-19) is associated with increased morbidity and mortality. The assessment of neurological symptoms in patients with critical illnesses, who are mechanically ventilated under deep sedation is challenging, which means doctors could be unaware of such symptoms until patients reach the weaning stage. Thus, this study aimed to identify potential prognostic predictors for COVID-19-related impaired consciousness in patients with critical illnesses.
Materials and Methods: This retrospective, multicenter, and observational cohort study was conducted among patients with COVID-19 who were admitted to the intensive care units of five hospitals between March 11, 2020, and September 18, 2020. The patient population was analyzed in two groups-cases with impaired consciousness and cases without impaired consciousness.
Results: Patients with impaired consciousness were found to be significantly younger (p=0.001) and to exhibit significantly more laboratory abnormalities, such as high ferritin (p=0.003), C-reactive protein (p=0.001), procalcitonin (p=0.019), and D-dimer (p=0.001) levels. Additionally, pathological magnetic resonance imaging findings were detected in 14 of 29 (48%) patients with impaired consciousness.
Conclusion: All patients with severe COVID-19 should be screened for signs of hyperinflammation due to the associated risk of neurological complications. The early detection of at-risk cases and the prompt initiation of specific treatment should result in better disease outcomes.
Keywords: COVID-19, neurological complications, inflammatory markers, hyperinflammation

ÖZ *Amaç:* Koronavirüs hastalığı-2019'un (COVID-19) neden olduğu merkezi sinir sistemi tutulumu, artan morbidite ve mortalite ile ilişkili bulunmuştur. Derin sedatize ve mekanik ventilasyon desteği uygulanan yoğun bakım hastalarında nörolojik semptomları değerlendirmek ciddi bir zorluktur, bu nedenle ventilatörden ayırma aşamasına gelene kadar yoğun bakım hekimi bu semptomlardan habersiz kalabilmektedir. Çalışmanın amacı, kritik yoğun bakım hastalarında COVID-19 ilişkili bilinç bozukluğu için potansiyel prognostik prediktörlerin belirlenmesidir.
Gereç ve Yöntem: Çalışma retrospektif, çok merkezli ve gözlemsel olarak dizayn edilmiştir. Beş hastanenin yoğun bakım ünitelerine 11 Mart 2020 ve 18 Eylül 2020 tarihleri arasında kabul edilen COVID-19 hastaları dahil edilmiştir. Hastalar iki grupta değerlendirilmiştir: Bilinç bozukluğu olan ve bilinç bozukluğu olmayan hastalar.
Bulgular: Bilinç bozukluğu olan hastaların yaş ortalaması daha düşük (p=0,001) ve daha fazla laboratuvar anormalliğine sahip bulunmuştur; ferritin (p=0,003), C-reaktif protein seviyeleri (p=0,001), prokalsitonin (p=0,019) ve D-dimer (p=0,001). Ayrıca bilinç bozukluğu olan 29 hastanın 14'ünde (%48) patolojik manyetik rezonans görüntüleme bulguları tespit edildi.
Sonuç: Yoğun bakımda COVID-19 hastaları nörolojik komplikasyon riskini belirlemek için hiperenflamasyon belirtileri açısından taranmalıdır. Erken tanı ve spesifik tedavinin başlatılması ile daha iyi sonuçlar alınabilecektir.
Anahtar Kelimeler: COVID-19, nörolojik komplikasyon, enflamasyon markerları, hiperenflamasyon

Introduction

Central nervous system involvement in patients with coronavirus disease-2019 (COVID-19) is associated with increased morbidity and mortality (1), although the mechanisms underlying COVID-19-related neurological complications are not yet fully understood (2,3). The expectation that most of the world's population will have been infected with COVID-19 before herd immunity develops indicates that the overall number of patients with neurological complications due to the disease could ultimately be very high. In light of this, supporting the development and manufacture of vaccines should be considered a priority because any delay to the vaccine rollout will result in additional deaths (4). In addition, given the ongoing nature of the COVID-19 pandemic, clinicians require accurate data to devise effective medical treatments for the disease and its complications (5). The assessment of neurological symptoms in critically ill patients who are mechanically ventilated and under deep sedation is challenging, which means that doctors could be unaware of such symptoms until patients reach the weaning stage.

Based on the above, the present study sought to identify potential prognostic predictors for COVID-19-related impaired consciousness in critically ill patients.

Materials and Methods

This retrospective, multicenter, observational cohort study was conducted among COVID-19 patients admitted to the intensive care units (ICUs) of five hospitals between March 11, 2020, and September 18, 2020. The study was approved by both the Republic of Turkey Ministry of Health and the Ethics Committee of Acıbadem University (decision no: 2020-09/12, date: 21.05.2020). The inclusion criteria for the study were as follows: patients >18 years old, all invasively mechanically ventilated, with an ICU stay longer than four days. Moreover, the exclusion criteria were as follows: patients <18 years old, patients administered only non-invasive mechanical ventilation, and patients with an ICU stay of less than four days (Figure 1).

The patients' clinical course was reviewed and data were collected concerning their age, sex, comorbidities, neurological findings, laboratory findings [including cerebrospinal fluid (CSF) analysis and inflammatory markers], and neuroimaging findings [computed tomography or magnetic resonance imaging (MRI)].

At the five ICUs, which were controlled by the same main intensivist, all COVID-19 patients were routinely treated in accordance with the Surviving Sepsis Campaign's COVID-19 treatment guidelines (6). More specifically, lung-protective ventilation strategies were used to limit the driving pressure and restrict both the tidal volume and plateau pressure while providing relatively high positive end-expiratory pressure. In addition, when respiratory acidosis and hypoxia persisted, early prone positioning ventilation was applied.

All COVID-19 patients also received the same sedation strategy. Due to the likelihood of the disease-causing acute respiratory distress syndrome (ARDS), deep sedation was used to improve both patients' tolerance of mechanical ventilation and patient-ventilator synchrony. To achieve deep sedation, a combination of midazolam and fentanyl was used as part of a sedation protocol, started with lower doses and titrate utilizing the Richmond Agitation Sedation scale to target standardized goals. Midazolam was only applied during the first few days of high-pressure ventilator support, and it was discontinued as soon as possible. When oxygenation was normalized, the chest X-rays showed better aeration, and the infectious markers were almost normalized, ventilatory support was gradually withdrawn, it was ensured that there were no underlying metabolic disorders, and sedation was gradually reduced before being stopped. As deep sedation was applied, the patients waited 48 hours for residual sedation.

After 48 hours, if unresponsiveness to stimulation or refractory agitation were noted despite the treatment and no other explanation could be found, both situations were accepted as impaired consciousness. In those patients, neuroimaging, including diffusion-weighted and contrast-enhanced MRI series, was performed following neurology consultation. For patients with pathological MRI findings, such as cortical signal abnormalities compatible with meningoencephalitis, a lumbar puncture (LP) was performed where possible. The patient population was analyzed in two groups, namely cases with impaired consciousness and cases without impaired consciousness (Figure 1).

Statistical Analysis

All data were presented as the mean, standard deviation, median, and interquartile range according to the distribution of the values. A t-test and a One-Way ANOVA were used for both groups' analyses. A multivariate binary logistic regression model and the backward elimination method were used to determine the patients' neurological

symptoms. A p-value <0.05 was considered to be statistically significant. All of the statistical analyses in this study were performed using Statistical Package for the Social Sciences version 23.0 software for Windows (IBM Corp., Armonk, NY, USA).

Results

A total of 115 ICU patients were admitted to our 5 ICUs. Sixty seven of them were included in the study (Figure 1). Of these, 62 (92.5%) were discharged to a ward, 5 (7.5%) did not survive. All the patient demographic and clinical characteristics are shown in Table 1. Patients with impaired consciousness were found significantly younger (p=0.001) than patients without impaired consciousness, with a median age of 55 vs 77 years. The two groups of patients had the similar mortality rate (p=0.433) and ICU stay (p=0.100).

Pathological MRI findings were detected in 14 of 29 (48%) patients with impaired consciousness. In 11 of 29 patients (38%), MRI showed cortical signal abnormalities. Other MRI findings included one patient with acute cerebrovascular disease (2.7%), two patients with hypoxic-ischaemic brain injury (5.4%), and one patient with acute transverse sinus thrombosis (2.7%). CSF analysis showed normal glucose and high protein levels; the cell count, IgG index, and albumin were within normal limits, and reverse transcriptase-polymerase chain reaction (RT-PCR) was negative for common respiratory viruses and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Oligoclonal bands were negative in all cases. However, RT-PCR taken from respiratory samples was positive for SARS-CoV-2.

Patients with impaired consciousness had significantly more laboratory abnormalities than patients without impaired consciousness, such as high ferritin (p=0.003), C-reactive protein (CRP) levels (p=0.001), procalcitonin (p=0.019), and D-dimer (p=0.001) (Table 1). We carried out a multivariate logistic regression model for the likelihood of neurologic impairment. According to cut-off values, age, D-dimer, ferritin, CRP, procalcitonin, a dose of midazolam, durations of midazolam, and fentanyl administrations were added to the multivariate binary logistic regression model (Table 2). The Backward method was used in the regression model and it was not found a significant relationship between the likelihood of neurologic impairment and each of age, CRP, and fentanyl administrations (Table 3).

Even severity of disease scores in ICU admission and their ventilation parameters was found to be similar, patients with impaired consciousness required deeper sedation. Higher doses of sedatives were given to help attenuate agitation associated with mechanical ventilation (p=0.005).

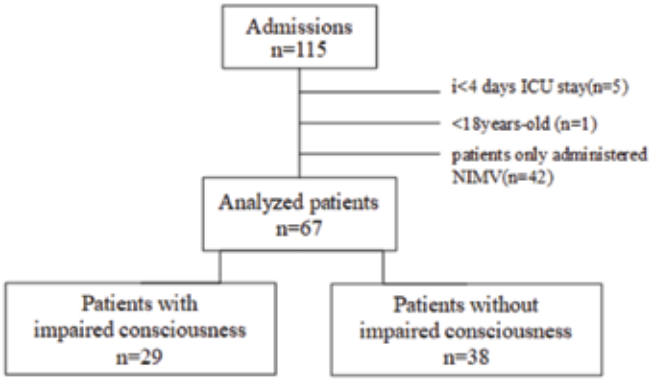


Figure 1. Flowchart of patient inclusion
ICU: Intensive care unit, NIMV: non-invasive mechanical ventilation

Discussion

It is challenging for intensivists to assess the neurological complications associated with COVID-19 in patients admitted to the ICU due to the requirement for deep sedation in cases of ARDS, which means that doctors could remain unaware of such neurological symptoms until patients reach the weaning stage. The present results indicated that the patients' age; their ferritin, D-dimer, CRP, and procalcitonin levels; and the requirement for deeper sedation might all be valuable prognostic indicators of impaired consciousness as a result of COVID-19.

Patients with suspected neurological complications must be aggressively investigated, as any delay in treatment could result in permanent neurological sequelae or even death. Although neuroimaging is not specifically designed for investigating cranial infections, it represents a useful way to document the extent of any neurological involvement, which is one of the key markers that determine prognosis (7). While neurological complications were identified at the weaning stage in the present study, this does not mean that MRI findings only come to prominence during the weaning period. Indeed, due to the use of deep sedation, it is possible that such complications were notified late. After the retrospectively obtained statistics had been analyzed, it was determined that the patients with neurological complications had required deeper sedation, which can be considered a predictor of neurological complications, especially when

accompanied by laboratory abnormalities. In some patients, individual responses to the disease may never be reflected in the MRI findings. In addition, if neurological involvement is suspected, so long as it is not contraindicated, the use of LP should always be considered. The present results concerning the patients' CSF point toward an autoimmune/antibody-mediated involvement hypothesis regarding both the meninges and the cerebral parenchyma, as mentioned in a previous report (3,8-12).

Table 1. Comparison between groups of patients with and without impaired consciousness

	Patients with impaired consciousness (n=29)	Patients without impaired consciousness (n=38)	p
Age, years	55 (46-67)	72 (60-82)	<0.001
Male, n (%)	23 (79.3)	28 (73.7)	0.593
APACHE-II	12 (9.5-16)	15 (11-20.5)	0.085
Bodyweight	85.83	84.18	0.532
Comorbidities			
Hypertension	15 (40.54%)	20 (25,64%)	0.501
Diabetes	10 (27%)	11 (14.10%)	
Chronic kidney	2 (5.4%)	5 (6.41%)	
Malignancy	3 (8.11%)	3 (3.85%)	
CVD	4 (10.81%)	9 (11.54%)	
Autoimmune disease	2 (5.40%)	0	
Ventilation			
FiO_2 (max)	70 (50-100)	77.5 (60-100)	0.543
PaO_2 (max)	96 (73-115)	95 (63-125)	0.904
PaO_2/FiO_2	137 (86-208)	138 (89-203)	0.889
Laboratory findings			
Lymphocyte count	0.50 (0.26-0.89)	0.56 (0.37-1.09)	0.299
C-reactive protein, (mg/dL)	29±15	18±10	<0.001
Procalcitonin, (ng/mL)	2.1 (1.1-4.8)	(0.3-2.5)	0.019
D-dimer, (mg/L)	5.8 (4.6-10)	3.4 (1.8-4.7)	<0.001
Ferritin, (ng/mL)	1,650 (1,102-2,802)	762 (304-1,504)	0.003
Lactate dehydrogenase, (U/L)	435 (337-611)	365 (244-451)	0.059
Creatinine, (mg/dL)	1.2 (0.9-2.6)	1.3 (0.9-3.1)	0.552
Blood urea, (mg/dL)	89 (56-160)	90 (49-219)	0.781
Administered sedation			
Duration of fentanyl administration, days	10 (8-12)	8 (7-12)	0.01
Duration of midazolam administration, days	9 (8-10)	6 (5-10)	0.007
Total dose of fentanyl, (mcg/kg)	191±65	170±55	0.153
Total dose of midazolam, (mg/kg)	13.7±2.8	11.3±4.7	0.012
Other characteristics, n (%)			
Persistent fever (>39 °C)	13 (44.8)	13 (34.2)	0.377
Vasoactive agent	12 (41.4)	12 (31.6)	0.407
Length of ICU stay, days	17 (13-21)	14 (11-18)	0.100
Mortality, n (%)	3 (10.3)	2 (5.3)	0.433

CVD: Cardiovascular disease, FiO_2: fraction of inspired oxygen, PaO_2: partial pressure of oxygen, ICU: intensive care unit, APACHE-II: Acute Physiology and Chronic Health Assessment-II, max: maximum

Table 2. Cut-off values for likelihood of neurologic impairment			
Variables	**Cut-off values**	**AUC (95% CI)**	**p**
Age	<66	0.81 (0.69-0.90)	<0.001
D-dimer, (ug/mL)	≥4.5	0.76 (0.63-0.89)	0.001
Ferritin, (ng/mL)	≥1,150	0.73 (0.59-0.86)	0.003
C-reactive protein, (mg/dL)	≥22.7	0.72 (0.59-0.85)	0.003
Dose of midazolam (mg/kg)	≥12.2	0.69 (0.57-0.82)	0.007
Duration of midazolam administration, (days)	≥7.5	0.69 (0.56-0.82)	0.007
Duration of fentanyl administration, (days)	≥8.5	0.68 (0.55-0.82)	0.010
Procalcitonin, (ng/mL)	≥1.62	0.67 (0.54-0.80)	0.019
AUC: Area of under curve, CI: confidence interval			

Table 3. Multivariate logistic regression model for likelihood of neurologic impairment		
Variables	**OR (95% CI)**	**p**
Ferritin ≥1,150 ng/mL	41.4 (3.0-563)	0.005
Duration of midazolam administration ≥7.5 days	37.1 (2.9-473)	0.005
Procalcitonin ≥1.62 ng/mL	13.4 (1.5-117)	0.020
D-dimer ≥4.5 ug/mL	10.2 (1.3-80)	0.028
CI: Confidence interval, OR: odds ratio. According to cut-off values, age, d-dimer, ferritin, C-reactive protein, procalcitonin, a dose of midazolam, durations of midazolam, and fentanyl administrations were added to the multivariate binary logistic regression model. The Backward method was used in the regression model and it was not found a significant relationship between the likelihood of neurologic impairment and each of age, C-reactive protein, durations of midazolam, and fentanyl administrations		

In this study, the fact that the patients with impaired consciousness were significantly younger (p=0.002) than the patients without impaired consciousness, as well as the fact that their inflammatory parameters were significantly higher, was not surprising because the decline of the immune system with age is typically reflected in a poorer response to infectious diseases (13). This could explain the uncontrolled inflammatory response seen in younger people in response to COVID-19. Yet, a younger age alone cannot always be associated with neurological complications. In fact, the immune system dysfunction seems to be somehow aggravated, possibly due to genetic factors yet to be described.

It must be acknowledged that this study had a number of limitations. First, the study had a retrospective and multicenter design, which meant that subclinical cases were not examined further. Second, the study included only a limited number of ICU patients and a limited number of patients who underwent cranial MRI and LP.

Conclusion

The use of sedative agents may not always be responsible for patients' delayed recovery from deep sedation. When other causes have been excluded, the possibility of neurological complications should be strongly considered. Moreover, all patients with severe COVID-19 should be screened for signs of hyperinflammation due to the associated risk of neurological complications. The early detection of at-risk cases and the prompt initiation of specific treatment could result in better disease outcomes. However, larger prospective studies are required to confirm the findings of the present study.

Ethics

Ethics Committee Approval: The study was approved by both the Republic of Turkey Ministry of Health and the Ethics Committee of Acıbadem University (decision no: 2020-09/12, date: 21.05.2020).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Helms J, Kremer S, Merdji H, Clere-Jehl R, Schenck M, Kummerlen C, et al. Neurologic Features in Severe SARS-CoV-2 Infection. N Engl J Med 2020;382:2268-70.
2. Kandemirli SG, Dogan L, Sarikaya ZT, Kara S, Akinci C, Kaya D, et al. Brain MRI Findings in Patients in the Intensive Care Unit with COVID-19 Infection. Radiology 2020;297:E232-5.
3. Dogan L, Kaya D, Sarikaya T, Zengin R, Dincer A, Akinci IO, et al. Plasmapheresis treatment in COVID-19-related autoimmune meningoencephalitis: Case series. Brain Behav Immun 2020;87:155-8.
4. Kaur SP, Gupta V. COVID-19 Vaccine: A comprehensive status report. Virus Res 2020;288:198114.
5. Sanders JM, Monogue ML, Jodlowski TZ, Cutrell JB. Pharmacologic Treatments for Coronavirus Disease 2019 (COVID-19): A Review. JAMA 2020;323:1824-36.
6. Alhazzani W, Møller MH, Arabi YM, Loeb M, Gong MN, Fan E, et al. Surviving Sepsis Campaign: Guidelines on the Management of Critically Ill Adults with Coronavirus Disease 2019 (COVID-19). Crit Care Med 2020;48:e440-69.
7. Bykowski J, Kruk P, Gold JJ, Glaser CA, Sheriff H, Crawford JR. Acute pediatric encephalitis neuroimaging: single-institution series as part of the California encephalitis project. Pediatr Neurol 2015;52:606-14.
8. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ; HLH Across Speciality Collaboration, UK. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet 2020;395:1033-4.
9. Baig AM, Khaleeq A, Ali U, Syeda H. Evidence of the COVID-19 Virus Targeting the CNS: Tissue Distribution, Host-Virus Interaction, and Proposed Neurotropic Mechanisms. ACS Chem Neurosci 2020;11:995-8.
10. Rosário C, Zandman-Goddard G, Meyron-Holtz EG, D'Cruz DP, Shoenfeld Y. The hyperferritinemic syndrome: macrophage activation syndrome, Still's disease, septic shock and catastrophic antiphospholipid syndrome. BMC Med 2013;11:185.
11. Agmon-Levin N, Rosário C, Katz BS, Zandman-Goddard G, Meroni P, Cervera R, et al. Ferritin in the antiphospholipid syndrome and its catastrophic variant (cAPS). Lupus 2013;22:1327-35.
12. Meisner M. Update on procalcitonin measurements. Ann Lab Med 2014;34:263-73.
13. Castelo-Branco C, Soveral I. The immune system and aging: a review. Gynecol Endocrinol 2014;30:16-22.

Turk J Intensive Care 2021;19(Suppl 1):87-94
DOI: 10.4274/tybd.galenos.2021.02419

ÖZGÜN ARAŞTIRMA / *ORIGINAL RESEARCH*

Cem Erdoğan,
Sibel Doğan,
Rümeysa Çakmak,
Oktay Olmuşçelik,
Deniz Kızılaslan,
Bahadır Çiftçi

Yeni Tip 2019 COVID ve COVID Dışı Servislerde Çalışan Hekimlerde Anksiyetenin Değerlendirilmesi

Evaluation of Anxiety in Doctors Working in New Type 2019 COVID and Non-COVID Services

Geliş Tarihi/Received : 30.09.2021
Kabul Tarihi/Accepted : 16.11.2021

Cem Erdoğan, Deniz Kızılaslan, Bahadır Çiftçi
İstanbul Medipol Üniversitesi Tıp Fakültesi, Anesteziyoloji ve Reanimasyon Anabilim Dalı, İstanbul, Türkiye

Sibel Doğan
İstanbul Medipol Üniversitesi Sağlık Bilimleri Yüksekokulu, Sağlık Yönetimi Bölümü, İstanbul, Türkiye

Rümeysa Çakmak
İstanbul Medipol Üniversitesi Tıp Fakültesi, Biyokimya Anabilim Dalı, İstanbul, Türkiye

Oktay Olmuşçelik
İstanbul Medipol Üniversitesi Tıp Fakültesi, İç Hastalıkları Anabilim Dalı, İstanbul, Türkiye

Dr. Öğr. Üyesi Cem Erdoğan (✉),
İstanbul Medipol Üniversitesi Tıp Fakültesi, Anesteziyoloji ve Reanimasyon Anabilim Dalı, İstanbul, Türkiye

E-posta : cerdogan@medipol.edu.tr
Tel. : +90 505 266 25 91
ORCID ID : orcid.org/0000-0002-5715-8138

ÖZ *Amaç:* Bu çalışma İstanbul'da bir vakıf üniversitesi hastaneler kompleksinde yeni tip 2019 koronavirüs hastalığı (COVID) ve COVID dışı servislerde çalışan hekimlerde anksiyetenin değerlendirilmesi amacıyla yapılmış tanımlayıcı bir çalışmadır.
Gereç ve Yöntem: Çalışma kapsamına, pandemi servislerinde çalışan 50, pandemi dışı servislerde çalışan 52 hekim alınmıştır. Veri toplama aracı olarak hekimlerin sosyo-demografik ve mesleki bazı özelliklerini içeren anket formu ve durumluk-süreklilik kaygı ölçeği kullanılmıştır. Veriler online anket uygulaması yoluyla toplanmıştır. Verilerin değerlendirilmesinde verilerin normal dağılım gösterip göstermediğine Shapiro-Wilk normallik testi ile bakılmıştır. Verilerin normal dağılım göstermediği için iki grup karşılaştırmalarında Mann-Whitney U testi, ikiden fazla grup karşılaştırmalarında ise Kruskal-Wallis testi kullanılmıştır. Korelasyon analizinde ise Pearson korelasyon analizi yapılmıştır.
Bulgular: Çalışmamızda pandemi servislerinde çalışan hekimlerin durumluk kaygı puan ortalamalarının, pandemi dışı servislerde çalışan hekimlerin kaygı puan ortalamalarından daha yüksek olduğu ve aradaki farkın istatistiksel olarak anlamlı olduğu saptanmıştır (p<0,05). Cinsiyete göre pandemi servisinde çalışan kadın hekimlerin durumluk kaygı puan ortalamalarının erkek hekimlerden daha yüksek ve farkın istatistiksel olarak önemli olduğu belirlenmiştir (p<0,05). Yaş gruplarına göre pandemi servislerinde çalışan 43 yaş ve üzerindeki hekimlerin süreklilik kaygı puan ortalamalarının diğer yaş gruplarındaki hekimlerden daha düşük ve farkın istatistiksel olarak önemli olduğu saptanmıştır (p<0,05). Hem pandemi servislerinde çalışan hekimlerin hem de pandemi servisleri dışında çalışan hekimlerin durumluk ve süreklilik kaygı ölçeği puan ortalamaları arasında pozitif yönlü kuvvetli ilişki saptanmıştır (p<0,05). Yani durumluk kaygı arttıkça süreklilik kaygı, süreklilik kaygı arttıkça durumluk kaygı da artmaktadır.
Sonuç: Çalışmamızda pandemi servislerinde çalışan hekimlerin durumluk kaygısının diğer servislerde çalışan hekimlerden daha fazla olduğu ve süreklilik kaygısı arasında bir fark bulunamaması pandemi servisinde çalışmanın anksiyeteye neden olduğunu göstermektedir.
Anahtar Kelimeler: Hekim, COVID-19, pandemi, anksiyete

ABSTRACT *Objective:* This descriptive study was conducted in a foundation university hospital complex in Istanbul and aimed to evaluate the anxiety in physicians who provide new type 2019 coronavirus disease (COVID) related and non-COVID-19-related services.
Materials and Methods: This study included 50 physicians who provide COVID-19-related services and 52 physicians with non-COVID-19-related services. A questionnaire that contains socio-demographic and occupational characteristics of physicians and a state-trait anxiety scale were used as data collection tools. Data were collected through an online survey application. Data analysis checked the variable distribution using the Shapiro-Wilk normality test. Since no normal distribution was found, the Mann-Whitney U test was used for comparisons of two groups, and the Kruskal-Wallis test was used for comparisons of more than two groups. The Pearson correlation analysis was performed for correlation analysis.
Results: Our study determined significantly higher mean state anxiety scores of physicians who provide COVID-19-related services than that of the other group (p<0.05). According to age groups, the mean trait anxiety scores of physicians aged 43 years and over who provide COVID-19-related services were significantly lower than that in physicians who provide non-COVID-19-related services (p<0.05). A strong positive correlation was found in the state and trait anxiety scale mean scores between both groups (p<0.05). Therefore, state and trait anxiety increase in correlation.
Conclusion: Our study revealed higher state anxiety of physicians who provide COVID-19-related services than that of physicians who provide non-COVID-19-related services. Additionally, no difference was found in the trait anxiety, which indicates that working in the pandemic services causes anxiety.
Keywords: Physician, COVID-19, pandemic, anxiety

Giriş

Hekimler ve diğer sağlık çalışanları normal iş aktiviteleri gereği en stresli iş kollarından birinde çalışmaktadır. Stres ve kaygıyla beraber tükenmişliği tüm meslek grupları içinde en fazla hissedenler sağlık çalışanlarıdır (1,2). Hekimlik mesleğinin eğitim ve çalışma koşullarının yol açtığı psikolojik sıkıntılar pek çok çalışmaya konu olmuştur. Ülkelerin güncel koşulları da hekimin ruh sağlığını etkilemekte, çoğu kez anksiyete (kaygı), depresyon ya da tükenmişlik sendromuna yol açmaktadır (3,4). Tüm bunlar mevcut iken, tüm dünyayı etkileyen ve Dünya Sağlık Örgütü (DSÖ) tarafından pandemi olarak ilan edilen yeni tip 2019 koronavirüs hastalığı (COVID) salgınında görev yapan sağlık çalışanları çok ciddi bir iş yükü ve psikolojik yük ile karşı karşıya kaldılar. DSÖ, 4 Mart 2020'de "COVID-19 virüsü bağlamında sağlık çalışanlarının maruz kalma risk değerlendirmesi ve yönetimi" için geçici kılavuz yayınladı (5). 19 Mart 2020'de yayınlanan bir sonraki kılavuzda ise (6), COVID-19 pandemisinde sağlık çalışanlarının kaçınılmaz bir şekilde risk altında olduğu belirtildi. Bu salgınla ön cephede savaşan sağlık personellerinin hemen hemen tamamı ilk defa böyle bir pandemi tecrübesi yaşarken, hastalarına müdahale etmenin zorluğunu, kendisinin ve sevdiklerinin tehlikede olduğunu görüp hissettiler. Hayatını kaybeden insanların içinde meslektaşlarının da olması hekimler için önemli bir stres faktörü olarak görülmektedir. Hekimlerin yaşadığı ruhsal sorunlar, mesleki performanslarına, hasta ile ilişkilerine ve iş tatminlerine yansıyabilmektedir (3,4). Sağlık çalışanlarının ve özellikle hekimlerin sık deneyimlediği duygulardan biri de anksiyetedir. Anksiyetenin değerlendirilmesinde çeşitli testler kullanılmaktadır. Anksiyete değerlendirilmesinde yaygın kullanılan testlerden biri de durumluk ve süreklilik kaygı testleridir. Durumluk kaygı; tehlikeli, istenmeyen bir durumla karşılaşıldığında ortaya çıkan kaygıdır. Sürekli kaygı ise ortada nesnel bir neden yokken de var olan ve böyle bir nedenle karşılaşıldığında, durumla orantısız biçimde uzun süren ve şiddetli olan kaygıdır (7).

Bu çalışmada; gelecekte buna benzer bir salgında sağlık çalışanları için sosyal ve psikolojik stratejileri belirlemek için pandemi servislerinde çalışan hekimlerin kaygı-anksiyete durumlarını pandemi servislerinde çalışmayan hekimlerle karşılaştırmayı amaçladık.

Gereç ve Yöntem

Çalışma, İstanbul'da bir vakıf üniversitesi hastaneler kompleksinde pandemi ve pandemi dışı servislerde çalışan hekimlerin katılımı ile yapılmıştır. Çalışma öncesinde İstanbul Medipol Üniversitesi Girişimsel Olmayan Etik Kurulu'ndan 05.05.2020 tarihli ve 366 sayılı etik kurul onayı alınmıştır. Çalışmamız etik kurul onayını takiben 06-31 Mayıs 2020 tarihleri arasında yapılmış olup, veriler online anket uygulaması yoluyla toplanmıştır. Çalışma kapsamına, pandemi servislerinde çalışan 50, pandemi dışındaki servislerde çalışan 52 hekim alınmıştır. Veri toplama aracı olarak hekimlerin sosyo-demografik ve mesleki bazı özelliklerini içeren 7 soruluk anket formu ve durumluk-süreklilik kaygı ölçeği kullanılmıştır.

Durumluk ve Süreklilik Kaygı Ölçeği (The State-Trait Anxiety Inventory-STAI)

Spielberger ve ark.'nın (7) geliştirdiği kaygı ölçeği (STAI), 20'şer maddelik iki bölümden oluşur: Durumluk kaygı düzeyini ölçen STAI-1, sürekli kaygı düzeyini ölçen STAI-2 Türkçe formun geçerlilik ve güvenilirliği Öner ve LeCompte (8) tarafından yapılmıştır. Ölçek Likert tipinde olup dört derecelidir: "Hiç, biraz, çok ve tamamıyla". Durumluk-sürekli kaygı envanterleri iki tür ifade içerir. Olumlu (doğrudan) ifadeler olumsuz duyguları, olumsuz (tersine dönmüş) ifadeler olumlu duyguları dile getirir. STAI-1'deki (Durumluk Kaygı Envanteri) olumsuz ifadeler 1, 2, 5, 8, 10, 11, 15, 16, 19 ve 20. maddelerdir. STAI-2'deki (Sürekli Kaygı Envanteri) olumsuz ifadeler ise 21, 26, 27, 30, 33, 36 ve 39. maddelerdir. Doğrudan ve tersine dönmüş ifadelerin ayrı ayrı toplam ağırlıkları hesaplanır, ters ifadelerin toplamı doğrudan ifadelerin toplamından çıkarılır. Bu sayıya önceden saptanmış ve değişmeyen bir değer eklenir. STAI-1 için bu değişmeyen değer 50, STAI-2 için 35'tir. En son elde edilen değer bireyin kaygı puanıdır. Yirmi madde içeren ölçekte 3'ten fazla ifadeye cevap verilmemişse form geçersiz sayılır. Her iki ölçekten elde edilen puanlar kuramsal olarak 20 ile 80 arasında değişir. Yüksek puan, yüksek kaygı düzeyini gösterir.

İstatistiksel Analiz

Araştırma verilerinin değerlendirilmesinde IBM SPSS Statistics 21 istatistik paket programından yararlanılmıştır. Verilerin tanımlayıcı istatistikleri olarak yüzde değerler, aritmetik ortalama, standart sapma, medyan, minimum ve maksimum değerleri verilmiştir. Verilerin normal dağılım gösterip göstermediğine Shapiro-Wilk normallik testi ile bakılmıştır. Verilerin normal dağılım göstermediği için iki grup karşılaştırmalarında Mann-Whitney U testi, ikiden fazla grup karşılaştırmalarında ise Kruskal-Wallis testi kullanılmıştır. Korelasyon analizinde ise Pearson korelasyon analizi

yapılmıştır. İstatistiksel anlamlılık düzeyi p<0,05 olarak kabul edilmiştir.

Bulgular

Hekimlerin tanıtıcı özelliklerine göre dağılımı Tablo 1'de yer almaktadır. Hem pandemi servislerinde çalışan hekimlerin hem de pandemi servisleri dışında çalışan hekimlerin çoğunluğunun kadın, (sırasıyla %58; %53,8), 43 yaş ve üzerinde (sırasıyla %42; %44,2), evli (sırasıyla %70; %61,5) ve 11 yıl ve üzeri mesleki deneyime sahip olduğu (sırasıyla %76,058; %61,5) görülmektedir. Hekimlerin mesleki ve çalışma özelliklerine göre dağılımı Tablo 2'de verilmiştir. Hem pandemi servislerinde çalışan hekimlerin hem de pandemi servisleri dışında çalışan hekimlerin çoğunluğunun uzman (sırasıyla %90; %70,2) ve şuan çalıştığı bölümde aylık çalışma saatinin 199 saatten az olduğu (sırasıyla %40; %40,4) belirlenmiştir.

Uzmanlık alanlarına göre ise pandemi servislerinde çalışan hekimlerin çoğunluğu (%60) anesteziyoloji ve reanimasyon uzmanı iken, pandemi servisleri dışında çalışan hekimlerin çoğunluğunun (%86,5) uzmanlık alanı ise diğer (her bölümden hekim pandemi sürecinde görev aldı) uzmanlık alanlarıdır. Tablo 3'te pandemi servisleri ve pandemi dışı servislerde çalışan hekimlerin kaygı puan ortalamaları verilmiştir. Pandemi servislerinde çalışan hekimlerin durumluk kaygı puan ortalamalarının, pandemi dışı servislerde çalışan hekimlerin kaygı puan ortalamalarından daha yüksek olduğu ve aradaki farkın istatistiksel olarak anlamlı olduğu saptanmıştır (p<0,05).

Süreklilik kaygı puan ortalamalarına göre ise pandemi servisleri ve pandemi dışı servislerde çalışan hekimlerin süreklilik kaygı puan ortalamaları arasında istatistiki olarak anlamlı ilişki bulunamamıştır (p>0,05).

Tablo 4'te hekimlerin tanıtıcı özelliklerine göre durumluk-süreklilik kaygı puan ortalamaları görülmektedir. Cinsiyete göre pandemi servisinde çalışan kadın hekimlerin durumluk kaygı puan ortalamalarının erkek hekimlerden daha yüksek

Tablo 1. Hekimlerin tanıtıcı özelliklerine göre dağılımı (n=102)

	Pandemi servisinde çalışan (n=50)		Pandemi dışı servislerde çalışan (n=52)	
Tanıtıcı Özellikler	**Sayı**	**Yüzde**	**Sayı**	**Yüzde**
Cinsiyet				
Kadın	29	58	28	53,8
Erkek	21	42	24	46,2
Yaş				
23-27 yaş	-	-	5	9,6
28-32 yaş	5	10	9	17,3
33-37 yaş	11	22	4	7,7
38-42 yaş	13	26	11	21,2
43 yaş ve üzeri	21	42	23	44,2
Medeni durum				
Bekar	11	22	17	32,7
Evli	35	70	32	61,5
Eşi ölmüş/ayrılmış	4	8	3	5,8
Toplam mesleki hizmet süresi				
1 yıldan az	-	-	3	5,8
1-2 yıl	1	2	4	7,7
3-4 yıl	1	2	3	5,8
5-6 yıl	3	6	4	7,7
7-8 yıl	3	6	2	3,8
9-10 yıl	4	8	4	7,7
11 yıl ve üzeri	38	76	32	61,5
Toplam	50	100	52	100

Tablo 2. Hekimlerin mesleki ve çalışma özelliklerine göre dağılımı (n=102)

	Pandemi servisinde çalışan (n=50)		Pandemi dışı servislerde çalışan (n=52)	
Özellikler	**Sayı**	**Yüzde**	**Sayı**	**Yüzde**
Uzman veya asistan olma durumu				
Uzman	45	90	37	71,2
Asistan	5	10	15	28,8
Uzmanlık alanı				
Anesteziyoloji ve reanimasyon	30	60	4	7,7
Enfeksiyon hastalıkları	4	8	1	1,9
Dahiliye	6	12	2	3,8
Göğüs hastalıkları	4	8	-	-
Diğer	6	12	45	86,5
Şu an çalıştığı bölümde aylık çalışma saati				
199 saatten az	20	40	21	40,4
200-219 saat	11	22	11	21,2
220-239 saat	7	14	5	9,6
240-259 saat	10	20	7	13,5
260 saat ve üstü	2	4	8	15,4
Toplam	50	100	52	100

Tablo 3. Pandemi servisleri ve pandemi dışı servislerde çalışan hekimlerin kaygı puan ortalamaları					
Durumluk-süreklilik kaygı	Pandemi servisinde çalışan		Pandemi dışı servislerde çalışan		Test/p
	Ortalama ± SS	Min-maks	Ortalama ± SS	Min-maks	
Durumluluk kaygı	46,5±11,16	26-71	40,92±9,77	23-61	*U=939.000 p=0,016
Süreklilik kaygı	39,44±8,38	25-74	39,65±8,48	23-63	*U=1264.000 p=0,809
*Mann-Whitney U testi uygulanmıştır. SS: Standart sapma, min: minimum, maks: maksimum					

Tablo 4. Hekimlerin tanıtıcı özelliklerine göre durumluk-süreklilik kaygı puan ortalamaları (n=102)				
Tanıtıcı özellikler	Pandemi servisinde çalışan (n=50)		Pandemi dışı servislerde çalışan (n=52)	
	Durumluk kaygı	Süreklilik kaygı	Durumluk kaygı	Süreklilik kaygı
	Ortalama ± SS	Ortalama ± SS	Ortalama ± SS	Ortalama ± SS
Cinsiyet				
Kadın	49,65±10,26	41,75±8,84	41,06±9,38	39,35±9,29
Erkek	42,14±11,11	39,95±10,87	37,19±6,28	40,0±7,60
Test p	*U=185.500 p=0,019	*U=244.000 p=0,233	*U=294.000 p=0,440	*U=311.000 p=0,646
Yaş				
23-27 yaş	-	-	42,20±10,15	47,20±10,84
28-32 yaş	55,0±16,23	41,40±6,65	45,33±9,53	42,55±9,38
33-37 yaş	50,36±7,20	46,27±10,90	35,50±3,69	34,0±9,86
38-42 yaş	45,92±8,52	38,61±6,89	40,18±7,70	38,09±5,39
43 yaş ve üzeri	42,80±11,93	35,90±5,92	40,21±11,24	38,60±7,89
Test p	**KW=6.165 p=0,104	**KW=10.052 p=0,018	**KW=3.823 p=0,430	**KW=6.325 p=0,176
Medeni durum				
Bekar	42,45±11,56	38,90±10,27	46,11±8,89	42,70±9,35
Evli	47,74±11,03	39,74±8,27	38,40±9,30	38,40±7,91
Eşi ölmüş/ayrılmış	46,75±11,55	38,25±3,86	38,33±11,01	35,66±6,02
Test p	**KW=1.284 p=0,526	**KW=0,024 p=0,988	**KW=7.923 p=0,019	**KW=3.139 p=0,208
Toplam mesleki hizmet süresi				
1 yıldan az	-	-	46,33±11,54	50,0±12,52
1-2 yıl	69,0±0,0	50,0±0,0	37,25±2,87	41,0±6,97
3-4 yıl	59,0±0,0	45,0±0,0	43,33±8,02	38,66±11,01
5-6 yıl	49,0±19,15	37,33±4,50	50,25±11,50	47,25±9,50
7-8 yıl	48,0±7,0	38,0±6,24	39,50±2,12	45,0±2,82
9-10 yıl	56,25±4,85	44,0±10,23	42,75±8,50	37,25±9,50
11 yıl ve üzeri	44,23±10,32	38,81±8,62	39,34±10,21	37,62±7,28
Test p	**KW=9.281 p=0,098	**KW=4.963 p=0,420	**KW=6.090 p=0,413	**KW=9.048 p=0,171
*Mann-Whitney U testi uygulanmıştır, **Kruskal-Wallis testi uygulanmıştır. SS: Standart sapma				

ve farkın istatistiksel olarak önemli olduğu belirlenmiştir (p<0,05). Yaş gruplarına göre pandemi servislerinde çalışan 43 yaş ve üzerindeki hekimlerin süreklilik kaygı puan ortalamalarının diğer yaş gruplarındaki hekimlerden daha düşük ve farkın istatistiksel olarak önemli olduğu saptanmıştır (p<0,05).

Medeni durum açısından pandemi dışı servislerde çalışan bekar hekimlerin durumluk kaygı puan ortalamalarından daha yüksek olduğu ve aradaki farkın istatistiksel olarak anlamlı olduğu belirlenmiştir (p<0,05). Toplam mesleki hizmet süresi değişkeninin hem pandemi servislerinde çalışan hekimlerin hem de pandemi servisleri dışında çalışan hekimlerin STAI puan ortalamalarını etkilemediği görülmüştür (p>0,05).

Tablo 5'te hekimlerin mesleki ve çalışma özelliklerine göre durumluk-süreklilik kaygı puan ortalamaları yer almaktadır. Tablo 5'teki mesleki ve çalışma özellikleri ile hem pandemi servislerinde çalışan hekimlerin hem de pandemi servisleri dışında çalışan hekimlerin STAI puan ortalamaları arasında istatistiki olarak anlamlı ilişki bulunamamıştır (p>0,05). Tablo 6'da Hekimlerin STAI'lardan aldıkları puanların korelasyonu görülmektedir. Hem pandemi servislerinde çalışan hekimlerin hem de pandemi servisleri dışında çalışan hekimlerin STAI puan ortalamaları arasında pozitif yönlü kuvvetli ilişki saptanmıştır (p<0,05). Yani durumluk kaygı arttıkça süreklilik kaygı, süreklilik kaygı arttıkça durumluk kaygı da artmaktadır.

Tartışma

Çalışmamızda pandemi servislerinde çalışan hekimlerin durumluk kaygısının pandemi dışı servislerde çalışan hekimlerden daha fazla olduğu ve süreklilik kaygısı arasında bir fark bulunamaması pandemi servisinde çalışmanın başlı başına anksiyete yarattığını göstermektedir. Bir dizi çalışmada da gösterilmiştir ki; COVID-19 ile enfekte olmuş hastaları

Tablo 5. Hekimlerin mesleki ve çalışma özelliklerine göre durumluk-süreklilik kaygı puan ortalamaları (n=102)

Özellikler	Pandemi servisinde çalışan (n=50)		Pandemi dışı servislerde çalışan (n=52)	
	Durumluk kaygı	Süreklilik kaygı	Durumluk kaygı	Süreklilik kaygı
	Ortalama ± SS	Ortalama ± SS	Ortalama ± SS	Ortalama ± SS
Uzman veya asistan olma durumu				
Uzman	45,68±10,16	39,33±8,52	39,75±9,85	37,72±7,34
Asistan	53,80±17,76	40,40±7,76	43,80±9,29	44,40±9,45
Test p	*U=81.000 p=0,308	*U=105.500 p=0,820	*U=202.000 p=0,127	*U=154.000 p=0,012
Uzmanlık alanı				
Anesteziyoloji ve reanimasyon	49,06±10,57	41,0±6,90	35,25±5,05	29,50±5,25
Enfeksiyon hastalıkları	39,0±3,55	34,75±2,36	23,0±0,0	37,0±0,0
Dahiliye	36,50±10,65	31,66±5,71	41,0±11,31	39,50±3,53
Göğüs hastalıkları	45,0±8,83	38,25±3,86	-	-
Diğer	49,66±13,66	43,33±15,57	41,82±9,75	40,62±8,41
Test p	**KW=8.321 p=0,081	**KW=9.502 p=0,05	**KW=4.358 p=0,225	**KW=6.246 p=0,100
Şu an çalıştığı bölümde aylık çalışma saati				
199 saatten az	48,15±10,92	41,15±9,75	38,47±10,97	39,09±9,48
200-219 saat	44,09±14,03	36,90±7,59	43,36±7,47	42,54±9,29
220-239 saat	47,28±9,74	41,42±7,11	49,20±3,27	42,0±4,52
240-259 saat	46,60±9,97	38,80±7,39	37,28±7,88	36,57±5,02
260 saat ve üstü	40,0±14,14	32,50±2,12	42,0±11,05	38,37±8,99
Test p	**KW=1.939 p=0,747	**KW=4.052 p=0,399	**KW=6.627 p=0,157	**KW=3.059 p=0,548

*Mann-Whitney U testi uygulanmıştır, **Kruskal-Wallis testi uygulanmıştır. SS: Standart sapma

tedavi etmenin zorlukları göz önüne alındığında, maruz kalan sağlık çalışanları psikolojik olarak daha çok etkilenmektedir (9-13). Yine benzer şekilde, pandeminin merkez üssü Wuhan'da hemşire ve hekimlerin %50'sinde depresyon ve %45'inde anksiyete olduğu, buna karşılık Çin'in daha az etkilenen bölgelerinde bu oranın %7,2 düzeyinde kaldığı bildirilmiştir (14). İtalya'da pandemi servislerinde çalışan sağlık çalışanları ile diğer birimler arasında yapılan bir karşılaştırmada, sağlık çalışanlarının hem depresif belirtilerinin hem de post-travmatik stres sendromu (PTSS) belirtilerinin daha yüksek düzeyde rapor ettiğini ortaya koymuştur. COVID-19 hastalarıyla çalışan profesyoneller arasında önemli ölçüde daha yüksek stres, tükenmişlik, ikincil travma, anksiyete ve depresyon gözlemlenmiştir. Bulaşma oranlarının daha yüksek olduğu bölgelerde çalışan profesyonellerde daha yüksek stres ve tükenmişlik seviyeleri ve daha düşük memnuniyet seviyeleri tespit edilmiştir. COVID-19'dan etkilenen hastalarla çalışmak (veya çalışmamak) ile bu pandeminin daha şiddetli yayıldığı bölgelerde çalışmak (veya çalışmamak) arasında herhangi bir etkileşim etkisi bulunamamıştır. Son olarak COVID-19 hastalarıyla çalışan profesyoneller grubunda psikolojik destek istemeyi düşünen profesyonellerin yüzdesi, COVID-19 hastalarıyla çalışmayan grubun iki katıydı. Genel bulgular, ön saflardaki sağlık çalışanlarının ruh sağlığının daha fazla dikkate alınması gerektiğini ve hedefe yönelik önleme ve müdahale programlarının gerekli olduğunu göstermektedir (15).

Çalışmamızda, pandemi servisinde çalışan kadın hekimlerin durumluk kaygısının erkek hekimlerden daha yüksek olduğu belirlenmiştir. Çelmeçe ve Menekay'ın (15) çalışmalarında; kadın, evli ve çocuk sahibi sağlık çalışanlarında stres ve sürekli kaygı diğer gruplara göre daha yüksek bulunmuş, Di Tella ve ark.'nın (16) çalışmasında ise kadın olmanın depresyon ve PTSS için predispozan faktör olduğu belirtilmiştir. Bizim çalışmamıza göre de kadın olmanın, cinsiyete özgü özellikleri ve baş etmeleri göz önüne alındığında, anksiyete için predispozan bir faktör olabileceği söylenebilir.

Çalışmamızda pandemi servislerinde çalışan 43 yaş ve üzerindeki hekimlerin süreklilik kaygısının diğer yaş gruplarından daha düşük olduğu saptanmıştır ancak mesleki hizmet süresinin her iki grupta da durumluk ve süreklilik kaygısını etkilemediği gözlenmiştir. Yaşla birlikte bireylerin deneyimlerinin ve bireysel gelişimlerinin de etkisiyle baş etmelerinin güçlendiği bilinmektedir.

Medeni durum açısından pandemi dışı servislerde çalışan bekar hekimlerin durumluk kaygısı daha yüksek olduğu belirlenmiştir. Di Tella ve ark. (16), özellikle kadın ve bekar olmanın daha yüksek depresif belirtilerle ve ayrıca kadın ve yaşlı olmanın da daha yüksek PTSS düzeyleri ile ilişkili olduğu belirtmişledir. Bekar olmak sosyal destek açısından evli bireylere göre dezavantaj yaratabileceğinden, bireylerin yaşadığı olumsuz duyguları ve baş etmelerini etkileyen bir faktör olabilmektedir.

Çalışmamızda, mesai süreleri arasındaki farkın her iki kaygı türünde de artışa neden olmadığı bulunmuştur. Çalışma sonucumuzun aksine, Hacimusalar ve ark.'nın (17) çalışmasında ise artan çalışma saatleri kaygıyı etkileyen önemli faktörlerden biri olarak belirtilmiştir. Hastanelerin çalışma düzeninin, hasta yoğunluğu ve ekipman gibi diğer faktörlerin bu duruma neden olduğunu düşünmekteyiz.

Çalışmamızda hem pandemi servislerinde hem de pandemi servisleri dışında çalışan hekimlerin durumluk ve süreklilik kaygıları arasında pozitif yönlü, yani durumluk kaygı arttıkça süreklilik kaygı, süreklilik kaygı arttıkça durumluk kaygının arttığı şeklinde bir ilişki bulunmuştur. Trumello ve ark.'nın (18) İtalya'da yaptıkları çalışmada; bulaş riskinin yüksek olduğu hastane ya da bölgede çalışan profesyoneller

Tablo 6. Hekimlerin durumluk ve süreklik kaygı ölçeklerinden aldıkları puanların korelasyonu (n=102)

	Ölçekler	Durumluk kaygı	Süreklilik kaygı
Pandemi servisinde çalışan (n=50)	Durumluk Kaygı	-	r= 0,597** p=0,000
	Süreklilik Kaygı	r= 0,597** p=0,000	-
Pandemi dışı servislerde çalışan (n=52)	Durumluk Kaygı	-	r= 0,679** p=0,000
	Süreklilik Kaygı	r= 0,679** p=0,000	-

**Korelasyon 0,01 düzeyinde anlamlıdır, Pearson korelasyon (r) analizi kullanılmıştır.

arasında önemli ölçüde daha yüksek stres, tükenmişlik, ikincil travma, anksiyete ve depresyon gözlemlenmiştir. COVID-19'dan etkilenen hastalarla çalışmak (veya çalışmamak) ile bu pandeminin daha şiddetli yayıldığı bölgelerde çalışmak (veya çalışmamak) arasında herhangi bir etkileşim etkisi bulunmamıştır. Ancak, COVID-19 hastalarıyla çalışan profesyoneller grubunda psikolojik destek istemeyi düşünen profesyonellerin yüzdesi, COVID-19 hastalarıyla çalışmayan grubun iki katı olarak bildirilmiştir. Kaygı evrensel bir duygudur, pandemi koşulları gibi belirsizlik ve öngörülemeyen durumların içerisinde olmak, bireylerin durumluk ve süreklilik kaygı düzeylerini eş zamanlı etkileyebilir.

Sonuç

Yoğun ve stresli iş yükleri olan hekimler özellikle pandemi döneminin hastalarda, yakın çevrelerinde ve kendilerinde yarattığı psikolojik ve sosyal yükle çok daha fazla karşı karşıya kalmışlardır. Pandemi servisinde çalışan hekimlerde durumluk kaygının pandemi servisinde çalışmayan hekimlere göre bile daha fazla olması durumun önemini göstermektedir. Süreklilik kaygı ve durumluk kaygının pozitif etkileşimde olması nedeni ile hekimlerin ve sağlık çalışanlarının pandemi koşullarından psikolojik olarak daha fazla etkilenmemesi için, çalışma koşullarının ve özel yaşamlarının göz önünde bulundurularak iş planlamalarının yapılmasının ve psikososyal destek sağlanmasının gerekli olduğunu düşünmekteyiz.

Etik

Etik Kurul Onayı: Çalışma öncesinde İstanbul Medipol Üniversitesi Girişimsel Olmayan Etik Kurulu'ndan 05.05.2020 tarihli ve 366 sayılı etik kurul onayı alınmıştır.

Hasta Onamı: Bilgilendirilmiş onam alınmıştır.

Hakem Değerlendirmesi: Editörler kurulu dışında olan kişiler tarafından değerlendirilmiştir.

Yazarlık Katkıları

Cerrahi ve Medikal Uygulama: C.E., S.D., O.O., D.K., B.Ç., Konsept: C.E., S.D., R.Ç., O.O., D.K., B.Ç., Dizayn: C.E., S.D., R.Ç., O.O., D.K., B.Ç., Veri Toplama veya İşleme: C.E., S.D., R.Ç., O.O., D.K., B.Ç., Analiz veya Yorumlama: C.E., S.D., R.Ç., D.K., Literatür Arama: C.E., B.Ç., Yazan: C.E., S.D.

Çıkar Çatışması: Yazarlar tarafından çıkar çatışması bildirilmemiştir.

Finansal Destek: Yazarlar tarafından finansal destek almadıkları bildirilmiştir.

Kaynaklar

1. Maslach C, Leiter LP. (1997). The truth about burnout: How organizations cause personal stress and what to do about it. San Francisco: Jossey Bass.
2. Poncet MC, Toullic P, Papazian L, Kentish-Barnes N, Timsit JF, Pochard F, et al. Burnout syndrome in critical care nursing staff. Am J Respir Crit Care Med 2007;175:698-704.
3. Ofili AN, Asuzu MC, Isah EC, Ogbeide O. Job satisfaction and psychological health of doctors at the University of Benin Teaching Hospital. Occup Med (Lond) 2004;54:400-3.
4. Vanagas G, Bihari-Axelsson S. The factors associated to psychosocial stress among general practitioners in Lithuania. Cross-sectional study. BMC Health Serv Res 2005;5:45.
5. World Health Organization. Health workers exposure and management in the context of COVİD-19-19 virus: interim guidance. Geneva: World Health Organization; 2020. Available from URL: https://apps.who.int/iris/handle/10665/331340. Accessed 4 Mar 2020.
6. World Health Organization. Coronavirus disease (COVİD-19-19) outbreak: rights roles and responsibilities of heath workers, including key considerations for occupational safety and health: interim guidance. Geneva: World Health Organization; 2020. Available from URL: https://apps.who.int/iris/handle/10665/331510. Accessed 19 Mar 2020.
7. Spielberger CD, Gorsuch RL, Lusahene RE. Manual for State and Trait Anxiety Inventory. California: Consulting Psychologists Press; 1970.
8. Öner N, LeCompte A. Durumluk-Sürekli Kaygı Envanteri El Kitabı, Boğaziçi Üniversitesi Yayınları, No:333; İstanbul: 1982.
9. Xiang YT, Jin Y, Wang Y, Zhang Q, Zhang L, Cheung T. Tribute to health workers in China: a group of respectable population during the outbreak of the COVİD-19-19. Int J Biol Sci 2020;16:1739-40.
10. Shanafelt T, Ripp J, Trockel M. Understanding and Addressing Sources of Anxiety Among Health Care Professionals During the COVID-19 Pandemic. JAMA 2020;323:2133-4.
11. Neto MLR, Almeida HG, Esmeraldo JD, Nobre CB, Pinheiro WR, de Oliveira CRT, et al. When health professionals look death in the eye: the mental health of professionals who deal daily with the 2019 coronavirus outbreak. Psychiatry Res 2020;288:112972.
12. El-Hage W, Hingray C, Lemogne C, Yrondi A, Brunault P, Bienvenu T, et al. Les professionnels de santé face à la pandémie de la maladie à coronavirus (COVID-19) : quels risques pour leur santé mentale ? [Health professionals facing the coronavirus disease 2019 (COVID-19) pandemic: What are the mental health risks?]. Encephale 2020;46(3S):S73-S80. French.
13. Bohlken J, Schömig F, Lemke MR, Pumberger M, Riedel-Heller SG. COVID-19-Pandemie: Belastungen des medizinischen Personals [COVID-19 Pandemic: Stress Experience of Healthcare Workers - A Short Current Review]. Psychiatr Prax 2020;47:190-7. German.
14. Lai J, Ma S, Wang Y, Cai Z, Hu J, Wei N, et al. Factors Associated With Mental Health Outcomes Among Health Care Workers Exposed to Coronavirus Disease 2019. JAMA Netw Open 2020;3:e203976.
15. Çelmeçe N, Menekay M. The Effect of Stress, Anxiety and Burnout Levels of Healthcare Professionals Caring for COVID-19 Patients on Their Quality of Life. Front Psychol 2020;11:597624.
16. Di Tella M, Romeo A, Benfante A, Castelli L. Mental health of healthcare workers during the COVID-19 pandemic in Italy. J Eval Clin Pract 2020;26:1583-7.
17. Hacimusalar Y, Kahve AC, Yasar AB, Aydin MS. Anxiety and hopelessness levels in COVID-19 pandemic: A comparative study of healthcare professionals and other community sample in Turkey. J Psychiatr Res 2020;129:181-8.
18. Trumello C, Bramanti SM, Ballarotto G, Candelori C, Cerniglia L, Cimino S, et al. Psychological Adjustment of Healthcare Workers in Italy during the COVID-19 Pandemic: Differences in Stress, Anxiety, Depression, Burnout, Secondary Trauma, and Compassion Satisfaction between Frontline and Non-Frontline Professionals. Int J Environ Res Public Health 2020;17:8358.

Turk J Intensive Care 2021;19(Suppl 1):95-101
DOI: 10.4274/tybd.galenos.2021.30316

ORIGINAL RESEARCH / *ÖZGÜN ARAŞTIRMA*

Mehtap Pehlivanlar Küçük,
Burcu Öksüz Güngör,
Ahmet Oğuzhan Küçük,
Olcay Ayçiçek,
Atila Türkyılmaz,
Funda Öztuna,
Yılmaz Bülbül,
Tevfik Özlü

Pneumothorax and Subcutaneous Emphysema Evaluation in Patients with COVID-19 in the Intensive Care Unit

COVID-19 Tanılı Yoğun Bakım Hastalarında Pnömotoraks ve Subkütan Amfizem Olgularının Değerlendirilmesi

Received/Geliş Tarihi : 26.03.2021
Accepted/Kabul Tarihi : 19.11.2021

Mehtap Pehlivanlar Küçük
Karadeniz Technical University Faculty of Medicine, Department of Chest Diseases, Division of Intensive Care Medicine, Trabzon, Turkey

Burcu Öksüz Güngör, Atila Türkyılmaz
Karadeniz Technical University Faculty of Medicine, Department of Thoracic Surgery, Trabzon, Turkey

Ahmet Oğuzhan Küçük
Karadeniz Technical University Faculty of Medicine, Department of Anesthesiology and Reanimation, Division of Intensive Care Medicine, Trabzon, Turkey

Olcay Ayçiçek, Funda Öztuna, Yılmaz Bülbül, Tevfik Özlü
Karadeniz Technical University Faculty of Medicine, Department of Chest Diseases, Trabzon, Turkey

Mehtap Pehlivanlar Küçük, PhD, (✉),
Karadeniz Technical University Faculty of Medicine, Department of Chest Diseases, Division of Intensive Care Medicine, Trabzon, Turkey

E-mail : mehtap_phlvnlr@hotmail.com
Phone : +90 505 242 44 90
ORCID ID : orcid.org/0000-0003-2247-4074

ABSTRACT *Objective:* Pneumothorax (PNX) and subcutaneous emphysema (SCE) have increased in importance as a frequently occurring complication. This study aimed to reveal the frequency, timing, and possible risk factors in patients with PNX and SCE who are followed up with coronavirus disease-2019 (COVID-19) diagnosis in our tertiary intensive care unit (ICU).
Materials and Methods: All patients with confirmed COVID-19 who were followed up and treated in our unit between August 8, 2020, and February 20, 2021, in a 16-bed tertiary ICU and who developed PNX and SCE during their hospitalization were included.
Results: PNX and SCE developed in 16 (9.6%) of 165 patients who were followed up in our ICU due to COVID-19. Of these 16 patients, 3 (18.8%) survived. The median age of patients was 66.5 years (interquartile range: 58.5-75.5). Diabetes mellitus was the most common comorbidity in patients with PNX and SCE. Additionally, 12 (75%) patients had a smoking history. Of 15 (93.8%) patients who developed PNX, 4 (25%) were bilateral, and SCE developed in 9 (56.3%) patients. Twelve (75%) patients with PNX and SCE were under invasive mechanical ventilation, 3 (18.8%) under spontaneous breathing, and 1 (6.2%) under non-invasive mechanical ventilation treatment. The number of oxygen support days until the time PNX and SCE developed was 9 (6.25-17) days in the whole group, the median time was 6 days in the survival group and 9 days in the non-survival group.
Conclusion: In the COVID-19 pandemic, complications, such as PNX and SCE, are more frequently observed (9.5%) than in the general intensive care population and the later period of intensive care admission (median 9 days). Smoking is defined as a risk factor in most of these patients; however, increased PNX rates are thought to be related to both COVID-19 pneumonia and parenchymal damage due to cytokine storms.
Keywords: COVID-19, pneumothorax, intensive care unit

ÖZ *Amaç:* Koronavirüs hastalığı-2019 (COVID-19) ile takipli yoğun bakım hastalarında pnömotoraks (PNX)/deri altı amfizem (SCE) pandeminin ilk zamanlarında yapılan tanımlamaların aksine sık ortaya çıkan bir komplikasyon olarak önemini artırmaktadır. Bu çalışma ile 3. düzey yoğun bakım ünitemizde (YBÜ) COVID-19 tanısı ile takip edilen PNX/SCE olgularının sıklığını, zamanlamasını ve olası risk faktörlerini ortaya koymak hedeflenmiştir.
Gereç ve Yöntem: On altı yataklı 3. düzey YBÜ'de, 28 Ağustos 2020 ve 20 Şubat 2021 arasında ünitemizde takip ve tedavi edilmiş tüm teyitli COVID-19 hastalarından, yatışları sırasında PNX ve SCE gelişen olgular dahil edilmiştir.
Bulgular: Hedef tarih aralığında YBÜ'de COVID-19 nedeni ile 165 hasta takip edilmiş olup bu hastaların 16'sında (%9,6) PNX/SCE gelişmiştir. Bu 16 hastanın 4'ü (%25) sağ kalmıştır. Hastaların medyan yaşı 66,5 (çeyrekler açıklığı: 58,5-75,5) idi. PNX/SCE gelişen hastalarda en sık komorbidite diabetes mellitus olarak tespit edildi. Hastaların 12'sinin (%75) sigara kullanım öyküsü mevcuttu. PNX gelişen 15 (%93,8) hastanın 4'ü (%25) bilateraldi. SCE ise 9 (%56,3) hastada gelişti. PNX/SCE saptanan 12 (%75) hasta invazif mekanik ventilasyon tedavisi altındayken, 3 (%18,8) hasta spontan solunumda, 1 (%6,2) hasta non-invazif mekanik ventilasyon tedavisi altındaydı. PNX/SCE geliştiği ana kadar oksijen desteği verilen gün sayısı tüm grupta 9 (6,25-17) gün iken, sağkalan grupta medyan değer 6 gün, ölen grupta 9 gün idi. Oksijen destek gün süresi ölen grupta yüksek olsa da istatistiksel anlamlı fark saptanmadı (p=0,439).
Sonuç: COVID-19 pandemisinde PNX/SCE gibi komplikasyonlar uzun süreli oksijen desteğini takiben genel yoğun bakım popülasyonundan daha sık (%9,5) ve yoğun bakım yatışının daha geç döneminde (medyan 9 gün) gözlenmektedir. Bu hastaların çoğunda bir risk faktörü olarak sigara tanımlansa da PNX oranlarındaki bu artışın hem COVID-19 pnömonisi hem de sitokin fırtınasına bağlı oluşan parankimal hasar ile ilgili olduğunu düşünüyoruz.
Anahtar Kelimeler: COVID-19, pnömotoraks, yoğun bakım ünitesi

Introduction

The nature of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus, which entered our lives as a pandemic agent, is still not clearly known. The virus, which can cause complex and fatal complications, involves many organ systems and often requires intensive care support. Respiratory failure in patients is usually characterized by air bronchograms, bilateral interstitial infiltrates, and multiple lobar and subsegmental consolidations which are seen as ground glass opacities on computed tomography (CT) (1). Coronavirus disease-2019 (COVID-19) has many diagnosed complications such as arrhythmia, cardiogenic shock, renal and hepatic involvement, thromboembolism, and acute respiratory distress syndrome (ARDS) (2-4). Pneumothorax (PNX) and pneumomediastinum are common complications of mechanical ventilation (5,6). While there is a noticeable increase in the frequency of these complications in COVID-19 patients, spontaneous PNX/pneumomediastinum cases have also been described without barotrauma (7). One large review reported 18 different COVID-19-related spontaneous PNX cases followed in different centers (8). In our study, we aimed to reveal the frequency, timing, and possible risk factors of PNX and subcutaneous emphysema (SCE) cases followed up with the diagnosis of COVID-19 in our tertiary intensive care unit.

Materials and Methods

Our study was carried out in Karadeniz Technical University Faculty of Medicine 16-bed tertiary intensive care unit with the approval of the local Ethics Committee of Karadeniz Technical University Faculty of Medicine (protocol no: 2021/62, date: 25.03.2021) and the Ministry of Health. All cases were diagnosed according to the typical radiological image on CT or Real time polymerase chain reaction diagnosis of SARS-CoV-2 infection. All confirmed COVID-19 patients who were followed up and treated in our unit between August 28, 2020 and February 20, 2021 and who developed PNX and SCE during their hospitalization were included in the study.

The diagnoses of the patients were made by bedside ultrasonography (USG) and direct anteroposterior chest radiographs taken in the bed.

Patient data were obtained from retrospective intensive care patient registry, data processing automation records, and clinical course. Radiological images of the patients were accessed from the hospital picture archiving and communication system.

In our study, demographic data of the cases, comorbidities, possible risk factors for PNX, clinical, radiological, and laboratory data, applied oxygen support system [high-flow nasal cannula (HFNC), invasive mechanical ventilation (IMV), non-invasive mechanical ventilation (NIMV)], whether prone position was applied, other medical treatments applied for primary disease, and patient outcome information was recorded. HFNC was administered at a flow rate of 60 l/min in each patient during the initial phase. In the follow-up, the flow rate was decreased according to respiratory effort of the patients. Surgical procedure (chest tube insertion, etc.) applied to the patient due to PNX/SCE was recorded.

Statistical Analysis

Data were analyzed with IBM SPSS V23 (Chicago, USA). The compliance of the data to normal distribution was examined using the Shapiro-Wilk test. Non-normally distributed data are presented as the median [interquartile range (IQR): 25-75]. Categorical data are presented as frequency and percentage. The study population was divided in to two groups according to outcome (survived and non-survived). Kruskal-Wallis test and Mann-Whitney U test were used to compare quantitative data that did not show normal distribution. Chi-square test was used to compare qualitative data. The significance level was taken as $p<0.05$.

Results

One hundred sixty-five patients were followed in our intensive care unit due to COVID-19, and 16 (9.6%) of these patients developed PNX/SCE (Figure 1).

Three (18.8%) of these 16 patients survived. Analyses were made by grouping the patients according to the mortality outcome. The median age of the patients was 66.5 years (IQR: 58.5-75.5), and 12 of the patients were male and 4 were female. While all of the female patients died, no mortality was observed in 25% of the male patients. Diabetes mellitus was the most common comorbidity in patients with PNX/SCE, and there was no significant difference in mortality in any of the comorbidities.

Four (25%) of the 15 (93.8%) patients who developed PNX were bilateral. SCE developed in 9 (56.3%) patients. While chest tube drainage system was set up in 11 (68.8%) patients, 5 (31.2%) patients were followed conservatively without surgical intervention. PNX/SCE was detected in one

of the cases in the regression period of covid pneumonia and in the others in ARDS.

HFNC was the most commonly used respiratory support treatment method and was applied to 13 (81.3%) patients. Twelve patients (75%) were placed in the prone position. While all 16 patients were receiving low dose methylprednisolone treatment, 5 (31.2%) patients received pulse methylprednisolone, 11 (68.8%) patients tocilizumab, 2 (12.5%) patients tocilizumab and pulse methylprednisolone together, and 9 (56.3%) patients received immune plasma treatment. There was no significant difference in mortality in patients who developed PNX/SCE according to these treatments.

Twelve (75%) patients with PNX/SCE were under IMV treatment, three (18.8%) patients were under spontaneous breathing, and one patient (6.2%) was under NIMV treatment (Table 1). The most dominant risk factor in all patients was smoking. While 12 (75%) of the patients had a smoking history, there was no significant difference in mortality between smoking and non-smoking groups (p=0.607). When the chest tomography at admission was evaluated, there was no dominant risk factor for PNX/SCE, while three patients had traction bronchiectasis.

The duration of smoking was 30 packs/year (IQR: 25-38.75) in all patients. While the number of days given oxygen support until the time PNX/SCE developed was 9 (6.25-17) days in the whole group, the median value was 6 days in the survival group and 9 days in the non-survival group. Although the time spent on oxygen support was higher in the non-survival group, no significant difference was found (p=0.439). There was no significant difference in terms of IMV duration (p=0.439). The duration of stay in the intensive care unit and the duration of hospital stay were significantly shorter in the non-survival group (p=0.005, p=0.014 respectively) (Table 2).

Discussion

Since the beginning of the COVID-19 pandemic, clinicians' experience with the disease and its complications has increased. Intensive care units have become units where COVID-19 patients under severe respiratory distress are closely monitored. PNX/SCE has increased in importance as a frequent complication in intensive care patients, contrary to the definitions made in the early stages of the pandemic. In a study, 94 of 3,430 intensive care patients had iatrogenic PNX; 42 of them were associated with barotrauma, while 52 were associated with the invasive procedure. The cumulative incidence was determined to be 1.4% (9). Although PNX/SCE is observed at a very low rate in general intensive care, it was seen at a much higher rate (20-34%) in intubated patients in the SARS outbreak caused by a coronavirus strain (10,11). Although PNX/SCE was defined in 16 (9.6%) of 165 intensive care patients in intensive care unit, this frequency was given as 1-2% in two separate studies conducted in the early stages of the pandemic in China (12,13). In addition, more recent case reports are available in the literature (7,8,14-17).

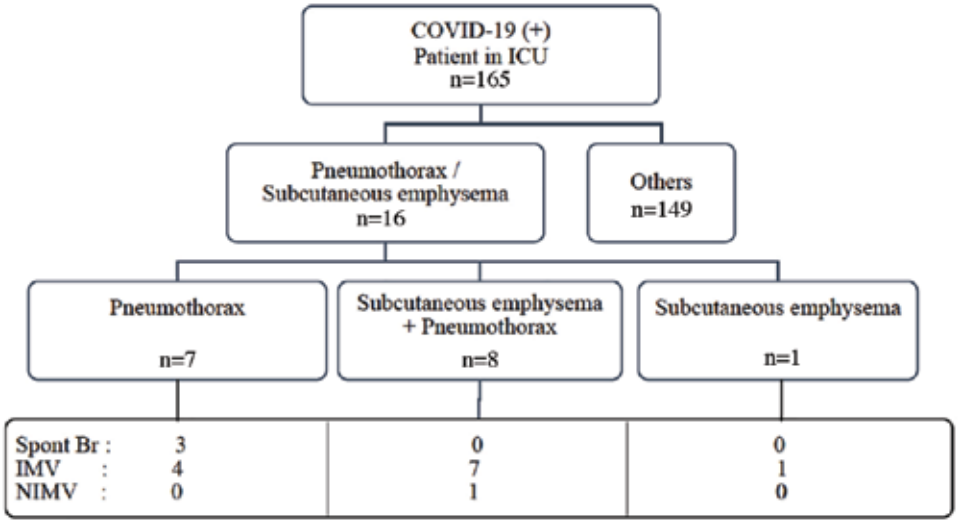


Figure 1. COVID-19 patient diagram
COVID-19: Coronavirus disease-2019, IMV: invasive mechanical ventilation, NIMV: non-invasive mechanical ventilation, ICU: intensive care unit

Even if PNX is suspected in intensive care units, confirmation of the diagnosis is much more difficult than in clinic patients whose condition is stable. PNX cases, which are mostly diagnosed by direct radiographs taken at the bedside, are also diagnosed by bedside USG in our unit (Figure 2). Lung sliding loss occurs in lung USG and stratosphere sign occurs in M mode in PNX. Lung sliding and/or B lines exclude the diagnosis of PNX (18,19). Lung USG was performed in all of the presented cases, and the diagnosis was confirmed by direct radiographs at the bedside.

PNX/SCE cases associated with barotrauma, which are among the complications of mechanical ventilation in intensive care units, can be considered as common complications. Therefore, lung protective mechanical ventilation strategies should be adopted. In the recently published Surviving Sepsis Campaign update, it is suggested as "For mechanically ventilated adults with COVID-19 and ARDS, targeting Pplat of <30 cm H_2O, they suggest using a higher positive end-expiratory pressure (PEEP) strategy over a lower PEEP strategy in moderate to severe ARDS, If using a higher PEEP strategy (i.e., PEEP >10 cm H_2O), clinicians should monitor patients for barotrauma." (20). There are also studies where mechanical ventilation does not increase the risk of barotrauma when lung protective mechanical ventilation rules apply (21,22).

Table 1. Demographic characteristics of the patients

			Total	Survived	Did not survive
			n	n (%)	n (%)
Risk factors	Smoking	No	4	1 (25)	3 (75)
		Yes	12	2 (16.7)	10 (83.3)
	Chronic lung disease	No	13	3 (23.1)	10 (76.9)
		Yes	3	0 (0)	3 (100)
	Cough attack	No	16	3 (18.8)	13 (81.3)
Admission CT findings	Air cyst	No	14	3 (21.4)	11 (78.6)
		Yes	2	0 (0)	2 (100)
	Bullae	No	15	3 (20)	12 (80)
		Yes	1	0 (0)	1 (100)
	Traction bronchiectasis	No	13	2 (15.4)	11 (84.6)
		Yes	3	1 (33.3)	2 (66.7)
Respiratory support on PNX	Spontaneous breathing	No	13	1 (7.7)	12 (92.3)
		Yes	3	2 (66.7)	1 (33.3)
	IMV	No	4	2 (50)	2 (50)
		Yes	12	1 (8.3)	11 (91.7)
	NIMV	No	15	3 (20)	12 (80)
		Yes	1	0 (0)	1 (100)

IMV: Invasive mechanical ventilation, NIMV: non-invasive mechanical ventilation, PNX: pneumothorax, CT: computed tomography

Table 2. Comparison of outcomes in survived and non-survived groups

	Total	Survived (n=13)	Non-survived (n=3)	p
Duration of smoking, (packs/year)	30 (25-38.75)	30 (25-36.25)	35 (25-)	0.758
Number of days given oxygen support until the time PNX/SCE developed	9 (6.25-17)	9 (7-17)	6 (1-)	0.439
Duration of IMV, (days)	11 (4.5-18.5)	10 (5-16.5)	19 (0-)	0.611
Duration of ICU stay, (days)	18 (11.75-24.75)	16 (10.5-21)	25 (24-)	0.005
Duration of hospital stay, (days)	21 (17.5-27)	19 (14-22.5)	31 (27-)	0.014

PNX: Pneumothorax, SCE: subcutaneous emphysema, IMV: invasive mechanical ventilation, ICU: intensive care unit

However, it is interesting to detect cases of PNX/SCE in COVID-19 pneumonia not only in the case of high-pressure ventilation but also in spontaneously breathing patients. Moreover, no risk factor was found in many of the reported cases (7,8). In three of our patients, PNX developed during spontaneous breathing under oxygen therapy with HFNC. Two of these patients were under the age of 45, without additional risk factors for PNX. One of the two patients developed PNX, which required chest tube drainage while spontaneously breathing on the 19th and the other on the 24th day of oxygen therapy; one of these patients died. In the general intensive care population, barotrauma is seen earlier, and the median time is reported to be 4-5 days after intubation (9).

In our patients, PNX/SCE complications generally developed in the later stages of the disease, on average at 9 (6-17) days of oxygen therapy. Moreover, there were facilitating factors such as air cyst, bullae, and traction bronchiectasis in 6 patients' thoracic CT at the time of admission to the hospital. This timing corresponds to days 11-28, which is defined as the early pulmonary phase/late pulmonary phase of the COVID pneumonic process and its intense oxygen demand (23). In general, known risk factors for the development of primary spontaneous PNX include age between 10 and 30 years, male gender, tall height, and weak body structure. Secondary causes include smoking, chronic obstructive pulmonary disease, infections, alpha-1 antitrypsin deficiency, and trauma (24,25). Not surprisingly, 75% of our patients were smokers, and most of them (83.3%) died.

In the COVID-19 pandemic, oxygen support systems have unfortunately had to be used in increasing doses and

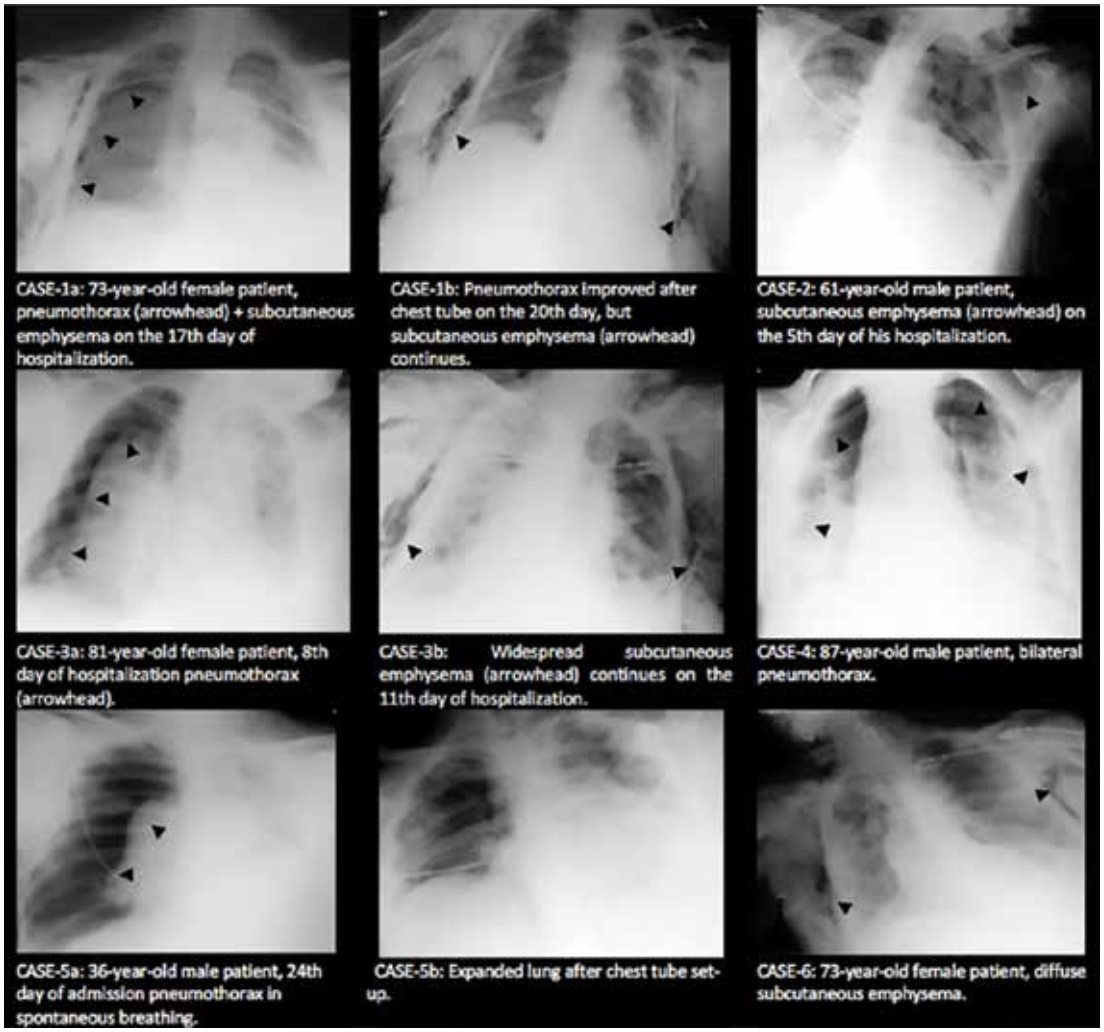


Figure 2. Examples of bedside radiography

for a long time. When focusing on acute respiratory failure treatment in COVID-19 patients, the long-term effects of intense oxygen exposure can be ignored. Many healthy volunteers experience pleuritic chest pain, cough, substernal heaviness, and shortness of breath within a day of inhaling 100% oxygen; these symptoms are comonly due to a combination of absorptive atelectasis and tracheobronchitis (26). Most patients treated with a high FiO_2 (> 90%) more than six hours may have edema and bronchoscopic erythema in the large airways, which is thought to reflect hyperoxic bronchitis (27). In addition, regardless of the presence of underlying lung disease the reactive oxygen intermediate concentration in the exhaled gas increases only one hour after inhaling 28% oxygen (28). Free oxygen radicals also stimulate the harmful inflammatory response caused to secondary tissue damage and/or apoptosis (29). Some of the hypotheses already put forward for the development of PNX/SCE in COVID-19 pneumonia can be listed as follows: oclusion of small airways due to inflammation rises alveolar pressure and causes ruptures with air leaks into the lung interstitium; air travels to the hilum through the bronchovascular sheaths and collects in the mediastinum causing pneumomediastinum; the rupture of the mediastinal parietal pleura causes PNX. In addition, inflammatory cells associated with interleukin-6, which are produced during the cytokine storm associated with SARS-CoV-2, cause bullae formation in the lung by destroying elastic fibers (30,31). On the other hand, edema, vascular occlusion, and microthrombi may contribute to the rupture of pre-existing bullae (26). In our patients, PNX/SCE generally developed in the later stages of the disease and on the ninth day of oxygen therapy, while six patients had facilitating factors such as air cyst, bulla, and traction bronchiectasis on thoracic CT at the admission to the hospital.

PNX should be suspected in patients even if there are no risk factors such as invasive or non-invasive positive pressure ventilator support, smoking and chronic lung disease, or severe cough. While mild cases can spontaneously resolve with close monitoring, oxygen support, and analgesia, patients with severe respiratory failure, such as our patients, may develop alveolar damage and alveolar rupture more easily and often require chest tube drainage. In these patients, chest tube drainage should be continued until the patients are extubated if they are intubated, and in patients with spontaneous breathing, when the lung is fully expanded and should be continued until 24 hours after the leak has ceased. The limitations of study were; CORADS classification was not used in radiological evaluation and total number of cases is low hence power of study wasn't reached wanted value.

Conclusion

In intensive care patients who are followed up due to COVID-19 and require high fractionated oxygen, in the case of acute or worsening dyspnea, PNX/SCE should be suspected in these patients with or without mechanical ventilation support. In the COVID-19 pandemic, these complications can be observed more frequently (9.5%) than in the general intensive care population and in the later period of intensive care admission (median 9 days). Although smoking is defined as a risk factor in most of these patients, we think that the increase in PNX rates is not only associated with the presence of a certain risk factor or barotrauma, but primarily related to both COVID-19 pneumonia and parenchymal damage caused by cytokine storm. These patients should be closely monitored for these complications in their long-term follow-up.

Ethics

Ethics Committee Approval: The approval of the local Ethics Committee of Karadeniz Technical University Faculty of Medicine (protocol no: 2021/62, date: 25.03.2021) and the Ministry of Health.

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.P.K., O.A., A.T., F.Ö., Y.B., T.Ö., Concept: M.P.K., B.Ö.G., A.O.K., O.A., A.T., F.Ö., Y.B., T.Ö., Design: M.P.K., A.O.K., O.A., A.T., F.Ö., Y.B., T.Ö., Data Collection or Processing: M.P.K., B.Ö.G., A.O.K., Analysis or Interpretation: M.P.K., A.O.K., O.A., Literature Search: M.P.K., B.Ö.G., Writing: M.P.K., A.O.K., B.Ö.G., O.A., A.T., F.Ö., Y.B., T.Ö

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

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Salehi S, Abedi A, Balakrishnan S, Gholamrezanezhad A. Coronavirus Disease 2019 (COVID-19): A Systematic Review of Imaging Findings in 919 Patients. AJR Am J Roentgenol 2020;215:87-93.
2. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. JAMA 2020;323:1061-9.
3. Klok FA, Kruip MJHA, van der Meer NJM, Arbous MS, Gommers DAMPJ, Kant KM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Thromb Res 2020;191:145-7.
4. Yang F, Shi S, Zhu J, Shi J, Dai K, Chen X. Analysis of 92 deceased patients with COVID-19. J Med Virol 2020;92:2511-5.
5. Yao W, Wang T, Jiang B, Gao F, Wang L, Zheng H, et al. Emergency tracheal intubation in 202 patients with COVID-19 in Wuhan, China: lessons learnt and international expert recommendations. Br J Anaesth 2020;125:e28-e37.
6. Jacobi A, Chung M, Bernheim A, Eber C. Portable chest X-ray in coronavirus disease-19 (COVID-19): A pictorial review. Vol. 64, Clinical Imaging. Elsevier Inc; 2020. p. 35-42.
7. Elhakim TS, Abdul HS, Pelaez Romero C, Rodriguez-Fuentes Y. Spontaneous pneumomediastinum, pneumothorax and subcutaneous emphysema in COVID-19 pneumonia: a rare case and literature review. BMJ Case Rep 2020;13:e239489.
8. Alhakeem A, Khan MM, Al Soub H, Yousaf Z. Case Report: COVID-19-Associated Bilateral Spontaneous Pneumothorax-A Literature Review. Am J Trop Med Hyg 2020;103:1162-5.
9. de Lassence A, Timsit JF, Tafflet M, Azoulay E, Jamali S, Vincent F, et al. Pneumothorax in the intensive care unit: incidence, risk factors, and outcome. Anesthesiology 2006;104:5-13.
10. Lew TW, Kwek TK, Tai D, Earnest A, Loo S, Singh K, et al. Acute respiratory distress syndrome in critically ill patients with severe acute respiratory syndrome. JAMA 2003;290:374-80.
11. Fowler RA, Lapinsky SE, Hallett D, Detsky AS, Sibbald WJ, Slutsky AS, et al. Critically ill patients with severe acute respiratory syndrome. JAMA 2003;290:367-73.
12. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020;395:507-13.
13. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med 2020;8:475-81.
14. George B, Megally M, Mrejen-Shakin K. Spontaneous pneumothorax and spontaneous pneumomediastinum in non-intubated patients in the setting of Severe Acute Respiratory Syndrome Coronavirus 2. Chest 2020;158:A1653-4.
15. Muhammad AI, Boynton EJ, Naureen S. COVID-19 with bilateral pneumothoraces- case report. Respir Med Case Rep 2020;31:101254.
16. Talan L, Şaşal Solmaz FG, Ercan U, Akdemir Kalkan İ, Yenigün BM, Yüksel C, et al. COVID-19 pneumonia and pneumothorax: case series. Tuberk Toraks 2020;68:437-43.
17. Vahapoğlu A, Akpolat B, Çavuş Z, Genç Moralar D, Türkmen A. Spontaneous Hemopneumothorax During the Course of COVID-19 Pneumonia. Turkish J Intensive Care 2020;18:46-9.
18. Lichtenstein D, Mezière G, Biderman P, Gepner A. The "lung point": an ultrasound sign specific to pneumothorax. Intensive Care Med 2000;26:1434-40.
19. Lichtenstein DA, Lascols N, Prin S, Mezière G. The "lung pulse": an early ultrasound sign of complete atelectasis. Intensive Care Med 2003;29:2187-92.
20. Alhazzani W, Møller MH, Arabi YM, Loeb M, Gong MN, Fan E, et al. Surviving Sepsis Campaign: guidelines on the management of critically ill adults with Coronavirus Disease 2019 (COVID-19) Intensive Care Med 2020;46:854-87.
21. Özdemir S, Bilgi DÖ, Köse S, Oya G. Pneumothorax in patients with coronavirus disease 2019 pneumonia with invasive mechanical ventilation. Interact Cardiovasc Thorac Surg 2021;32:351-5.
22. Guven BB, Erturk T, Kompe Ö, Ersoy A. Serious complications in COVID-19 ARDS cases: pneumothorax, pneumomediastinum, subcutaneous emphysema and haemothorax. Epidemiol Infect 2021;149:e137.
23. EVMS COVID-19 Management protocol An overview of the MATH+ and I-MASK+ Protocols. 2020.
24. Gupta D, Hansell A, Nichols T, Duong T, Ayres JG, Strachan D. Epidemiology of pneumothorax in England. Thorax 2000;55:666-71.
25. Sahn SA, Heffner JE. Spontaneous pneumothorax. N Engl J Med 2000;342:868-74.
26. Comroe JH, Dripps RD, Dumke PR, Deming M. Oxygen toxicity: The effect of inhalation of high concentrations of oxygen for twenty-four hours on normal men at sea level and at a simulated altitude of 18,000 feet. J Am Med Assoc 1945;128:710-7.
27. Sackner MA, Landa J, Hirsch J, Zapata A. Pulmonary effects of oxygen breathing. A 6-hour study in normal men. Ann Intern Med 1975;82:40-3.
28. Carpagnano GE, Kharitonov SA, Foschino-Barbaro MP, Resta O, Gramiccioni E, Barnes PJ. Supplementary oxygen in healthy subjects and those with COPD increases oxidative stress and airway inflammation. Thorax 2004;59:1016-9.
29. Mantell LL, Lee PJ. Signal transduction pathways in hyperoxia-induced lung cell death. Mol Genet Metab 2000;71:359-70.
30. Zhang C, Wu Z, Li JW, Zhao H, Wang GQ. Cytokine release syndrome in severe COVID-19: interleukin-6 receptor antagonist tocilizumab may be the key to reduce mortality. Int J Antimicrob Agents 2020;55:105954.
31. Marini JJ, Gattinoni L. Management of COVID-19 Respiratory Distress. JAMA 2020;323:2329-30.

Turk J Intensive Care 2021;19(Suppl 1):102-9
DOI: 10.4274/tybd.galenos.2021.04706

ORIGINAL RESEARCH / *ÖZGÜN ARAŞTIRMA*

Khin Zar Li Aung,
Rabia Yılmaz,
Ezgi Güngördü,
Sinan Aşar,
Yasemin Tekdos Şeker

Does Favipiravir Reduce Mortality in Patients with COVID-19 ARDS and Severe Pneumonia?

COVID-19 ARDS ve Ağır COVID Pnömonisi Hastalarında Favipiravir Mortaliteyi Azaltır Mı?

Received/Geliş Tarihi : 11.05.2021
Accepted/Kabul Tarihi : 08.12.2021

Khin Zar Li Aung, Rabia Yılmaz, Ezgi Güngördü, Sinan Aşar, Yasemin Tekdos Şeker
University of Health Sciences Turkey, İstanbul Bakırköy Dr. Sadi Konuk Research and Training Hospital, Intensive Care Unit, İstanbul, Turkey

Rabia Yılmaz MD, (✉),
University of Health Sciences Turkey, İstanbul Bakırköy Dr. Sadi Konuk Research and Training Hospital, Intensive Care Unit, İstanbul, Turkey

E-mail : drrabiayilmaz@gmail.com
Phone : +90 539 840 27 19
ORCID ID : orcid.org/0000-0003-1707-4607

ABSTRACT *Objective:* Although there is no antiviral treatment specific to the virus, favipiravir has entered the treatment routine as an antiviral in our country in May 2020. In this study, in patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) acute respiratory distress syndrome (ARDS) in the intensive care unit; The effects of favipiravir antiviral regimen on mortality and morbidity were evaluated.
Materials and Methods: Patients admitted to the intensive care unit were divided into two groups as those who received favipiravir (group F; n=208) and those who did not (group N; n=101). The treatment of the cases is arranged according to current national guidelines. Metavision/QlinICU Clinical Decision Support Software, in intensive care unit; Acute Physiology and Chronic Health Evaluation-II, Sequential Organ Failure Assessment score, aspartate aminotransferase, alanine aminotransferase, urea, creatinine, lactate dehydrogenase, ferritin, C-reactive protein (CRP), procalcitonin, Pro-BNP, D-dimer, fibrinogen, white blood cell, neutrophil count (NEU), lymphocyte count (LYM), NEU/LYM, CRP, t1 acceptance (0^{th} hour), t2 follow-up (24^{th} hour) and t3 (discharge or ex) values of acute phase parameters, and the comorbidity is obtained by Structured Query Language queries. The primary outcome is mortality; secondary outcomes are possible drug-related organ toxicities, sudden change of the level of the acute phase reactants, requirement of continuous renal replacement therapy (CRRT), hospitalization time, ventilator dependent days.
Results: One hundred eight women (35%), 201 men (65%), a total of 309 cases were evaluated in the study. In the demographic data of the groups, no statistically significant difference was found between the frequency of comorbidity, mortality rate, CRRT need, and secondary infection. The mean increase of 107.66±628.99 units between the t1 and t3 measurement was found to be statistically significant in F group cases. In the F group, the neutrophil/lymphocyte ratio (NLR) during the follow-up period and the last NLR were found to be lower than the initial value.
Conclusion: It was determined that favipiravir used in the treatment of SARS-CoV-2 ARDS has no superiority in preventing mortality.
Keywords: Favipiravir, COVID-19, ARDS, mortality

ÖZ *Amaç:* Virüse özgü antiviral tedavi olmamakla birlikte, favipiravir Mayıs 2020'de ülkemizde antiviral olarak tedavi rutinine girmiştir. Bu çalışmada yoğun bakım ünitesinde şiddetli akut solunum sendromu koronavirüs 2 (SARS-CoV-2) akut solunum sıkıntısı sendromlu (ARDS) hastalarda favipiravir antiviral rejiminin mortalite ve morbidite üzerindeki etkileri değerlendirildi.
Gereç ve Yöntem: Yoğun bakım ünitesine kabul edilen hastalar, favipiravir alanlar (grup F; n=208) ve almayanlar (grup N; n=101) olarak iki gruba ayrıldı. Olguların tedavisi güncel ulusal kılavuzlara göre düzenlendi. Metavision/QlinICU Yoğun Bakım Ünitesi'nde Klinik Karar Destek Yazılımı; Akut Fizyoloji ve Kronik Sağlık Değerlendirmesi-II, komorbidite, Sıralı Organ Yetmezliği Değerlendirmesi skoru, aspartat aminotransferaz, alanin aminotransferaz, üre, kreatinin, laktat dehidrogenaz, ferritin, C-reaktif protein (CRP), prokalsitonin, Pro-BNP, D-dimer, fibrinojen, beyaz kan hücresi, nötrofil sayısı (NEU), lenfosit sayısı (LYM), NEU/LYM, CRP, t1 kabulü (0. saat), akut faz parametrelerinin t2 takip (24. saat) ve t3 (taburcu veya eks) değerleri, Yapısal Sorgulama Dili (Structured Query Language) sorguları ile elde edilir. Birincil sonuç mortalitedir; ikincil sonuçlar, ilaca bağlı olası organ toksisiteleri, akut faz reaktanlarının seviyesinde ani değişiklik, sürekli renal replasman tedavisi (CRRT) gereksinimi, hastanede kalış süresi, ventilatöre bağlı günlerdir.
Bulgular: Çalışmada 108 kadın (%35), 201 erkek (%65), toplam 309 olgu değerlendirildi. Grupların demografik verilerinde komorbidite sıklığı, mortalite oranı, CRRT ihtiyacı ve sekonder enfeksiyon arasında istatistiksel olarak anlamlı fark bulunmadı. F grubu olgularda t1 ve t3 ölçümleri arasında 107,66±628,99 birimlik ortalama artış istatistiksel olarak anlamlı bulundu. F grubunda takip süresince nötrofil/lenfosit oranı (NLO) ve son NLO başlangıç değerinden düşük bulundu.
Sonuç: SARS-CoV-2 ARDS tedavisinde kullanılan favipiravirin mortaliteyi önlemede üstünlüğü olmadığı belirlendi.
Anahtar Kelimeler: Favipiravir, COVID-19, ARDS, mortalite

Introduction

Currently, there isn't any precise effective antiviral treatment specific to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus that causes coronavirus disease-2019 (COVID-19) disease (1). Since there is no known specific antiviral treatment, generic antiviral agents such as remdesivir, hydroxychloroquine and chloroquine, favipiravir, lopinavir-ritonavir (lop/r), umifenovir, and ribavirin are used in the management of the disease (2). In our country, Hydroxychloroquine and/or favipiravir are still recommended in the Treatment Guide for Adult Patients with COVID-19 created by the Scientific Committee (latest update 29/06/2021) (3) and these drugs are routinely used in all patients.

Favipiravir is a new type of drug that is a RNA dependent RNA polymerase inhibitor. Therefore, favipiravir may have potential antiviral effect on SARS-CoV-2, an RNA virus (4). In a clinical study conducted in China which favipiravir and lop/r were compared shows that favipiravir has stronger antiviral activity (5).

Several scoring methods such as Sequential Organ Failure Assessment (SOFA) score and Acute Physiology and Health Assessment-II (APACHE-II) score are used in intensive care units (ICU) for mortality prediction; some biomarkers are also used for this purpose. Factors such as advanced age (≥65 years of age), accompanying comorbidities, high fever (>39 °C), lymphopenia, neutrophilia, C-reactive protein (CRP) level, serum ferritin level, coagulation parameters (D-dimer and prothrombin time) have been shown to increase the risk of severe pneumonia and developing of acute respiratory distress syndrome (ARDS) (6).

The COVID-19 pandemic is a health problem that affects the whole world and the antiviral treatments used in the treatment of the disease are still being updated. As in our country, favipiravir is recommended in treatment guidelines in many countries and it is routinely used for many patients. In this study, we aimed to reveal the effects of favipiravir as an antiviral regimen used in the treatment of patients with severe pneumonia and ARDS associated with COVID-19 on mortality and morbidity in the ICU.

Materials and Methods

After the approval of the Turkish Ministry of Health Clinical Research Board; our study was approved by the Local Ethics Committee of the Bakırköy Dr. Sadi Konuk Training and Research Hospital with the decision number 2020/389 (date: 07.09.2020).

The treatment of patients with severe pneumonia and ARDS associated with COVID-19 admitted to Health Sciences University Turkey Bakırköy Dr Sadi Konuk Training and Research Hospital Anesthesiology and Reanimation Department ICU are reviewed observationally and retrospectively between 15 March 2020 and 29 November 2020 in this study. We examined 208 patients who had favipiravir in their treatment regimen (named as group F) (2x1,600 mg at first day as a loading dose, followed by 2x600 mg per day in next 4-9 days, 5-10 days treatment in total) and 101 patients who had not favipiravir in their treatment regimen (named as group N).

According to the current guideline (7); the patients infected by SARS-CoV-2 were diagnosed with polymerase chain reaction (PCR) test in the first line. The diagnosis was determined in PCR negative patients through positive chest computed tomography scan or/with lower respiratory tract infection findings such as fever, cough, dyspnea.

Severe pneumonia was described according to the Surviving Sepsis Campaign Guidelines on the Management of Adults with COVID-19 (7), and ARDS was described according to the Berlin criteria (8).

The study was planned as a retrospective observational study on the systemic effects of antiviral treatment before and after updates in the Treatment Guide for Adult Patients with COVID-19 compiled by the Ministry of Health's General Directorate of Public Health. Standardized supportive treatments were applied to both groups of patients; such as antibiotic therapy directed to the source in the presence of secondary infection, sedation agents, nutritional support, cardiovascular support therapy, steroids, immunomodulatory drugs, non-invasive positive pressure ventilation or invasive ventilation therapy, continuous renal replacement therapy (CRRT), extracorporeal membrane oxygenation treatment for patients whom conventional mechanical ventilation support is insufficient for. Since both groups were followed by the same intensive care team and with the same treatment protocol, we think that there is no obvious difference in terms of supportive treatments.

Cases with procalcitonin level >1 during follow-up were considered to be accompanied by secondary infection.

Patients younger than 18 years old, patients were followed for less than 24 hours in ICU, patients were pregnant or breastfeeding, patients whose treatment

was interrupted due to drug side effects were excluded from the study. We determined the primary outcome as mortality and secondary outcomes as possible drug-related organ toxicities, sudden change of the level of the acute phase reactants, requirement of CRRT, hospitalization time, ventilator dependent days.

Demographic data of patients diagnosed with COVID-19 pneumonia or ARDS in the Anesthesiology and reanimation intensive care unit registered in 'ImdSoft-Metavision/QlinICU Clinical Decision Support Software'. APACHE-II, SOFA score, level of aspartate aminotransferase (AST), alanine aminotransferase (ALT), urea, creatinine, lactate dehydrogenase (LDH), ferritin, CRP, procalcitonin, Pro-BNP, D-dimer, fibrinogen, white blood cell (WBC), neutrophil count (NEU), lymphocyte count (LYM), NEU/LYM ratio, acute phase parameters at admission (0^{th} hour), at follow-up (24^{th} hour) and at discharge or time of death is obtained by Structured Query Language queries. Admission time is defined as t1, 24^{th} hour of follow up defined as t2, and discharge or exitus time defined as t3. The presence of secondary infection was decided through procalcitonin level >1 during follow-up.

Statistical Analysis

The Number Cruncher Statistical System program was used for statistical analysis. Descriptive statistical methods (to identify the mean, standard deviation, median, frequency, percentage, minimum value, maximum value) were used for evaluating the study data. The suitability of quantitative data to normal distribution was tested by Shapiro-Wilk test and graphical analysis. Studen t-test was used for comparing parametric quantitative variables between two groups. T-test and Mann-Whitney U test were used to compare non-parametric quantitative variables to analyze quantitative independent data. Paired samples test was used for in-group comparisons of quantitative variables with normal distribution. The Wilcoxon signed-rank test was used for in-group comparisons of non parametric quantitative variables and for analysis of dependent quantitative data. Pearson chi-square test and Fisher-Freeman-Halton Exact test were used to analyze and compare qualitative independent data. The distribution of variables is measured by the Kolmogorov-Smirnov test. The SPSS 27.0 program was used in the analyzes. Statistical significance was accepted as $p<0.05$.

Results

Of the patients participating in the study, 35% (n=108) were female and 65% (n=201) were male. The ages of the cases ranged from 18 to 100, and the mean value was 60.29±16.56 years. There was no statistically significant difference in terms of age, height, weight and gender distributions between the two groups. Total mortality rate was 48.5%, and there was no statistically significant difference between the mortality rates between group F (48.6%) and group N (48.5%). There was no statistically significant difference between the groups in terms of secondary outcomes, comorbidities, the presence of secondary infection and horowitz index at the time of admission to intensive care unit (t1). There was no statistically significant difference in APACHE-II and SOFA scores between the groups at t1. The ratio of the intubated patients was similar in both groups ($p<0.05$) (Table 1).

The increases in AST level between t1 and t2, by an average of 99.23±1294.29 units and between t1 and t3, by an average of 446.75±1868.19 units were found to be statistically significant ($p=0.014$; $p=0.005$). The difference between AST level between at t1 and t2 in F group cases was found to be statistically significantly higher than the group N cases ($p=0.039$).

The mean increase of ALT level from t1 to t3 is 107.66±628.99 units, it was found to be statistically significant in F group cases ($p=0.001$). The transaminase levels of the groups are shown in Table 2.

The urea and creatinine levels of the cases do not show statistically significant differences depending on the groups ($p>0.05$).

Acute phase physiological parameters such as CRP, ferritin, LDH, D-dimer, procalcitonin, and fibrinogen levels were evaluated. There was no difference between the groups in the follow-up process. Hemogram parameters were evaluated, no significant difference was observed in WBC levels at t1, t2 and t3 times in group F and group N cases. No significant difference was observed in the lymphocyte levels between group F and group N. A significant increase was found in the lymphocyte levels at t3 of both groups compared to the initial measurement (t1) ($p<0.05$). In the F group, the neutrophil/lymphocyte ratio (NLR) during the follow-up period and the last NLR were found to be lower than the initial value ($p<0.05$) (Table 3).

Discussion

Favipiravir was reported to be particularly useful in the treatment of mild to moderate disease with its safety and efficacy profile (9,10). Unlike these studies, our patients were critically ill patients and we didn't determine any difference in mortality.

Clinical trials of COVID-19 infection in China suggest that favipiravir has a faster viral clearance than lop/r and better recovery rate than umifenovir and has a positive effect on morbidity and mortality (10,11). Favipiravir + INF inhalation and lop/r + INF inhalation treatment was compared in a total of 80 COVID-19 patients in a study conducted by Chen et al. (11). It was shown that the favipiravir group has shorter viral clearance time (4 days, 11 days) and better radiological recovery rate (91.4%, 62.2%) compared to the other group in this study. The frequency of side effects was also found to be less in the favipiravir group. Contrary to these literature, no reduction in mortality was observed in patients receiving favipiravir in our study.

In a randomized clinical study in China comparing favipiravir and umifenovir as antiviral therapy, recovery rates on the seventh day of the treatment were examined, no significant difference was found between these two

Table 1. Comparisons of descriptive characteristics between groups

		Groups			
		Total	Favipiravir	Non-favipiravir	p
Age (year)	Min-max (median)	18-100 (62)	18-100 (61.5)	19-87 (62)	[a]0.809
	Mean ± SD	60.29±16.56	60.45±17.17	59.96±15.32	
Gender n (%)	Female	108 (35.0)	78 (37.5)	30 (29.7)	[b]0.178
	Male	201 (65.0)	130 (62.5)	71 (70.3)	
Height (m)	Min-max (median)	1.4-1.96 (1.7)	1.4-1.96 (1.7)	1.4-1.87 (1.7)	[a]0.333
	Mean ± SD	1.69±0.09	1.68±0.09	1.69±0.09	
Weight (kg)	Min-max (median)	35-180 (80)	35-180 (80)	50-165 (80)	[a]0,554
	Mean ± SD	78.99±17.8	78.57±18.41	79.85±16.52	
BMI (kg/m^2)	Min-max (median)	14.69-55.6 (26.3)	14.69-55.6 (26.2)	19.53-53.88 (26.3)	[a]0.770
	Mean ± SD	27.71±5.93	27.64±6.02	27.85±5.78	
Length of stay (hours)	Min-max (median)	1-1348 (146)	1-1348 (147)	1-744 (146)	[c]0.976
	Mean ± SD	216.03±215.01	220.12±226.25	206.68±187.65	
Duration of mechanical ventilation (hours)	Mean ± SD	188.29±189.44	191.23±200.40	182.14±165.08	[c]0.866
Mechanical ventilation type	Invasive	239 (77.3)	163 (78.4)	76 (75.2)	[b]0.539
	HFNC	70 (22.7)	45 (21.6)	25 (24.8)	
Horowitz index (t1)	Mean ± SD	209.79±114.69	210.54±113.72	208.16±117.46	[a]0.879
SOFA (t1)	Min-max (median)	-	0-23 (9)	0-44 (9)	[a]0.243
	Mean ± SD	-	8.55±5.13	9.35±5.93	
APACHE-II (t1)	Min-max (median)	-	2-44 (21)	4-42 (21)	[a]0.560
	Mean ± SD	-	20.88±8.93	21.55±9.17	
Duration of CRRT (hours)	Mean ± SD	103.81±122.27	95.78±106.39	122.21±153.68	[c]0.915
Mortality (%)	Survival	159 (51.5)	107 (51.4)	52 (51.2)	[d]1.000
	Non-survival	150 (48.5)	101(48.6)	49 (48.5)	
Comorbidity (%)	No	113 (36.6)	72 (4.6)	41 (40.6)	[b]0.306
	Yes	196 (63.4)	136 (65.4)	60 (59.4)	
Secondary infection (%)	No	140 (45.3)	93 (44.7)	47 (46.5)	[b]0.763
	Yes	169 (54.7)	115 (55.3)	54 (53.5)	

[a]Student t test, [b]Pearson chi-square test, [c]Mann-Whitney U test, [d]Fisher Exact test, HFNC: high-flow nasal cannula, min: minimum, max: maximum, SD: standard deviation, BMI: body mass index, APACHE-II: Acute Physiology and Health Assessment-II, CRRT: continuous renal replacement therapy, SOFA: Sequential Organ Failure Assessment

drugs (11). Ribavirin + corticosteroid as a standard treatment in newly diagnosed SARS-CoV-1 patients and lop/r + ribavirin + corticosteroid treatment was compared by Chan et al. (10). at the time of the SARS-CoV-1 epidemic. A statistically significant difference was found in terms of mortality and ARDS development on the 21st day in this study.

In a randomized controlled trial including 199 COVID-19 cases, patients received standard care (SC) + lop/r or only SC were compared. It was stated that lop/r + SC was not different from SC in terms of time of clinical recovery and mortality in 28 days. (lop/r + SC 19.2%, SC 25%). The authors stated that lop/r does not contribute to SC in the treatment of patients infected by COVID-19. They stated that although mortality was reported as 11-14.5% in patients hospitalized due to COVID-19, the high rate of mortality 22.1% in this study might be due to the fact that the patients included in the study were severe patients (12).

Our study was conducted in patients followed-up in intensive care. Total mortality is 48.5%, and there is no significant difference between the groups.

Favipiravir has a well-characterized safety profile over 4,000 patients. Similar rates of side effects have been reported between low and high doses of favipiravir. Gastrointestinal side effects, increased uric acid levels, decreased neutrophil count, increased AST and ALT levels, psychiatric symptom reactions, and increased blood lipid profile are among the common side effects. The rates of serious side effects are 0.4% and 1.1% (13). Use of favipiravir in patients with moderate renal impairment

Table 2. Evaluation of AST and ALT Levels between groups

		Groups		
		Favipiravir	**Non-favipiravir**	**p**
AST level (t1) (U/L)	Min-max (median)	9-5884 (49.5)	12-6,106 (60)	[c]0.047*
	Mean ± SD	164.82±574.03	200.12±668.64	
AST level (t2) (U/L)	Min-max (median)	8-15,026 (40)	12-9,282 (40)	[c]0.338
	Mean ± SD	264.05±1333,67	192.49±946.93	
AST level (t3) (U/L)	Min-max (median)	8-15,026 (59)	12-12,688 (55)	[c]0.467
	Mean ± SD	613.53±1868,65	625.27±1837,29	
Difference between AST level (t1-t2) (U/L)	Difference	99.23±1294,29	-7.63±1160,16	[c]0.039*
	p	[f]0.014*	[f]0.001**	-
Difference between AST level (t1-t3) (U/L)	Difference	446.75±1868,19	424.63±1649,89	[c]0.533
	p	[f]0.005**	[f]0.162	-
ALT level (t1) (U/L)	Min-max (median)	3-7,174 (29)	2-4,772 (53)	[c]0.003**
	Mean ± SD	116.91±538.64	171.61±541.43	
ALT level (t2) (U/L)	Min-max (median)	4-8,184 (28)	2-9,124 (36)	[c]0.068
	Mean ± SD	129.88±638.41	242.83±1074,17	
ALT level (t3) (U/L)	Min-max (median)	4-4,076 (37)	2-9124 (50)	[c]0.067
	Mean ± SD	224.57±592.22	387±1174,11	
Difference between ALT level (t1-t2) (U/L)	Difference	12.97±370.05	71.22±1204,85	[c]0.090
	p	[f]0.217	[f]0.022*	-
Difference between ALT level (t1-t3) (U/L)	Difference	107.66±628.99	226.26±1014,91	[c]0.641
	p	[f]0.001**	[f]0.091	-

[c]Mann-Whitney U test, [f]Wilcoxon signed-ranks test, *p<0.05, **p<0.01, min: minimum, max: maximum, SD: standard deviation, ALT: alanine aminotransferase, AST: aspartate aminotransferase

[Glomerul filtration rate (GFR) between 30-60 mL/min] results in a 1.5-fold increase in Ctrough compared to patients with normal renal function. However, there is no evidence for its use among patients with GFR <30 mL/min (14).

Organ toxicities that affect mortality were examined in our study, an increase was observed in AST and ALT levels in the favipiravir group, however this did not cause toxic hepatitis in the cases. There was no significant difference in the times of the CRRT need, urea and creatinine levels

Table 3. Evaluation of NEU, LYM levels and NEU/LYM ratio between groups

		Groups		
		Favipiravir	Non-favipiravir	p
t1 NEU levels (x10³) (µL)	Min-max (median)	0.01-36.99 (9.97)	1.92-56.11 (10.55)	[c]0.188
	Mean ± SD	11.07±6.52	12.65±8.06	
t2 NEU levels (x10³) (µL)	Min-max (median)	0.32-56.11 (9.24)	1.44-56.11 (10.09)	[c]0.055
	Mean ± SD	10.56±6.82	12.33±8.03	
t3 NEU levels (x10³) (µL)	Min-max (median)	0.01-45.91 (9.22)	0.92-51.96 (9.29)	[c]0.789
	Mean ± SD	11.05±8	12.79±11.31	
Difference between NEU levels t1-t2(x10³) (µL)	Difference	-0.51±5.88	-0.32±5.52	[c]0.701
	p	[f]0.074	[f]0.407	
Difference between NEU levels t1-t3 (x10³) (µL)	Difference	0.09±8.19	0.33±10.41	[c]0.495
	p	[f]0.585	[f]0.454	
t1 LYM levels (x10³) (µL)	Min-max (median)	0.07-5.86 (0.67)	0.18-7.33 (0.8)	[c]0.133
	Mean ± SD	0.88±0.68	1.05±0.96	
t2 LYM levels (x10³) (µL)	Min-max (median)	0.04-4.08 (0.8)	0.07-5.86 (0.87)	[c]0.487
	Mean ± SD	0.97±0.66	1.1±0.89	
t3 LYM levels (x10³) (µL)	Min-max (median)	0.07-4.2 (1.03)	0-6.25 (1.09)	[c]0.226
	Mean ± SD	1.23±0.83	1.42±1.1	
Difference between LYM levels t1-t2 (x10³) (µL)	Difference	0.09±0.72	0.05±1.04	[c]0.796
	p	[f]0.004**	[f]0.038*	
Difference between LYM levels t1-t3 (x10³) (µL)	Difference	0.36±0.83	0.39±0.93	[c]0.793
	p	[f]0.001**	[f]0.001**	
t1 NEU/LYM ratio	Min-max (median)	0.08-177.29 (13.16)	2.96-113.96 (12.17)	[c]0.798
	Mean ± SD	17.2±16.54	17.51±16.24	
t2 NEU/LYM ratio	Min-max (median)	0.48-181 (11.39)	1.64-251.29 (11.52)	[c]0.704
	Mean ± SD	15.5±17.71	19.23±28.88	
t3 NEU/LYM ratio	Min-max (median)	0.08-81.11 (8.65)	0.51-125.63 (7.98)	[c]0.534
	Mean ± SD	12.43±12.09	14.12±19.28	
Difference between NEU/LYM ratio t1-t2	Difference	-1.70±18.84	1.71±25.03	[c]0.415
	p	[f]0.002**	[f]0.299	
Difference between NEU/LYM ratio t1-t3	Difference	-4.81±18.77	-3.51±21.02	[c]0.943
	p	[f]0.001**	[f]0.001**	

[c]Mann-Whitney U test, [f]Wilcoxon signed-ranks test, *p<0.05, **p<0.01, min: minimum, max: maximum, SD: standard deviation, NEU: neutrophil count, LYM: lymphocyte count

during follow-up between the groups. It was demonstrated that the cases included in our study had a similar clinical status in terms of known organ failure at the beginning of the intensive care unit.

In COVID-19 patients, coagulopathy with high D-dimer level and high fibrinogen level are frequently encountered. The group with high D-dimer values was found to be associated with higher mortality in a study (15). Increased D-dimer levels and normal fibrinogen levels were shown as laboratory evidence of COVID-19 disease in a study by Mucha et al. (14). In our study, no relationship was shown between D-dimer levels and mortality rates between these groups. Fibrinogen value was generally found to be normal or high.

Henry et al. (16) found that ferritin levels of deceased patients were higher than normal in a study they conducted. Likewise, in another study conducted in China, it was stated that it may be beneficial to monitor ferritin values in high-risk patients (17). In our study, ferritin values in both groups at the time of admission were also found to be higher than normal values. In our study, there was no significant difference in the follow-up of both groups in terms of acute phase reactants.

Deng et al. (18) compared non survival and survival patients in their study, they concluded that increased leukocyte count and decreased lymphocyte count were associated with mortality. Since there was no significant change in the presence of secondary infection between the groups, it suggests that the increased leukocyte count is not directly related to secondary infection. It has been determined that the cytokine release syndrome is associated with decreased lymphocyte level in new types of coronavirus patients (19). Significant reduction of T lymphocytes has been associated with mortality and is considered a poor prognosis factor and has been associated with disease severity in severely ill patients (20). When lymphocyte levels were evaluated in our study, the lymphocyte levels of the both groups were low at the time of hospitalization, a significant improvement was found in both groups during and at the end of the treatment. In a multicenter retrospective cohort study that included 60 inpatients and 42 outpatients, a total of 102 patients, NLR was calculated from hemogram parameters. As a result, advanced age, high LDH and high NLR values were considered as poor prognostic parameters in COVID-19 patients and hospitalization was recommended to such patients (21). In our study, in the F group, the NLR was found to be lower than the initial value during the follow-up period and during discharge, however we could not find any effect of this situation on mortality.

It is difficult to conduct controlled studies in such a life-threatening epidemic. Therefore, the study was planned as a retrospective observational study. It was unethical to allocate patients to receive different experimental drugs, and a randomization process was impossible. Therefore, we chose to conduct a before-after-designed study in which patients hospitalized in two consecutive periods were included in two groups, respectively. Lack of randomization, the absence of standard control groups and the additional use of glucocorticoids and lop/r made it difficult to evaluate the effect of favipiravir. The limitations of our study are that; it is retrospective and viral clearance was not examined.

Conclusion

There are many factors affecting mortality and morbidity in COVID-19 patients followed up in intensive care. In our study, no significant difference was found in terms of mortality and secondary outcome related favipiravir treatment in intensive care units. We determine that favipiravir treatment causes significant increases in liver enzymes. Therefore, we think that liver enzyme levels should be monitored more tightly in favipiravir treatment.

Ethics

Ethics Committee Approval: After the approval of the Turkish Ministry of Health Clinical Research Board; our study was approved by the Local Ethics Committee of the Bakırköy Dr. Sadi Konuk Training and Research Hospital with the decision number 2020/389 (date: 07.09.2020).

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: K.Z.L.A., S.A., Concept: K.Z.L.A., R.Y., S.A., Y.T.Ş., Design: R.Y., Y.T.Ş., Data Collection or Processing: K.Z.L.A., E.G., S.A., Analysis or Interpretation: E.G., S.A., Y.T.Ş., Literature Search: K.Z.L.A., R.Y., Writing: R.Y., Y.T.Ş.

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

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Carlos WG, Dela Cruz CS, Cao B, Pasnick S, Jamil S. Novel Wuhan (2019-nCoV) Coronavirus. Am J Respir Crit Care Med 2020;201:P7-8.
2. Song Y, Zhang M, Yin L, Wang K, Zhou Y, Zhou M, et al. COVID-19 treatment: close to a cure? A rapid review of pharmacotherapies for the novel coronavirus (SARS-CoV-2). Int J Antimicrob Agents 2020;56:106080.
3. Treatment Guide for Adult Patients with Covid-19 compiled by the Scientific Committee (latest update 29/06/2021)
4. Furuta Y, Komeno T, Nakamura T. Favipiravir (T-705), a broad spectrum inhibitor of viral RNA polymerase. Proc Jpn Acad Ser B Phys Biol Sci 2017;93:449-63.
5. Dong L, Hu S, Gao J. Discovering drugs to treat coronavirus disease 2019 (COVID-19). Drug Discov Ther 2020;14:58-60.
6. Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, et al. Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. JAMA Intern Med 2020;180:934-43.
7. Surviving Sepsis Campaign Guidelines on the Management of Adults With Coronavirus Disease 2019 (COVID-19) in the ICU: First Update critical care medicine 2020. doi: 10.1097/CCM.0000000000004899
8. ARDS Definition Task Force, Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, et al. Acute respiratory distress syndrome: the Berlin Definition. JAMA 2012;307:2526-33.
9. Cai Q, Yang M, Liu D, Chen J, Shu D, Xia J, et al. Experimental Treatment with Favipiravir for COVID-19: An Open-Label Control Study. Engineering (Beijing) 2020;6:1192-8.
10. Chan KS, Lai ST, Chu CM, Tsui E, Tam CY, Wong MM, et al. Treatment of severe acute respiratory syndrome with lopinavir/ritonavir: a multicentre retrospective matched cohort study. Hong Kong Med J 2003;9:399-406.
11. Chen C, Huang J, Cheng Z, Zhang Y, Cheng Z, Wu J, et al. Favipiravir versus arbidol for COVID-19: a randomized clinical trial [online]. Medrxiv preprint 2020. doi:https://doi.org/10.1101/2020.03.17.20037432
12. Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G, et al. A Trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe Covid-19. N Engl J Med 2020;382:1787-99.
13. Pilkington V, Pepperrell T, Hill A. A review of the safety of favipiravir - a potential treatment in the COVID-19 pandemic? J Virus Erad 2020;6:45-51.
14. Mucha SR, Dugar S, McCrae K, Joseph D, Bartholomew J, Sacha GL, et al. Coagulopathy in COVID-19: Manifestations and management. Cleve Clin J Med 2020;87:461-8.
15. Zhang L, Yan X, Fan Q, Liu H, Liu X, Liu Z, et al. D-dimer levels on admission to predict in-hospital mortality in patients with Covid-19. J Thromb Haemost 2020;18:1324-9.
16. Henry BM, de Oliveira MHS, Benoit S, Plebani M, Lippi G. Hematologic, biochemical and immune biomarker abnormalities associated with severe illness and mortality in coronavirus disease 2019 (COVID-19): a meta-analysis. Clin Chem Lab Med 2020;58:1021-8.
17. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet 2020;395:1033-4.
18. Deng Y, Liu W, Liu K, Fang YY, Shang J, Zhou L, et al. Clinical characteristics of fatal and recovered cases of coronavirus disease 2019 in Wuhan, China: a retrospective study. Chin Med J (Engl) 2020;133:1261-7.
19. Lu R, Zhao X, Li J, Niu P, Yang B, Wu H, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet 2020;395:565-74.
20. Xu B, Fan CY, Wang AL, Zou YL, Yu YH, He C, et al. Suppressed T cell-mediated immunity in patients with COVID-19: A clinical retrospective study in Wuhan, China. J Infect 2020;81:e51-e60.
21. Li G, Xu F, Yin X, Wu N, Li Y, Zhang T, et al. Lactic dehydrogenase-lymphocyte ratio for predicting prognosis of severe COVID-19. Medicine (Baltimore) 2021;100:e24441.