TÜRK YOĞUN BAKIM DERGİSİ

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AMAÇ VE KAPSAM

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

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

Türk Yoğun Bakım Dergisi, **Emerging Sources Citation Index (ESCI), Directory of Open Access Journals (DOAJ), ProQuest Health & Medical Complete, EBSCO Database, British Library, Index Copernicus, Tübitak/ Ulakbim, Türk Tıp Dizini, Türkiye Atıf Dizini, Hinari, GOALI, ARDI, OARE, AGORA, J-Gate, IdealOnline, ROOT INDEXING, EuroPub** ve **Türk Medline'da** indekslenmektedir.

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

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AIMS AND SCOPE

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

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

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

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

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

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

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

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

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

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

Yayına kabul edilmeyen yazılar, sanatsal resimler hariç geriye yollanmaz.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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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.

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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.

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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.

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

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

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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/);

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DERLEME / *REVIEW*

Yasin Levent Uğur,
Necati Gökmen

Tele-Yoğun Bakım ve Türkiye'deki Mevcut Durum, Fırsatlar, Kısıtlamalar

Tele-Intensive Care and the Current Situation in Turkey, Opportunities, Restrictions

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ÖZ Ülkemizde ve dünyada yaşlanan nüfus ile birlikte yoğun bakım tedavi gereksinimlerinin ve yoğun bakım maliyetlerinin artması beklenmektedir. Tele-yoğun bakım ünitesi (Tele-YBÜ) uygulamaları kritik hastaların takip ve tedavilerinin uzaktan düzenlenmesine, mevcut kaynakların verimli kullanımına imkan sağlayarak yeni bir çözüm aracı olabilir. Tele-YBÜ programları sayesinde yoğun bakım uzmanlarının yer ve zaman sınırlaması olmadan ülkedeki tüm yoğun bakım yataklarına ulaşabileceği, hastalardan gelen tüm verileri elektronik kayıt sistemleri ile değerlendirebileceği ve bu veriler ışığında hastalara kanıta dayalı en iyi tedavi önerilerini sunabilecekleri öngörülmektedir. Ancak Tele-YBÜ'nün kullanılması sırasında karşılaşabilecek altyapı yetersizlikleri, hasta-hekim, hekim-hasta yakını ilişkisinin bozulmasının yaratabileceği problemler, hasta verilerinin korunması, depolanması ile ilgili güçlükler, yasal mevzuat ve görev tanımlarının eksikliği gibi problemler bu yeni çözüm stratejisinin potansiyel yararının önüne geçebilir. Bu derleme, Tele-YBÜ konusunda bilgilendirme, ülkemizde Tele-YBÜ uygulanırsa bu konudaki fırsatlarımıza, eksikliklerimize ve kısıtlamalarımıza dikkat çekmek ve bu eksikliklerin tamamlanması için gerekli adımların atılmasını sağlamak amacıyla yazılmıştır.
Anahtar Kelimeler: Tele-tıp, yoğun bakım, Tele-YBÜ

ABSTRACT Intensive care treatment needs and costs are expected to increase with the ageing population in our country and the world. Tele-intensive care unit (Tele-ICU) applications can provide an alternative solution to treat and follow up critical patients remotely. It can help use existing resources efficiently. With the Tele-ICU program, intensive care specialists will reach all intensive care beds in the country without restrictions. They will evaluate the patients' situations with all data from electronic recording systems. However, problems with some legal regulations or terms of job descriptions, deterioration of patient-doctor, doctor-patient's relative relationships, or some infrastructure deficiencies when using the Tele-ICU system could override the potential benefit of the new solution strategy. This review was written to inform about Tele-ICU, draw attention to opportunities, shortcomings, and limitations if Tele-ICU is applied in our country, and ensure that the necessary steps are taken to resolve these deficiencies.
Keywords: Telemedicine, intensive care, Tele-ICU

Giriş

Dünyada ve ülkemizde nüfus artışına paralel bir şekilde sağlık harcamaları da hızla artmaktadır. Yaşlanan nüfus ile birlikte kritik hasta bakımına ihtiyacı olan kişi sayısının ve yoğun bakım tedavi gereksinimlerinin artacağı öngörülmektedir (1). Yoğun bakımlarda kritik hastanın bakımından sorumlu ve alanında uzman olan kişi sayısı artıyor olsa da; gelecekte yoğun bakımların daha verimli çalıştırılabilmesi ve daha kaliteli bakımın sağlandığı yerler olması için birtakım çözümlere ihtiyaç vardır (2). Sağlık sistemleri mevcut yoğun bakım yatak sayısını, yoğun bakımlarda istihdam edilen personeli ve mali kaynakları maliyet etkin şekilde kullanarak en iyi sağlık hizmetini sunmayı amaçlamaktadır. Bu hedef doğrultusunda Tele-yoğun bakım ünitesi (Tele-YBÜ) uygulamasının kritik hastaların takip ve tedavilerinin düzenlenmesinde, mevcut kaynakların verimli kullanımında ve konusunda uzman kişilerin bilgilerine ulaşılmasını kolaylaştırması sayesinde potansiyel bir çözüm aracı olabileceği düşünülmektedir (3-7).

Tele-YBÜ uygulaması kritik hasta bakımına odaklanan, kritik hastanın değerlendirilmesi, tanı konması, standart tıbbi müdahale/tedavilerin sağlanması ve kritik hastaların

uzaktan sürekli izlenmesine imkan veren görsel-işitsel iletişim ve bilgisayar ağıdır. Tele-YBÜ iki yönlü video, e-posta, akıllı telefonlar, kablosuz araçlar ve diğer telekomünikasyon teknolojisi biçimlerini kullanan, gittikçe artan çeşitli teknolojik uygulamaları ve hizmetleri içerir (8,9).

Tele-YBÜ programları sayesinde yoğun bakım uzmanlarının yer ve zaman sınırlaması olmadan ülkedeki tüm yoğun bakım yataklarına ulaşabileceği, hastalardan gelen tüm verileri elektronik kayıt sistemleri ile değerlendirebileceği ve bu veriler ışığında hastalara kanıta dayalı en iyi tedavi önerilerini sunabilecekleri öngörülmektedir (10,11). Yoğun bakımlardan üretilen kritik hasta verileri ışığında bilime katkı sağlanmasında artış ve bu bilgilerin değerlendirilmesi ile hasta bakımında her geçen gün daha iyi standartlara ulaşılabileceği beklenmektedir. Ayrıca klinik karar destek sistemleri de dahil olmak üzere Tele-YBÜ sistemlerinin yoğun bakımda iyi klinik uygulamaya uyumu artırdığı gösterilmiştir (12). Ancak Tele-YBÜ'nün kullanılması sırasında karşılaşabilecek altyapı yetersizlikleri, hasta-hekim, hekim-hasta yakını ilişkisinin bozulmasının yaratabileceği problemler, hasta verilerinin korunması, depolanması ile ilgili güçlükler, yasal mevzuat ve görev tanımlarının eksikliği gibi problemler bu yeni çözüm stratejisinin potansiyel yararının önüne geçebilir.

Koronavirüs hastalığı-2019 (COVID-19) pandemisi ile birlikte dünyada ve ülkemizde yoğun bakım alanında eğitimli personel (gerek uzman hekim gerek hemşire) ihtiyacının önemi bir kez daha ortaya çıkmıştır. COVID-19 pandemisi süresince tüm sağlık kuruluşları hızlıca yoğun bakım yatak kapasitelerini artırmışlardır. Ancak yetişmiş yoğun bakım çalışanı sayısını (gerek doktor gerekse hemşire) kısa süre içinde artırmak pek mümkün olamamaktadır. Yapılan çalışmalar, yoğun bakımlarda sürekli, alanında uzman personel istihdam edilmesinin, azalmış mortalite ve daha iyi hasta bakımı ile ilişkili olduğunu göstermiştir (13-15). Yetişmiş yoğun bakım çalışanlarına duyulan ihtiyacın kısa sürede arttığı, afet ve salgın hastalık durumlarında kesintisiz ve kaliteli yoğun bakım hizmeti sunmak için Tele-YBÜ altyapısı ve rehberler geliştirilmesi buna benzer süreçlerin daha güçlü yönetilmesine olanak sağlayabilir (16,17).

Ülkemizde 2020 Temmuz ayında T.C. Sağlık Bakanlığı, Sağlık Bilgi Sistemleri Genel Müdürlüğü tarafından duyurusu yapılan yoğun bakım bilgi yönetim sistemi kılavuzu ile Tele-YBÜ kullanılması zorunlu yazılım programları listesine alınmıştır (18). Günümüzde hastane bilgi yönetim sistemi çözümleri sunan kırktan fazla yerel yazılım şirketi mevcuttur. Ancak yoğun bakımda, yazılım çözümleri sunan firma sayısı sınırlı sayıdadır ve T.C. Sağlık Bakanlığı kayıt tescil sisteminde kaydı bulunan aktif çalışan firma sayısı on üç tanedir. Yoğun bakım yazılım çözümleri sunan firmaların önemli bir bölümü bu spesifik alanlardaki bilgi ve ürün eksikliğini son yıllarda yerli girişimci firmaların AR-GE çalışmaları ile kapatmaya çalışmaktadır. Bu durum ülkemizin bu sektörde önemli derecede dışa bağımlılığını ortadan kaldırmaktadır. Yayınlanan sağlık bilgi yönetim sistemi alım kılavuzu ile birlikte kamu, özel ve üniversite hastaneleri bu yönde alım için çalışmalarına başlamış olmasına rağmen gerek mevzuat gerekse sistemin teknik bileşenleri anlamında hastanelere yönelik tam anlamıyla aydınlatıcı bir bilgi kılavuzu yayınlamamıştır. Bunun sonucunda hastanelerin yönetim kadrolarında bu durum hakkında bir bilinmezlik ortaya çıktığı anlaşılmaktadır.

Tüm bilgiler ışığında bu derleme Tele-YBÜ konusunda bilgilendirme yanında ülkemizde Tele-YBÜ uygulanırsa bu konudaki fırsatlarımıza, eksikliklerimize ve kısıtlamalarımıza dikkat çekmek ve bu eksikliklerin tamamlanması için gerekli adımların atılmasını sağlamak amacıyla yazılmıştır.

Tele-YBÜ

Sistematik derleme ve meta-analizler, Tele-YBÜ yaklaşımlarının yoğun bakım ve hastane mortalitesini azalttığını, yoğun bakımda kalış süresini kısalttığını göstermektedir (19-21). Tele-YBÜ uygulamasının YBÜ'de artan maliyet-etkililik oranını tahmin etmek için yapılan çalışmaların sonuçları değerlendirildiğinde Tele-YBÜ'nün çoğu durumda maliyet etkin olduğunu ve bazı durumlarda maliyet tasarrufu sağladığı belirtilmiştir (22). Lilly ve ark. (23) çalışmalarında verimlik düzeyi yüksek Tele-YBÜ programları ile yıllık olgu hacminin artırılabileceği, daha kısa kalış süreleri neticesinde doğrudan maliyetlere göre daha fazla olgu geliri sağlanabileceği sonucuna ulaşmışlardır.

Nüfus yaşlandıkça yoğun bakım kaynaklarına duyulan ihtiyacın, yoğun bakım uzmanı ve yetişmiş yoğun bakım personeline olan talebin önümüzdeki yıllarda artmaya devam edeceği açıktır. Amerika Birleşik Devletleri'nde 64 yaşından büyük hastalar, 64 yaşından küçük olan hastalara göre YBÜ kaynaklarını 3,5 kat daha fazla kullanmaktadır (1). Türkiye İstatistik Kurumu verilerine göre 1950 yılında Türkiye'de 65 yaş üzeri nüfusun tüm nüfusa oranı %3,3 iken, 2017 yılında bu oran %8,5'e yükselmiştir. 2050 yılında ise 65 yaş üzeri nüfusun tüm nüfusa oranının %25,6 olacağı öngörülmektedir (24). 2016 yılında Türkiye'de toplam sağlık harcaması 119.756 milyon TL iken, toplam sağlık harcamasının gayri safi

yurt içi hasılaya oranı %4,6 olarak hesaplanmıştır (25). Yaşlı nüfusun ve sağlık harcamalarının giderek artması, mevcut yoğun bakım yataklarının ve yoğun bakımda hizmet verecek eğitimli personelin verimli kullanılması hem yoğun bakım hizmet kalitesini iyileştirmek hem de maliyetleri azaltmak için zorunludur. Tele-YBÜ yoğun bakım uzmanlarının hastalara ulaşımını sağlayarak bölgesel eşitsizlikleri ortadan kaldırabilir. Hastalardaki fizyolojik bozulmanın erken tanınmasını ve yatak başındaki ekibin katına dayalı uygulamalar eşliğinde tedavi-bakım vermesini sağlayarak yoğun bakım sonuçlarını iyileştirebilir. Ayrıca kritik hastaların üretmiş oldukları birçok verinin değerlendirilmesi sayesinde gerek bilimsel araştırmalar gerekse geleceğe yönelik planlamalarda yol gösterici olabilir (26). Tele-YBÜ sistemleri, yerel servislerin yerini almak için değil, süreçlerin standartlaştırılması yoluyla kaynakların özenle kullanılması için tasarlanmıştır.

Amerika Birleşik Devletleri'nde Tele-YBÜ

Tele-YBÜ sistemlerinin en sık kullanıldığı ülke Amerika Birleşik Devletleri'dir. The American Telemedicine Association (ATA) çeşitli grupları (geleneksel tıp, akademi, teknoloji ve telekomünikasyon şirketleri, e-sağlık, meslek ve hemşirelik dernekleri, tıp toplulukları, hükümet) sağlık hizmetlerinin sunumunu profesyonel, etik ve hakkaniyetli sağlayabilmek adına Tele-tıbbın ilerlemesinin önündeki engelleri aşmak için bir araya getirmiştir. ATA, Tele-tıbbın gelişmesini sağlamak ve hastalara kaliteli standart bir hizmet sunmak için pratik kılavuzlar oluşturmuştur (27). Bu rehberler uygulayıcılara güncel bilgiler ışığında, mevcut kaynaklar ve hasta ihtiyaçları üzerine kurulu etkili ve güvenli bir tıbbi bakım sağlamak için yardımcı olmaktadır. Tele-YBÜ, Tele-tıbbın kritik bakım hastalarında uygulamasıdır. "Tele-YBÜ", "Sanal YBÜ" ve "Uzak YBÜ" terimlerinin tümü aynı bakım konseptini ifade eder; merkezi veya uzaktan temelli bir yoğun bakım ekibi, son teknoloji görsel-işitsel iletişim ve bilgisayar sistemleri aracılığıyla hasta başı yoğun bakım ekibi ve hasta ile ağa bağlanır. Amerika Birleşik Devletleri'nde yetişkin yoğun bakım ünitesi yataklarının %13'ünden fazlası, daha çok akademik ve özel hastanelerde olmak üzere Tele-YBÜ kapsama alanına sahiptir (28).

Tele-YBÜ ile ilgili organizasyon, insan kaynakları yönetimi, sağlık profesyonelleri ile ilgili düzenleyici hususlar (lisanslandırma), hasta hakları, hasta mahremiyeti, gizlilik, hasta kaynaklarının yönetimi, dokümantasyon, kalite-yoğun bakım çıktıları, mali yönetim ve araştırma protokolleri ile ilgili idari rehberler düzenlenmiştir. Ayrıca Tele-YBÜ klinik uygulamasının nasıl yapılacağı ile ilgili rehberler de bulunmaktadır. Tele-YBÜ programları sıklıkla iyileştirilmiş hasta sonuçları, maliyet tasarrufu ve kaynakların verimli kullanılması gibi benzer hedeflere sahiptir. Ancak her programın yapısı kurumsal hedeflere, mevcut teknik ve insan kaynakları türlerine ve klinik hizmet alan yoğun bakım türlerine bağlı olarak değişebilir. Teknik altyapının kurulumu ile ilgili standartların yer aldığı kılavuzlar da mevcuttur. Organizasyon, klinik değerlendirmenin iyileştirilmesi için ses ve görsel netliği optimize eden bir teknoloji ile sağlanmaktadır. Kuruluşlar program hedeflerini desteklemek ve kaliteli hasta bakım hizmetlerini sağlamak için yakın ve uzak ekipmanı bağlamak için yeterli telekomünikasyon bant genişliğine sahiptir. Verilerin aktarımı, paylaşılması ve korunması belirli ulusal standartlar çerçevesinde sağlanmaktadır (8).

Tele-YBÜ Modelleri

Tele-YBÜ modelleri, sürekli izlem, konsültasyon esaslı izlem (planlı bakım) ve yanıtlı (reaktif) bakım modeli olarak üçe ayrılır. Sürekli izlem modelinde 24/12/8 saat boyunca Tele-YBÜ uzmanı ve Tele-YBÜ hemşiresi, hasta başındaki sağlık personeli ile iletişim kurarak hasta takibini gerçekleştirir. Konsültasyon esaslı izlem modelinde, hastayı takip eden primer ekip ile Tele-YBÜ ekibi arasında planlanmış bir bağlantı kurularak düzenli takip-tedavi sağlanır. Yanıtlı (reaktif) bakım modelinde ise çeşitli elektronik tıbbi kayıt sistemleri kullanılır, bu modelde hasta bakımı monitör alarmı gibi sesli veya görüntülü bir uyarı tarafından istenir ve sanal vizit gerçekleştirilir (8,29).

Operasyonel olarak ise merkezi sürekli bakım modeli ve merkezi olmayan bakım modeli olarak sınıflandırılabilir. Merkezi sürekli bakım modelinde Tele-YBÜ lideri, tüm yatak başı yoğun bakım çalışanları ile çalışma saatlerinde açık bir şekilde iletişim sağlamaktadır. Sürekli bakım modellerinin çoğu, 7 gün 24 saat hemşirelik varlığı ile hizmet vermektedir. Sürekli Tele-YBÜ hekiminin var olduğu saatler program hedefleri ve yoğunluk arasındaki dengeye bağlıdır. Yoğun bakım uzmanının varlığı 12-24/7 arasında değişebilir. Tele-YBÜ doktoru program tasarımına bağlı olarak 100-250 hastayı izleyebilir. Tele-YBÜ kayıtlı hemşiresinin hasta personel düzeylerine yönelik mevcut ulusal eğilimleri kayıtlı hemşire başına ortalama 30-35 hastadır ve Tele-YBÜ hemşireliği pozisyonu için minimum 3-5 yıllık yoğun bakım deneyimine ve uzmanlık sertifikasına sahip personelleri önermektedir (8,27).

Merkezi olmayan bakım modelinde programlanmış veya yanıt veren Tele-YBÜ modelleri ve servis saatleri, model yapısına ve kaynağın kullanılabilirliğine göre değişir. Bu modelde tanımlı bir merkezi izleme tesisi yoktur. Merkezi olmayan model tipik olarak uygun yerlere yerleştirilmiş kameralar, hoparlörler ve mikrofonlarla donatılmış bilgisayarları içerir. Dizüstü bilgisayar ve akıllı telefonların kullanıldığı doktor ofisi veya evlerden ulaşım sağlanabilir.

Tele-YBÜ lideri mevcut kanıtlar dahilinde etkinlik, komuta zinciri ve Tele-YBÜ kaynaklarının optimizasyonuna dayanan Tele-YBÜ programı dahilindeki iş akışlarını belirler. İş akışı algoritmaları hem normal hem de beklenmeyen iş modellerini ele almak için adım adım rehberlik sağlayacak şekilde düzenlenmelidir. İş akışları Tele-YBÜ merkezinin iç çalışmalarına özgü planlamalar gerektirebilir. Tele-YBÜ ekibi ve yatak başı ekibinin iletişim yöntemi, hasta durumundaki değişimin aciliyetine ve önceden belirlenmiş iletişim yollarına bağlı olarak değişebilmektedir. Optimum Tele-YBÜ performansı Tele-YBÜ ile yoğun bakım ekibi arasındaki ortak çalışmaya ve entegrasyon düzeyine bağlıdır. Kılavuzlarda personelin rolleri, sorumlulukları, yeterlilik şartları ve eğitimleri ile ilgili düzenlemeler belirtilmeli ve standartlar oluşturulmalıdır.

Türkiye'de Mevcut Durum

Ülkemizde ilk kez 1998 yılında özel bir kanser merkezi Tele-tıp sistemini kullanarak hastalarının yurtdışına gitmeden istediği üniversite ve hekimle iletişim sağlayarak, tanı ve tedavi uygulamaları sağlamıştır. 2002 yılında seyir halindeki gemilerde gemicilere daha iyi tıbbi hizmet sağlanması amacıyla resmi gazetede yönetmelik yayınlanmıştır (30). Bu yönetmelikte gemicilere tedavi sağlanabilmesi için belli merkezlerden radyo ile hekimlerin tıbbi tavsiyede bulunabileceği belirtilmiştir. 2006 yılından itibaren Sağlık Bakanlığı tarafından Tele-tıp uygulamaları ile çalışmalar hızlandırılmıştır. Günümüzde radyolojik raporların yorumlanması, elektrokardiyografi yorumlanması, patoloji sonuçlarının raporlanması ve konsültasyon hizmeti gibi alanlarda Tele-tıp hizmetleri ve teknoloji yoğun bir şekilde kullanılmaya devam etmektedir. Tele-YBÜ ile ilgili çalışmalar gerek özel sektör gerekse bakanlık nezdinde devam etmektedir. Tele-YBÜ ile ilgili ülkemizde yapılması gerenler Tablo 1'de özetlenmiştir.

T.C. Sağlık Bakanlığı Sağlık Hizmetleri Genel Müdürlüğü 2018 verilerine göre; ülkemizde erişkin yoğun bakım yatak sayısı Sağlık Bakanlığı hastanelerinde 11.171, üniversite hastanelerinde 4.049, özel hastanelerde 8.851 olmak üzere toplam 24.071'dir. Çocuk ve yeni doğan yoğun bakım yatak sayısı da dahil edildiğinde bu sayı 38.098'e ulaşmaktadır (31). 10.000 kişiye düşen yoğun bakım yatağı ortalaması 4,6'dır. Her ne kadar ülkemizdeki nüfusa oranla yoğun bakım yatak sayısı yeterli düzeyde olsa da uzman hekim dağılımındaki sıkıntılar devam etmektedir. Sağlık Hizmetleri Genel Müdürlüğü 2018 istatistikleri, Yönetim Hizmetleri Genel Müdürlüğü verilerine göre; Batı Anadolu'da 100.000 kişi başına düşen uzman hekim sayısı 144, Orta Anadolu'da 80, Kuzey Doğu Anadolu'da 69, Güney Doğu Anadolu'da 62'dir (31). Yetişmiş yoğun bakım uzmanı sayısı yaklaşık 700 tanedir ve bölgelere göre dağılımı ise çok daha düşük seviyelerdedir.

Uzman hekim dışında yoğun bakımda çalışan deneyimli hemşire ve personel de kritik hasta bakımında çok önemli bir yere sahiptir. Kritik hasta bakımda standardizasyonun sağlanması, yara bakımı, ağız bakımı, enfeksiyon izolasyon önlemlerine uyulması, hastalara uygun pozisyon verilmesi yoğun bakımda mortalitenin azaltılması için gereklidir. Tele-YBÜ sayesinde deneyimli hemşirelerin daha fazla yoğun bakım yatağına ulaşarak daha kaliteli bakım sunulması sağlanabilir. Yoğun bakımda kritik hastanın bakımında olmazsa olmaz koşul hastanın 7/24 kesintisiz takibinin yapılması ve fizyolojik parametrelerde, mekanik ventilatör verilerindeki değişikliklerin hızlıca farkedilerek gerekli müdahalenin yapılmasıdır. Ancak ülkemizde yoğun bakımda tedavi yaklaşımları, aldıkları eğitim doğrultusunda klinisyene göre değişmekte ve standardizasyonun sağlanması güçleşmektedir. Ayrıca yoğun bakım alanında literatürdeki yeni gelişmeler ve tedavi uygulamalarındaki değişikler her klinisyen tarafından takip edilmesi güç olabilmektedir. Tele-YBÜ sayesinde kritik hastalarda algoritma bazlı tedavi ve takip planlaması ile hem standart yaklaşım uygulanmış

Tablo 1. Tele-YBÜ için ülkemizde yapılması gerekenler
Tele-YBÜ organizasyon ve teknolojik altyapı çalışmalarının tamamlanması
Tele-YBÜ çalışanları için sertifikasyon ve yetki tanımlamaları belirlenmesi
Tele-YBÜ uygulaması için uygulama rehberleri oluşturulması
SGK tarafından Tele-YBÜ uygulamalarının geri ödeme kapsamına alınması
Hem Tele-YBÜ hem de hastaların haklarının korunması için yasal düzenlemelerin hayata geçirilmesi
YBÜ: Yoğun bakım ünitesi, SGK: Sosyal Güvenlik Kurumu

olacak hem de algoritmaya bağlı kalmak gelişebilecek hukuki sorunlar karşısında hekimlerin güçlü olmasını sağlayacaktır. Kliniğimizde altyapı çalışması devam eden Tele-YBÜ işleyişi Şekil 1'de sunulmuştur.

Tele-YBÜ ile gereksiz yoğun bakım yatışlarının önüne geçilmesi ve uygunsuz hasta sevklerinin önlenmesi de sağlanabilir. Bu sayede hem bakım maliyetlerinin azaltılması sağlanmış olacak hem de ihtiyaç halinde boş yoğun bakım yatağına ulaşım kolaylaşacaktır.

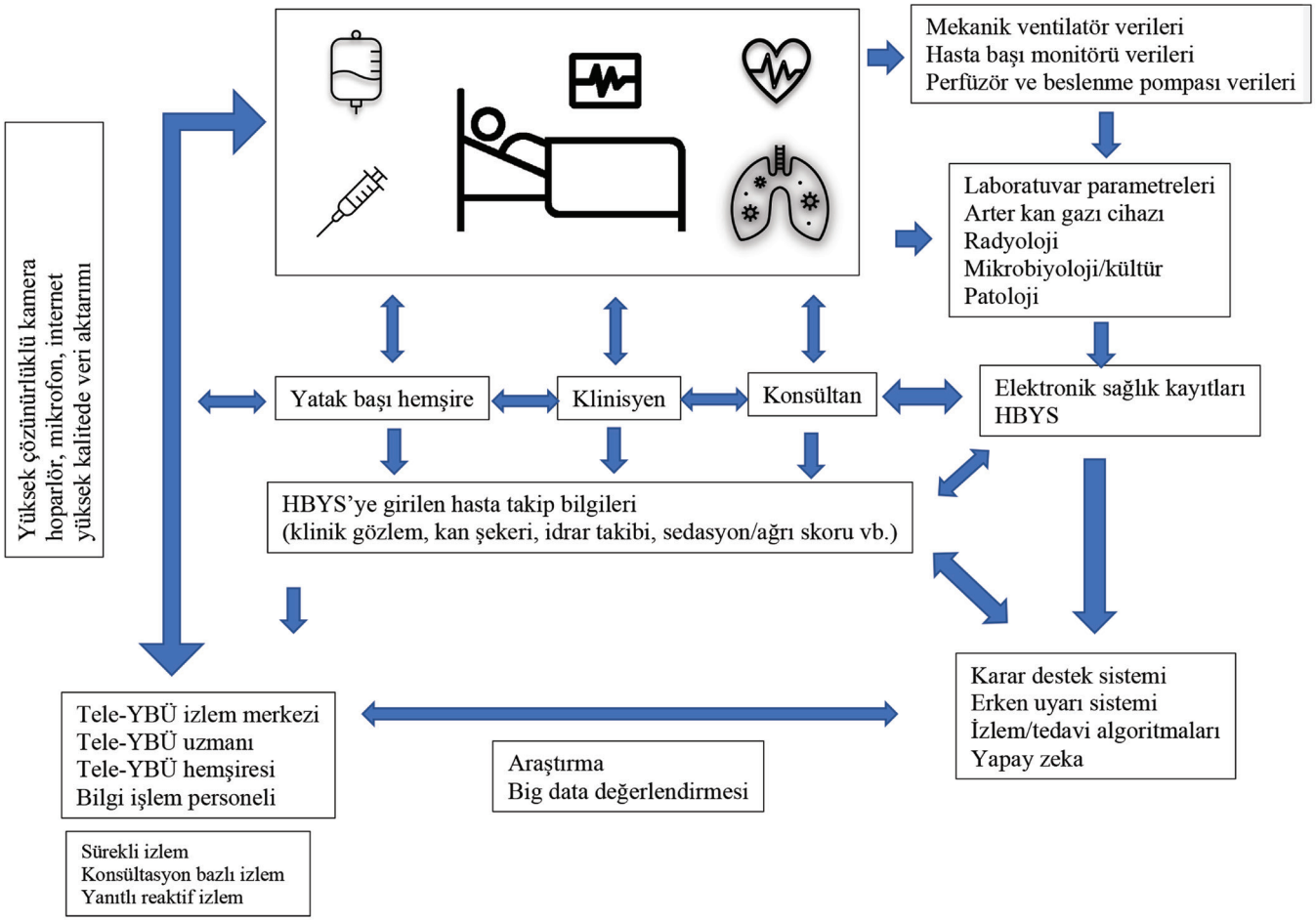
Türkiye'de Neler Yapılmalı?

Tele-YBÜ Organizasyonu

Tele-YBÜ hizmetini sağlayan ve bu hizmetten yararlanan kuruluşlar için ruhsatlandırma, standart işletme ve idari politikaların belirlenmesi gerekmektedir. Tele-YBÜ kurulması ve idare edilmesi için prosedürler oluşturulmalı ayrıca her aşamadaki denetleyici mekanizmaların tanımlanması gerekmektedir. Kuruluşlar arası veri aktarımını sağlayacak teknik altyapı oluşturulmalı, verilerin nasıl depolanacağı, güvenliğinin nasıl sağlanacağı ile ilgili protokoller oluşturulmalıdır. Tele-YBÜ merkezi veya merkezleri oluşturulmalı, Tele-YBÜ kapsamına alınacak yataklar veri aktarımına uygun ekipmanlarla desteklenmelidir.

İnsan Kaynakları Yönetimi

Tele-YBÜ uygulaması kapsamında merkezde ve hasta başında çalışacak yoğun bakım ekibinin rollerini, sorumluluklarını, uygun personel modellerini, çalışma saatlerini, iletişim yöntemlerini, rutin ve acil bakım sunumu ile ilgili prosedürleri ve eskalasyon süreçleri için komuta zincirini açıklayan kılavuzlar oluşturmalıdır. Bu kılavuzlar, hasta popülasyonuna ve hasta başı sağlık uzmanlarının ihtiyaçlarına uygun olmalıdır. Tele-YBÜ personelinin çalışma koşulları, sorumluluk alanları, yetkileri belirlenmelidir. Acil,



Şekil 1. Tele-YBÜ çalışma şeması
HBYS: Hastane bilgi yönetim sistemi, YBÜ: yoğun bakım ünitesi

afet ve salgın durumlarında personelin çalışma koşulları belirlenmelidir.

Sağlık Uzmanları ve Yasal Yetkiler

Tele-YBÜ hizmeti vermek üzere görev yapacak hekim ve hemşirelerin otorite tarafından belirlenen akreditasyon eğitimlerinin tamamlanmasının ardından, yetkilendirilmiş ve lisanslandırılmış olmaları gereklidir. Tele-YBÜ hizmeti alacak kurumların ihtiyaçları doğrultusunda görev tanımları ve yasal sorumlulukları belirlenmelidir. Tele-YBÜ kapsamında çalışacak personelin yeterlilikleriyle ilgili standartları belirlenmeli, gerekli durumlarda re-sertifikasyon programları oluşturulmalı ve hizmet içi eğitimin devamlılığının sağlanması adına planlama yapılmalıdır.

Mahremiyet ve Gizlilik

Tele-YBÜ ile ilgili geliştirilecek politikalar ve prosedürler yoğun bakım hastasının mahremiyet ve güvenlik gereksinimlerini hem teknolojik hem de insan hakları açısından ele almalıdır. Tele-YBÜ hizmeti alan tüm yoğun bakım hastaları ve aileleri bu programın hasta yönetimi üzerindeki rolü, teknolojinin kullanımı ve gizliliğin nasıl korunduğu konusunda bilgilendirilmelidir.

Hasta verilerinin ve bilgilerinin sistemden çalınması ve sızdırılması gibi sorunlar karşısında gerek donanımsal gerek fiziksel anlamda önlemler alınmalıdır. Tele-YBÜ ilişkisinin kurulmasından önce toplanan verilerin nasıl, nerede, ne kadar süreyle depolanacağı, işlenip işlenmeyeceği, kimlerin bu bilgilere ulaşabileceği, gizliliğin nasıl korunacağı, bilgilerin hangi koşullarda ne amaçlarla kullanılabileceği gibi konuların açıklığa kavuşturulması gereklidir.

Mali Yönetim

Tele-YBÜ hizmetini alacak kuruluşlar altyapı kurulum maliyeti, donanım, yazılım, veri hatları, lisans ücretleri, personel giderleri, sarf malzemeleri ve işletme maliyetlerini kapsayan bütçe planı oluşturmalıdır. Tele-YBÜ hizmetleri Sosyal Güvenlik Kurumu (SGK) tarafından geri ödeme kapsamına alınmalı ve altyapısı oluşturulmalıdır. Geri ödemeler ile ilgili tüm paydaşların (Sağlık Bakanlığı, SGK, yoğun bakım uzmanlık dernekleri, hukuk alanında yetki sahibi kuruluşlar vb.) ortak çalışacağı komisyonlar oluşturulmalıdır.

Hasta Kayıtlarının Yönetimi ve Dokümantasyon

Tele-YBÜ hizmeti sunulurken sağlık kayıtlarının belgelendirilmesi, depolanması ve geri alınması için organizasyonel, endüstri ve hükümet standartlarıyla tutarlı süreçler ve politikalar kullanılmalıdır. Klinik desteği artırmak ve kritik hastanın bakımına sürekliliğini sağlamak için hasta bilgi sistemleri arasında kesintisiz bilgi akışını sağlamak için mevcut sistemlerin birlikte çalışabilirliğe öncelik verilmelidir. Tele-YBÜ ile hastanenin elektronik tıbbi kayıtları, laboratuvar, eczane ve başucu monitör sistemi arasındaki doğrudan arayüzler yüksek standartta birlikte çalışabilir olmalıdır. Tele-YBÜ kaynaklı klinik dokümantasyona ilişkin politika ve prosedürler, kurumsal yasal ve risk yönetimi gözetimine uygun olarak oluşturulmalıdır.

Hasta Hakları ve Sorumlulukları

Hastalar ve aileler Tele-YBÜ uygulamasının hasta bakımındaki rolü hakkında bilgilendirilmeli ve eğitilmelidir. Sağlık çalışanları, hasta ve aile mahremiyetinin sağlanması, kültürel hususlara duyarlılığın sağlanması için işitsel ve görsel teknolojinin kullanımı konusunda özellikle dikkatli olmalıdır. Tele-YBÜ'nün rolü ve/veya işitsel-görsel teknolojinin bileşenleri ile ilgili endişeler hasta/aile, Tele-YBÜ ve hasta başında görevli ekibin iş birliği ile ele alınmalıdır. Bireyin özerkliğinin sağlık alanına yansıması hastadan aydınlatılmış onam alınması ile olanaklıdır. Tele-YBÜ uygulamaları sürecinde aydınlatılmış onamın tüm öğelerinin (bilgilendirme, anlama, gönüllülük, yeterlilik ve onam) nitelikli bir şekilde gerçekleştirilmesi konusunda tüm paydaşlarla ortak olarak çalışılmalıdır.

Kalite ve Sonuçlar

Kalite göstergeleri Tele-YBÜ hizmetlerinin sağlanması için idari, teknik ve klinik bileşenleri içerecek şekilde yeni gelişen teknolojiye, uygulama ilkelerine, kanıta dayalı kılavuzlara ve klinik araştırmaya veya değişen hizmet gereksinimlerine dayalı olarak teknik, programatik ve klinik değişiklikler yapmak için kullanılmalıdır. Tele-YBÜ personeli, yöneticileri ve YBÜ sağlık uzmanları, paylaşılan hedeflere ek olarak YBÜ ve Tele-YBÜ'nün programa farklı katkılar sağlayabileceklerini kabul ederek belirli program çıktılarını karşılamak için uyumlu çalışmaları gerekmektedir. Hem idari hem de operasyonel personel analizi için kalite ölçütlerinin ve sonuçlarının

raporlanması ve yaygınlaştırılmasına yönelik bir süreç tanımlanmalıdır.

Araştırma Protokolleri

Tele-YBÜ'nün hasta bakımı ve klinik sonuçlara katkılarını içeren bilimsel araştırmalar kuruluş tarafından desteklenmeli ve teşvik edilmelidir. Tele-YBÜ uygulaması ile elde edilecek kritik hasta verileri birden fazla YBÜ'nün verilerini yansıtacak olup bilimsel anlamda gelişime katkı sağlayacaktır.

Hukuksal Durum

Tele-YBÜ uygulamasının hukuki altyapısı uygun hale getirilmeli, konuyla ilgili paydaşların ortak çalışması sonucunda kurum ile yönetimsel ve işleyiş kılavuzları oluşturulmalıdır. Ülkemiz hukuk sisteminde hekimin hastasını fiziksel olarak görmeden teşhis ve tedavi uygulaması genel olarak yasak ve hatta olayın özelliğine göre görevi kötüye kullanma veya evrakta sahtecilik suçu olarak tanımlanabilir. Ancak Doğramacı (32) tarafından belirtildiği üzere hukuksal anlamda hekimin bizzat muayene yükümlülüğünün uzaktan muayene, tanı, tedavi ve değerlendirme yasağı anlamı taşımayacağı, hekimin bilgi ve iletişim teknolojileri vasıtasıyla doğrudan iletişime geçerek hastasını muayene ve tedavi yetkisine sahip olduğu, yani hukuk sistemimiz Tele-tıp uygulamalarına uygunluk verdiği anlaşılmaktadır. Aynı şekilde konsültasyon hizmetleri de hastayı fiziksel olarak görmeden gerçekleştirilebilir. Uzaktan muayeneye ilişkin yetki ve sorumluluk tedaviyi yürüten hekimde olmasına rağmen Tele-YBÜ uygulaması ile ilgili merkezdeki hekim ve konsültan hekimler ile ilgili standartların belirlenmesi gereklidir. Hastaları yatak başında değerlendirecek olan hekimin ve Tele-YBÜ hekiminin görev tanımı ve yetki alanları belirlenmelidir. Tele-YBÜ uygulamalarıyla hastaya uzaktan tedavi önerileri sunması ile ilgili yasal düzenlemelerin yapılması ve hizmet sağlayıcıların standartlarının belirlenerek ruhsatlandırılmasına gerek vardır. Ülkemizde konuya ilişkin herhangi bir yasal düzenleme olmadığından bir zarar oluşması durumunda sorumluluğun kimde olduğu ve nasıl tazmin edileceği belirlenmelidir. Ülkemizde hukuki anlamda Tele-tıp uygulamalarında hasta tüketici olarak kabul edilmektedir. Tele-tıp hizmetlerinin tüketici hukukuna özgü mesafeli sözleşmeler ile ilgili olduğu için gerekli yasal düzenlemelerin yanında sağlık hizmetlerinin tüketici hukuku kapsamından çıkarılması gerektiği vurgulanmaktadır (32).

Etik Problemler

Tele-YBÜ uygulamasının önümüzdeki yıllarda dünyada ve ülkemizde artarak kullanıma gireceği beklenmektedir. Bu yeni teknolojinin sağlamış olduğu faydalar yanında etik anlamda endişeler de oluşmaktadır. Bu endişelerin başında hasta-hekim ilişkisi ve güven duygusunun azalabileceği gelmektedir. Hekim ve hasta doğru tanı ve tedaviyi gerçekleştirmek için karşılıklı iletişim halindedir. Oysa Tele-YBÜ uygulamalarında iletişimin bir cihaz üzerinden sağlanmasının nitelikli hasta-hekim ilişkisini olumsuz etkileyeceği öngörülebilir. Sağlık hizmetine erişimdeki adaletsizliğin giderilmesine katkı sunacağı gerekçesiyle kullanımı yoğunlaşan Tele-YBÜ uygulamalarında nitelikli, etkin hasta-hekim ilişkisinin kurulabilmesinin zorlukları ve sınırlılıkları olduğu açıktır. Ancak bu durum yatak başında çalışan Tele-YBÜ personeli tarafından sorun olmaktan çıkarılabilir. İkinci bir endişe konusu hastanın ve hekimin mahremiyet hakkının korunmasıdır. Tele-YBÜ uygulamaları sırasında üçüncü kişilerin ortamda bulunması engellenmeli her koşulda hasta mahremiyeti korunmalıdır. Aynı şekilde her zaman her koşulda ulaşılabilir hale gelecek olan Tele-YBÜ hekiminin mahremiyet hakları da korunmalıdır. Bir diğer önemli konuda özerkliğin korunması adına Tele-YBÜ ile ilgili aydınlatılmış onam formları titizlikle düzenlenmeli ve hasta yakınları belirli aşamalarda bilgilendirilmelidir.

Sonuç

Gelişen teknoloji ile birlikte Tele-YBÜ uygulamaları gün geçtikçe gelişmekte ve günlük rutinimizde yerini almaya başlamaktadır. Tele-YBÜ sistemi ile kaynakların verimli kullanılması, yoğun bakım uzmanlarının ülke çapındaki tüm hastanelerdeki yoğun bakımlara ulaşabilmesi, güncel kılavuzlara yönelik tedavilerin standardize edilmesi amaçlanmaktadır. Ancak teknolojinin getirdiği kolaylıklar yanında Tele-YBÜ uygulaması ile ilgili yaşanabilecek problemlerin önlenmesi hem hastaların hem de sağlık çalışanlarının haklarının korunması adına tüm paydaşların katılımının sağlanarak hızla yasal, hukuksal ve organizasyonel düzenlemelerin yapılmasına ihtiyaç vardır.

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ORIGINAL RESEARCH / *ÖZGÜN ARAŞTIRMA*

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Reasons for Hospitalisation, Sepsis Development and Mortality Among Syrian Patients in an Intensive Care Unit

Suriyeli Hastaların Yoğun Bakım Ünitesinde Yatış Nedenleri, Sepsis Gelişimi ve Mortalite

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ABSTRACT *Objective:* This study aims to investigate the reasons for the hospitalisation of Syrian patients in an intensive care unit (ICU), the development of sepsis, relevant causes of pathogens and mortality rates.
Materials and Methods: We conducted this study between 2012 and 2016. Patient information was analysed retrospectively from records and files in the information system.
Results: During the study period, 139 Syrian patients were hospitalised in an ICU. The most common ICU diagnoses were respiratory tract infection (29 patients: 20.9%) and trauma (26 patients: 18.7%). Of these patients, 35 were diagnosed with sepsis during their treatment in the ICU. *Acinetobacter baumannii* and *Escherichia coli* were isolated in the culture of the patients with sepsis (17, 12, respectively). *A. baumannii* was most common in tracheal cultures and *E. coli* in urine cultures. In addition, seven patients were diagnosed with sepsis on their first admission to the hospital. H1N1 was detected in two patients, *Streptococcus pneumoniae* in three, *Haemophilus influenzae* in one, and *Staphylococcus aureus* and aspergilloma in another patient. While 45 of 139 patients died, 28 of 35 patients diagnosed with sepsis died. Acute Physiologic Assessment and Chronic Health Evaluation II scores, the duration of mechanical ventilation, the number of days spent in the ICU was all higher in the deceased patients than in the surviving patients ($p<0.001$, $p<0.001$, $p<0.001$, respectively).
Conclusion: Respiratory diseases were the most common causes of Syrian patients' hospitalisation in the ICU and for developing sepsis. For these patients, sepsis remained an important factor for mortality.
Keywords: Syrian patients, sepsis, mortality, intensive care unit

ÖZ *Amaç:* Suriyeli hastaların yoğun bakım ünitesine (YBÜ) yatış nedenlerini, sepsis gelişimlerini, sepsise neden olan patojenleri ve hastaların ölüm oranlarını araştırmaktır.
Gereç ve Yöntemler: Çalışmamız 2012-2016 tarihleri arasında YBÜ'de yapıldı. Hastane bilgi sistemindeki kayıt ve dosyalar geriye dönük olarak analiz edildi.
Bulgular: Çalışma süresi içinde 139 Suriyeli hasta YBÜ'ye yatırıldı. En sık YBÜ'ye yatış tanıları solunum yolu enfeksiyonu (29 hasta: %20,9) ve travma (26 hasta: %18,7) idi. Bu hastaların yoğun bakım tedavileri sırasında 35 hasta sepsis tanısı aldı. Sepsis tanısı alan hastaların kültürlerinin 17'sinde *Acinetobacter baumannii* ve 12'sinde *Escherichia coli* üredi. *A. baumannii* trakea kültürlerinde, *E. coli* idrar kültürlerinde en yaygındı. Ayrıca, yedi hastaya hastaneye müracaat ettiği ilk anda sepsis tanısı kondu. Bu hastalardan 2'sinde H1N1, 3'ünde *Streptococcus pneumoniae*, 1'inde *Haemophilus influenzae*, 1'inde *Staphylococcus aureus* ve aspergilloma saptandı. YBÜ'de yatan 139 hastanın 45'i ölmüş iken sepsis tanısı alan 35 hastanın 28'i öldü. Akut Fizyoloji ve Kronik Sağlık Değerlendirmesi II skorları, mekanik ventilasyon süresi, YBÜ yatış süresi ölenlerde sağ kalan hastalara göre daha yüksekti ($p<0,001$, $p<0,001$, $p<0,001$).
Sonuç: Suriyeli hastalarda en sık YBÜ yatış ve sepsis gelişme nedeni solunum yolu enfeksiyonlarıydı. Bu hastalarda sepsis mortalite için önemli bir faktördü.
Anahtar Kelimeler: Suriyeli hastalar, sepsis, mortalite, yoğun bakım ünitesi

Introduction

More than 43,3 million people worldwide are fleeing war, and there are some political or ethnic pressures regarding taking refugees in another country (1,2). The war in Syria is tragically deadly and devastating enough to affect not only Syria's neighbors; Lebanon, Egypt, Iraq, and Turkey, but also European nations bordering Turkey (3,4). Since March, 2016, Turkey, with 2,7 million Syrians, has been one of the countries who have hosted the most refugees (3-5). There are approximately 300,000 refugees living in camps in the vicinity of Turkish cities near the Syrian border (Şanlıurfa, Gaziantep, Kilis, Hatay, Kahramanmaraş, Adıyaman, Adana, and Osmaniye). Additionally, there are about 2,440,000 refugees living outside the camps, who have spread from the south of Turkey to her central and western cities, like İstanbul, Ankara, and İzmir (4-6).

The disease profiles of refugees, who were at first exposed to traumatic injuries as a result of violent conflicts, then made dangerous journeys to other countries. They would take refugees in different from the disease profiles of the local people, both because of regional differences in some infectious diseases and insufficient living conditions in the nations to which the refugees had migrated (7,8).

In studies conducted in the early stages of the migration, the most important reasons for hospitalization in the intensive care units (ICUs) were traumatic pathologies and high-velocity gunshot wounds (9,10). Later, an increase was reported in reasons like respiratory system, cardiac, and tumoral pathologies (11,12). As far as we know, there are no studies to date on the pathogen profiles and sepsis rates of Syrian patients in the ICUs.

The aim of this study was to perform a general evaluation of the indications of hospitalization among Syrian patientsin ICU, and to analyze these patients' rates of sepsis development, effective pathogens, and mortality rates and causes.

Materials and Methods

The study was carried out between June 1, 2012, and December 31, 2016, in two separate 14-bed Anesthesiology and Reanimation Intensive Care Units (ARICUs). Approval for the study (decision no: 04, date: 05.04.2017) was obtained from Kahramanmaraş Sütçü İmam University's Ethics Committee.

Of the 4,912 patients hospitalized in the units, 300 (6.1%) were Syrian. A total of 139 (46.3%) patients whose records could be accessed were included in the study. Patient information was analyzed retrospectively from the records and patient files in the hospital's information management system.

There were a plethora number of factors for the evaluation stage. Namely, the following were considered for this purpose: patients' ages, gender, diagnoses at hospitalization, comorbid diseases, mechanical ventilation (MV) and number of days on MV, surgeries, diagnoses of sepsis, presence of sepsis originating from intensive care, areas from which cultures were obtained, microorganisms found, antibiotics used, number of days in the ICU, mortality rates, and Acute Physiologic Assessment and Chronic Health Evaluation (APACHE) II scores. For the patients who developed sepsis, the following data were recorded upon admission: The blood glucose level, the Sequential Organ Failure Assessment (SOFA) score and presence or absence of sepsis, the number of days before sepsis set in, the neutrophil/lymphocyte ratio, and the present microorganisms and the parts of the body where they were being produced.

Definitions

In the study, patients were considered septic when they had SOFA scores of 2 or more and septic pathogens were found, as defined in the international guidelines of the Surviving Sepsis Campaign.

A community acquired infection was detected within the first 48-72 hours of hospitalization or acquired in daily life without significant immune deficiency (11).

Statistical Analysis

The SPSS 24.0 program (IBM Corporation, Armonk, New York, United States) was used in analysis of the variables. The Shapiro-Wilk test was used to determine the normal distribution of the data. The Mann-Whitney U test was used with the Monte Carlo simulation technique in the comparison of two independent groups with regard to the quantitative data. For comparing categorical variables with one another, Pearson's chi-squared test, Fisher's Exact test, and the Fisher-Freeman-Halton test were performed with the Exact and Monte Carlo Simulation techniques. Column ratios were compared to one another and expressed in accordance with the Benjamini-Hochberg adjusted p-values. An odds ratio with a 95% confidence interval was used to show the odds of an outcome occurring in

the presence of an exposure as compared to the odds of the outcome occurring in the absence of the exposure. Quantitative variables are shown in the tables as median (minimum/maximum), and categorical variables as n (%). Variables were examined at a confidence level of 95%, and a p-value was accepted as less than 0.05.

Results

General Findings

The mean age of the 139 patients who were included in the study was 46 (1-90), and 90 (647%) of them were male. Diagnoses at the initial hospitalization included 20 patients (14.4%) with gunshot wounds and 29 (20.9%) with respiratory tract infections. The patients were separated into two groups; survivor and deceased. A total of 45 (32.4%) of the patients died in the ARICU.

APACHE-II scores, the length of time connected to MV, and the number of days hospitalized in intensive care were all found to be greater in the deceased patients than in the living patients ($p<0.001$, $p<0.001$, and $p<0.001$, respectively). Twenty-three (24.5%) of the survivors were trauma patients, and 16 (35.5%) of the deceased were respiratory disease patients. Surgery had been performed on 51 (54.2%) of the surviving patients and on 16 (17%) of the deceased ones ($p=0.047$). The distributions of the patients according to their diagnoses and socio-demographic characteristics are given in Table 1.

In 43 patients (30.9%), the most common comorbid diseases after their initial diagnosis was cardiac disease (Table 2).

Antimicrobial Therapy, Infection Type and Sepsis Findings

Of the living patients, 62 (66%) received single antibiotics while 27 (60%) of the deceased patients received multiple antibiotics ($p<0.001$). The blood cultures were positive in 8 (8.5%) of the surviving patients and the trachea cultures were positive in 5 (5.3%). In addition, 15 (33.3%) of the deceased patients' blood cultures were positive, as were 18 (40%) of their trachea cultures ($p<0.001$ and $p<0.001$, respectively) (Table 3).

While 89 (48.9%) of all the patients did not produce microorganisms, *Acinetobacter baumannii* was found in 17 (9.3%) and *Escherichia coli* in 15 (8.2%). Of the patients who developed sepsis, 17 (23.6%) produced *A. baumannii* and 12 (16.7%) *E. coli. A. baumannii* was detected most frequently in trachea cultures and *E. coli* in urine cultures (Table 4).

The 35 patients with sepsis were divided into two groups: Those who survived (n=7) and those who did not (n=28). The patients' clinical information is given in Table 5.

Ten of the septic patients (28.6%) had diseases of the respiratory system, seven (20%) had gunshot injuries, and five (14.3%) were diagnosed with trauma (Table 6).

β-lactam/β-lactamase inhibitor-type antibiotics were used on 65 (28.6%) of the patients, while 2nd, 3rd, and 4th generation cephalosporins were used on 43 (18.9%). Of the patients with sepsis, carbapenems were used on 17 (19.5%), colistin on 16 (18.4%), and tigecycline on 11 (12.6%) patients (Table 7).

A Community-acquired Infection

Seven patients were diagnosed with sepsis at the time of hospitalization. Oseltamivir treatment was begun on two patients with initial diagnoses, later confirmed, of H1N1. *Streptococcus pneumoniae* was found in three patients, *Haemophilus influenzae* in one, and *Staphylococcus aureus* and aspergilloma in one.

Discussion

In our study, we investigated the reasons for hospitalization, the sepsis development rates, the pathogens causing sepsis, and the mortality rates and causes for Syrian patients in ICU.

In the early period of the studies relating to the Syrian civil war, patients underwent surgery due to trauma (9,10). In a study evaluating arrivals of both refugees and locals at emergency service units, it was reported that refugees' medical emergencies included high rates of many types of trauma, especially of the head, neck, and extremities, as compared to those rates for local residents (9). Another study showed that the most common surgical site regions were head and neck (52.7%), followed by the thorax and abdomen (27.8%), and multiple-system injuries (13.8%) (10). In another study on trauma, 24.2% of the patients had head and neck trauma, and 15.3% had chest, abdomen and back trauma (13). Duramaz et al. (14) reported that injuries were more common in lower extremities, upper extremities and axial skeleton. Blunt trauma was significantly higher in upper extremity injuries compared to other types of injuries. In a study conducted in central Europe, the most common reasons for admission among Syrian patients were

surgery (43.3%), medical (36.5%) and psychiatric (15.6%). In addition, the most common acute infectious diseases (43.9%) were respiratory, gastrointestinal and urinary tract infections (15).

In our study, it was seen that the most important causes of hospitalization were pathologies of the respiratory system (20.9%) trauma (18.7%) and gunshot wound (14.4%). Besides, 67 (48.2%) of our patients underwent surgical intervention. 44 (65.7%- multiple injuries) of patients had thorax and abdominal injuries. It was further noted that tumoral causes, which were not mentioned in the literature, accounted for as high a rate as 10.1%. In the present study,

Table 1. Surviving and deceased patients' demographic and clinical characteristics

		Surviving (n=94)	Deceased (n=45)	Total (n=139)	p	OR (95% CI)
Age	Median (min/max)	43 (1/87)	54 (3/90)	46 (1/90)	0.068	-
APACHE-II	Median (min/max)	11 (6/29)	29 (9/38)	13 (6/38)	<0.001	-
DMV	Median (min/max)	0 (0/43)	7 (0/270)	1 (0/270)	<0.001	-
DIC	Median (min/max)	3 (1/46)	9 (1/270)	4 (1/270)	<0.001	-
Sex						
Female	n (%)	36 (38.3)	12 (26.7)	48 (34.5)	0.189	-
Male	n (%)	58 (61.7)	33 (73.3)	91 (65.5)		
Province-referral from						
Patient from other province	n (%)	7 (7.4)	5 (11.1)	12 (8.6)	0.588	-
Same-province patient	n (%)	78 (83.0)	34 (75.6)	112 (80.6)		
Hatay State Hospital	n (%)	9 (9.6)	6 (13.3)	15 (10.8)		
Diagnosis						
Gunshot wound	n (%)	11 (11.7)	9 (20.0)	20 (14.4)	0.004	-
Respiratory disease	n (%)	13 (13.8)	16 (35.6)	29 (20.9)		3.4 (1.5-8.01)
Renal disease	n (%)	0 (0.0)	2 (4.4)	2 (1.4)		-
Trauma	n (%)	23 (24.5)	3 (6.7)	26 (18.7)		4.5 (1.3-16.02)
Cardiac disease	n (%)	5 (5.3)	5 (11.1)	10 (7.2)		-
Cancer	n (%)	12 (12.8)	2 (4.4)	14 (10.1)		-
Cerebrovascular disease	n (%)	6 (6.4)	3 (6.7)	9 (6.5)		-
Intoxication	n (%)	6 (6.4)	1 (2.2)	7 (5.0)		-
Gastrointestinal disease	n (%)	10 (10.6)	2 (4.4)	12 (8.6)		-
Other	n (%)	8 (8.5)	2 (4.4)	10 (7.2)		-
MV usage						
No	n (%)	55 (58.5)	2 (4.4)	57 (41.0)	<0.001	-
Yes	n (%)	39 (41.5)	43 (95.6)	82 (59.0)		30.3 (6.9-132.6)
Surgery						
No	n (%)	43 (45.7)	29 (64.4)	72 (51.8)	0.047	-
Yes	n (%)	51 (54.3)	16 (35.6)	67 (48.2)		2.1 (1.03-4.5)
Anatomical region injured						
Head	n (%)	6 (11.8)	6 (37.5)	12 (17.9)	0.091	-
Thorax and abdomen	n (%)	36 (70.6)	8 (50.0)	44 (65.7)		
Extremities	n (%)	9 (17.6)	2 (12.5)	11 (16.4)		

Mann-Whitney U test (Monte Carlo), Pearson's chi-squared test (Exact/Monte Carlo), Fisher-Freeman-Halton test (Monte Carlo), Fisher Exact test (Exact), odds ratio (95% confidence interval). OR: odds ratio, CI: confidence interval, min: minimum, max: maximum, DMV: days on mechanical ventilator, DIC: days in intensive care, MV: mechanical ventilation

Table 2. Comorbid diseases	
	n=163 (%) *X
None	67 (41.1)
Cardiac diseases	43 (26.4)
Diabetes mellitus	17 (10.4)
Renal diseases	15 (9.2)
Respiratory diseases	10 (6.1)
Cerebrovascular diseases	6 (3.7)
Other	5 (3.1)
Total	163
*One patient has more than one disease	

respiratory failure was found to be the most important cause (35.6%) of mortality. In the diagnostic-based evaluation of the patients, it was observed that the most septic complications were in patients with respiratory failure, and it was thought that this had an effect on the development of mortality (28%). In the correlation analysis we performed, the most important factor affecting mortality was the development of sepsis. In all Syrian patients, the overall mortality rate was 32.37%, while the same rate in Syrian patients with sepsis was 80%.

One of the aims of our study was the evaluation of the mortality and of the pathogens that cause sepsis development

Table 3. Evaluation of cultures taken from surviving and deceased patients						
		Surviving (n=94)	Deceased (n=45)	Total (n=139)	p	OR (95% CI)
Culture taken from						
None taken	n (%)	77 (81.9)	14 (31.1)	91 (65.5)	<0.001	-
Tracheal aspirate	n (%)	2 (2.1)	8 (17.8)	10 (7.2)		22 (4.2-114.6)
Blood	n (%)	5 (5.3)	7 (15.6)	12 (8.6)		7.7 (2.1-27.7)
Urine	n (%)	0 (0.0)	2 (4.4)	2 (1.4)		-
Injury site	n (%)	6 (6.4)	3 (6.7)	9 (6.5)		-
Two or more regions	n (%)	4 (4.3)	11 (24.4)	15 (10.8)		15.1 (4.2-54.3)
Microorganism found						
None	n (%)	74 (78.7)	15 (33.3)	89 (64.0)	<0.001	-
Single microorganism	n (%)	10 (10.6)	15 (33.3)	25 (18.0)		7.7 (2.9-20.4)
Multiple microorganisms	n (%)	10 (10.6)	15 (33.3)	25 (18.0)		7.7 (2.9-20.4)
Antibiotic administered						
None	n (%)	12 (12.8)	1 (2.2)	13 (9.4)	<0.001	-
Single antibiotic	n (%)	62 (66.0)	17 (37.8)	79 (56.8)		3.2 (0.4-27.1)
Multiple antibiotics	n (%)	20 (21.3)	27 (60.0)	47 (33.8)		16.2 (1.9-135.01)
Urine culture						
Negative	n (%)	89 (94.7)	38 (84.4)	127 (91.4)	0.056	-
Positive	n (%)	5 (5.3)	7 (15.6)	12 (8.6)		-
Blood culture						
Negative	n (%)	86 (91.5)	30 (66.7)	116 (83.5)	<0.001	-
Positive	n (%)	8 (8.5)	15 (33.3)	23 (16.5)		5.4 (2.1-13.9)
Tracheal culture						
Negative	n (%)	89 (94.7)	27 (60.0)	116 (83.5)	<0.001	-
Positive	n (%)	5 (5.3)	18 (40.0)	23 (16.5)		11.9 (4.02-34.9)
Injury site culture						
Negative	n (%)	85 (90.4)	42 (93.3)	127 (91.4)	0.751	-
Positive	n (%)	9 (9.6)	3 (6.7)	12 (8.6)		-
Sepsis						
No	n (%)	86 (91.5)	19 (40.4)	104 (75.5)	<0.001	-
Yes	n (%)	7 (7.5)	28 (59.6)	35 (24.5)		14.7 (5.8-37.5)
Mann-Whitney U test (Monte Carlo), Pearson's chi-squared test (Exact/Monte Carlo), Fisher-Freeman-Halton test (Monte Carlo), Fisher Exact Test (Exact), odds ratio (95% confidence interval). OR: odds ratio, CI: confidence interval						

in Syrian patients. In a multicenter international study, the hospital mortality rate of sepsis patients was found to be 47.2% in Africa and 13.1% in North America (16). Another study showed that mortality rate of severe sepsis was 36.7 % in South/Central America and 44% Eastern Europe (17). In Uganda, hospital mortality associated with sepsis was 43% (18), in Thailand 50% (19). In a study conducted in an ICU in Turkey, the sepsis mortality rate was reported as 87.3%. The most commonly isolated agent in the development of sepsis, according to that study, was Gr (-) bacteria, at 65.9 % (20). In our study, it was seen that the sepsis mortality rates of the Syrian patients were similar to those of the local population (80%).

The most common pathogen among sepsis patients was *A. baumannii*, the second most common was *E. coli*. While death from sepsis in high-income countries has been 30%-40% in the last decade and is steadily falling (21,22), the mortality rate in low-income regions of the world has risen as high as 80% (23-26). In a multicenter study conducted in Turkey, the mortality was found to be very high among patients with sepsis and septic shock in the ICU (55.7% and 70.4%, respectively). The most isolated microorganism was *Acinetobacter* spp. (33.7%) and approximately 74.8% of Acinetobacters were resistant to carbapenems (27). In our study, the rate of *Acinetobacter* spp. in all Syrian patients was 9.3% and 23.6% in patients with sepsis. Carbapenem use rates were 11.9% in all Syrian patients and 19.5% in sepsis patients.

In the study of Turktan et al. (11), 37 patients in an ICU were hospitalized because of infection. The most common community infection was pneumonia (49%) and urinary infection (16.3%). In eight of them, the infection developed as a result of community-acquired microorganisms, the most important of which was *Mycobacterium tuberculosis*. This situation was thought to have been caused by the difficulty of the refugees' living conditions, and high population density of their living quarters. *E. coli* was the second most common pathogen reported in that study (11). In our study, although *M. tuberculosis* was not observed as a causative pathogen, it was noted that at the time of admission, seven patients had

Table 4. Distribution of microorganisms detected, by culture type

	All patients n=139	Sepsis patients n=35	Blood culture	Tracheal culture	Urine culture	Injury site culture
Microorganism	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
None detected	89 (48.9)	-	-	-	-	-
Acinetobacter baumannii	17 (9.3)	17 (23.6)	5 (17.8)	9 (34.7)	3 (21.4)	3 (42.8)
Streptococcus pneumoniae	3 (1.6)	3 (4.2)	2 (7.1)	0 (0.0)	1 (7.1)	0 (0.0)
Candida fungus	9 (4.9)	8 (11.1)	4 (14.3)	2 (7.7)	2 (14.4)	0 (0.0)
MSSA	6 (3.3)	4 (5.6)	2 (7.1)	1 (3.8)	1 (7.1)	0 (0.0)
CNS	12 (6.5)	5 (6.9)	4 (14.3)	0 (0.0)	1 (7.1)	0 (0.0)
Escherichia coli	15 (8.2)	12 (16.7)	1 (3.6)	3 (11.5)	6 (42.9)	2 (28.6)
Klebsiella pneumoniae	8 (4.4)	7 (9.7)	0 (0.0)	6 (23.2)	0 (0.0)	1 (14.3)
VRE	1 (0.6)	1 (1.4)	1 (3.6)	0 (0.0)	0 (0.0)	0 (0.0)
Stenotrophomonas maltophilia	4 (2.2)	4 (5.5)	3 (10.7)	1 (3.8)	0 (0.0)	0 (0.0)
Pseudomonas aeruginosa	7 (3.9)	4 (5.5)	1 (3.6)	2 (7.7)	0 (0.0)	1 (14.3)
Enterococcus	4 (2.2)	3 (4.1)	2 (7.1)	1 (3.8)	0 (0.0)	0 (0.0)
Haemophilus influenzae	1 (0.6)	1 (1.4)	0 (0.0)	1 (3.8)	0 (0.0)	0 (0.0)
Aspergillus fumigatus	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Enterobacteriaceae	2 (1.1)	1 (1.4)	1 (3.6)	0 (0.0)	0 (0.0)	0 (0.0)
MRSA	1 (0.6)	1 (1.4)	1 (3.6)	0 (0.0)	0 (0.0)	0 (0.0)
Viruses (H1N1)	2 (1.1)	1 (1.4)	1 (3.6)	0 (0.0)	0 (0.0)	0 (0.0)
Toplam	182/100	72/100	28/100	26/100	14/100	7/100

MSSA: methicillin-susceptible *Staphylococcus aureus*, CNS: coagulase-negative staphylococci, VRE: vancomycin-resistant enterococci, MRSA: methicillin-resistant *Staphylococcus aureus*

Table 5. Evaluation of sepsis patients' data					
		Surviving (n=7)	Deceased (n=28)	Total (n=35)	p
Age	Mean ± SD	41.29±19.11	49.93±22.24	48.20±21.67	0.290
Day sepsis developed (+)	Median (min/max)	7 (2/18)	5 (1/75)	5 (1/75)	0.774
NLR	Median (min/max)	9.63 (5.75/150)	11.50 (0.67/110.34)	11.34 (0.67/150)	1
NLR %	Median (min/max)	9.65 (6.58/15.68)	11.19 (2.10/47.25)	11.01 (2.10/47.25)	0.749
Blood glucose value at admission	Median (min/max)	145 (83/229)	194 (73/475)	175 (73/475)	0.177
SOFA score	Median (min/max)	5 (2/5)	5 (2/10)	5 (2/10)	0.214
DIC	Median (min/max)	31 (11/46)	17 (2/270)	17 (2/270)	0.121
Sex					
Female	n (%)	2 (28.6)	8 (28.6)	10 (28.6)	1
Male	n (%)	5 (71.4)	20 (71.4)	25 (71.4)	
ARF					
No	n (%)	5 (71.4)	14 (50.0)	19 (54.3)	0.415
Yes	n (%)	2 (28.6)	14 (50.0)	16 (45.7)	
Blood culture					
Negative	n (%)	3 (42.9)	11 (39.3)	14 (40.0)	1
Positive	n (%)	4 (57.1)	17 (60.7)	21 (60.0)	
Tracheal culture					
Negative	n (%)	3 (42.9)	11 (39.3)	14 (40.0)	1
Positive	n (%)	4 (57.1)	17 (60.7)	21 (60.0)	
Urine culture					
Negative	n (%)	5 (71.4)	20 (71.4)	25 (71.4)	1
Positive	n (%)	2 (28.6)	8 (28.6)	10 (28.6)	
Injury site culture					
Negative	n (%)	5 (71.4)	25 (89.3)	30 (85.7)	0.256
Positive	n (%)	2 (28.6)	3 (10.7)	5 (14.3)	

Mann-Whitney U test (Monte Carlo), independent samples t-test, Pearson's chi-squared test (Exact/Monte Carlo), Fisher-Freeman-Halton test (Monte Carlo), Fisher Exact test (Exact), odds ratio (95% confidence interval). Min: Minimum, Max: maximum, SD: standard deviation, ARF: Acute renal failure, NLR: Neutrophil/lymphocyte ratio DIC: days in intensive care, SOFA: Sequential Organ Failure Assessment

developed sepsis as a result of other community-acquired factors. Two of those patients were initially diagnosed with H1N1, and oseltamivir treatment was begun; the diagnosis was later confirmed. *S. pneumoniae* was detected in three of the remaining patients, *H. influenzae* in one, and *S. aureus* and aspergilloma in the last one.

It has been reported that ICU admission rates are high in migrant populations because such factors as a lack of prevention and protection in healthcare services, the withdrawal of vaccination programs, low environmental hygiene standards, outdoor living conditions, overcrowding, and exposure to low temperatures have raised the sensitivity to infection (28-33).

Regarding the limitations of our study, it was not possible to evaluate the ICU hospitalization among the local population in the same period, and the number of cases was low. However, its most important advantage is the fact that it is the first study evaluating sepsis among the Syrian patients in an ICU in our country; as such, it can shed light on wider studies to be conducted.

Conclusion

Syrian patients were admitted to the ICU mostly due to respiratory system disease. Comorbid disease was the most common heart disease. *A. baumanii* and *E. coli* were

Table 6. Diagnostic classification of sepsis patients	
Diagnosis	**n=35 (%)**
Gunshot wound	7 (20.0)
Respiratory diseases	10 (28.6)
Renal diseases	2 (5.7)
Trauma	5 (14.3)
Cardiac diseases	5 (14.3)
Cancer	3 (8.6)
Intoxication	1 (2.9)
Gastrointestinal disease	1 (2.9)
Other	1 (2.9)

Table 7. Classification of antibiotics used		
Antibiotic	**All patients n (%) (X*)**	**Sepsis patients n (%) (X*)**
None used	13 (5.7)	-
β-lactam/β-lactamase inhibitor	65 (28.6)	12 (13.8)
2nd, 3rd, & 4th generation cephalosporins	43 (18.9)	2 (2.3)
Carbapenems	27 (11.9)	17 (19.5)
Colistin	15 (6.6)	16 (18.4)
Tigecycline	12 (5.3)	11 (12.6)
Quinolones	11 (4.8)	3 (3.4)
Anti-anaerobic agents	8 (3.5)	3 (3.4)
Linezolid	8 (3.5)	4 (4.6)
Macrolides	7 (3.1)	3 (3.4)
Antifungals	7 (3.1)	7 (8.0)
Sulfonamides	4 (1.8)	4 (4.6)
Oseltamivir	3 (1.3)	2 (2.3)
Aminoglycosides	2 (0.9)	1 (1.1)
Glycopeptides	2 (0.9)	2 (2.3)
X*: One patient used more than one		

isolated most frequently in Syrian patients and 2nd, 3rd, & 4th generation cephalosporins were used most frequently in septic patients, and carbapenems also were used in these patients. APACHE-II scores, the duration of MV, and the number of days hospitalized in ICU were all found to be higher for deceased patients than for the survivors.

Ethics

Ethics Committee Approval: Approval for the study (decision no: 04, date: 05.04.2017) was obtained from Kahramanmaraş Sütçü İmam University's Ethics Committee.

Informed Consent: Patient information was analyzed retrospectively from the records and patient files in the hospital's information management system.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Ş.P.T., H.T.G., S.Ç., Concept: Y.O., Ş.P.T., H.T.G., S.Ç., F.O., F.M.Y., Ö.F.B., A.D., Design: Y.O., Ş.P.T., S.Ç., F.O., F.M.Y., Ö.F.B., Data Collection and Process: Y.O., Ş.P.T., H.T.G., S.Ç., F.O., A.D., Analysis or Interpretation: Y.O., H.T.G., F.O., F.M.Y., Ö.F.B., A.D., Literature Search: Y.O., F.O., F.M.Y., Ö.F.B., A.D., Writing: Y.O., F.O., F.M.Y., Ö.F.B., A.D.

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ÖZGÜN ARAŞTIRMA / *ORIGINAL RESEARCH*

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Yoğun Bakım Ünitelerinde İzole Edilen *Acinetobacter Baumannii* İzolatlarının Kolistin MİK Değerlerinin ve Direnç Genlerinin İrdelenmesi

Colistin MICs and Resistance Genes of *Acinetobacter Baumannii* Isolated in Intensive Care Units

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ÖZ *Amaç: Acinetobacter baumannii* yoğun bakım ünitelerinde yatan hastalarda sağlık bakımı ilişkili enfeksiyonlara neden olan fırsatçı bir patojendir. *A. baumannii* farklı mekanizmalarla hızlı bir şekilde antimikrobiyallere karşı direnç geliştirebilmektedir. Çoklu ilaç dirençli (ÇİD) izolatlarının oluşturduğu enfeksiyonlar; morbidite ve mortalitesi yüksek, uzun süreli hospitalizasyon gerektiren enfeksiyonlardır. Kolistin, ÇİD *A. baumannii* izolatlarına karşı kullanılabilen son antimikrobiyallerden biridir. Bu izolatlarının artmasına bağlı olarak kolistin kullanımı tüm dünyada artmıştır. Çalışmamızda yoğun bakım ünitelerinde yatan hastaların kan kültürlerinden izole edilen ÇİD *A. baumannii* izolatlarında kolistin direnç oranlarının, minimum inhibitör konsantrasyon (MİK) değerlerinin ve kolistin direncine neden olan plazmid aracılı yayılım gösteren direnç genlerinin araştırılması amaçlanmıştır.
Gereç ve Yöntem: Çalışmamıza Ocak 2017-Aralık 2018 tarihleri arasında laboratuvarımızda kan kültür örneklerinden izole edilen 97 *A. baumannii* izolatı alındı. İzolatların MİK değerleri Avrupa Antimikrobiyal Duyarlılık Testi Komitesi önerileri doğrultusunda broth mikrodilüsyon yöntemiyle araştırıldı. Polimeraz zincir reaksiyonu ile kolistin direnç gen bölgeleri mcr 1-5 çalışıldı.
Bulgular: Çalışılan *A. baumannii* izolatlarının 8'i (%8,2) dirençli, 89'u (%91,8) duyarlı saptandı. Kolistin $MİK_{50}$ değeri 0,5 µg/mL, $MİK_{90}$ değeri 2 µg/mL olarak bulundu. Kolistin direncinin horizontal yayılım tehlikesi açısından araştırılan plazmid aracılı mcr gen bölgeleri (1-5 mcr genleri) belirlenemedi.
Sonuç: Kolistin hastanemiz yoğun bakım ünitelerinde yatan hastaların, *A. baumannii* izolatlarına bağlı enfeksiyonlarının tedavisinde hala etkin olarak kullanılabilecek önemli bir antimikrobiyaldir. Ancak kolistine karşı direnç gelişimini önlemek için, irrasyonel antibiyotik kullanımı engellenerek antimikrobiyal duyarlılık testi sonuçlarına göre tedavi uygulanması gerekmektedir. Ayrıca dirençli izolatların hastanelerde kolonizasyonunun önlemesi için gerekli enfeksiyon kontrol önlemlerinin alınmasının önemli olduğu kanısındayız.
Anahtar Kelimeler: *Acinetobacter baumannii*, kolistin, yoğun bakım ünitesi

ABSTRACT *Objective: Acinetobacter baumannii* is an opportunistic pathogen that causes healthcare-associated infections in hospitalised patients in intensive care units. *A. baumannii* can quickly develop resistance to antimicrobials through different mechanisms. Infections caused by multidrug-resistant (MDR) isolates have high morbidity and mortality and require long-term hospitalisation. Colistin is one of the last antimicrobials that can be used against MDR *A. baumannii* isolates. Due to the increase of these isolates, the use of colistin has increased worldwide. Our study aimed to investigate colistin resistance rates, minimum inhibitory concentration (MIC) values and plasmid-mediated resistance genes in isolates from the blood cultures of patients hospitalised in intensive care units.
Materials and Methods: A total of 97 *A. baumannii* isolates from blood culture samples were included in our study. MIC values of the isolates were investigated by the broth microdilution method according to The European Committee for Antimicrobial Susceptibility Testing recommendations. Colistin resistance gene regions mcr 1-5 were studied by polymerase chain reaction.
Results: Eight (8.2%) of the *A. baumannii* isolates were resistant, and 89 (91.8%) were sensitive. The colistin MIC_{50} value was 0.5 µg/mL, and its MIC_{90} value was 2 µg/mL. The plasmid-mediated mcr gene regions (1-5 mcr genes) investigated for the risk of horizontal spread of colistin resistance could not be determined.

Conclusion: Colistin is an important antimicrobial that can still be used effectively to treat infections due to *A. baumannii* isolates in our intensive care units. However, to prevent the development of resistance against colistin, irrational antibiotic use should be prevented, and treatment according to antimicrobial susceptibility test results is required. In addition, we believe that it is important to take the necessary infection control measures to prevent the colonisation of resistant isolates in hospitals.
Keywords: *Acinetobacter baumannii*, colistin, intensive care units

Giriş

Yoğun bakım ünitelerinde (YBÜ) yatan hastalarda gelişen enfeksiyonlar gerek hastaların çoklu organ yetmezliği ve gerekse de etken mikroorganizmanın antimikrobiyal direnci nedeniyle yüksek mortalite ve morbiditeye neden olmaktadır (1-3). Bu enfeksiyonlar tüm sağlık bakım ilişkili enfeksiyonların yaklaşık yarısını oluşturmaktadır. *Acinetobacter baumannii* immün yetmezlikli, ventilatör bağımlı hastalarda sepsis, pnömoni, menenjit ve yara enfeksiyonlarına neden olan fırsatçı bir patojendir (1,2). *A. baumannii*'nin sağlık bakım ilişkili enfeksiyonların %3-20'den sorumlu olduğu ve YBÜ *A. baumannii*'ye bağlı enfeksiyonlarının mortalite oranının %50-60 arasında olduğu bildirilmektedir (2,3). Dolayısıyla YBÜ gelişen enfeksiyonlarda etkenlerin takibi, kontrol önlemlerinin planlanması, uygulanması, sonuçların gözlenmesi ve uygun tedavi stratejilerinin geliştirilmesi için önem taşımaktadır.

A. baumannii çoklu ilaç direnci (ÇİD) ve enfeksiyonlarının artması nedeniyle tedavi yönetiminde önemli sorunlara yol açmaktadır. *A. baumannii* günümüzde antimikrobiyal direnç krizindeki temel faktörlerden biri olarak kabul edilmektedir. Ayrıca YBÜ en sık rastlanılan fırsatçı patojendir (4,5). Orta Asya ve Doğu Avrupa Antimikrobiyal Direnç Sürveyans Ağı (CAESAR) 2017 yılı raporunda dünyada invaziv örneklerden YBÜ izole edilen *Acinetobacter* oranının %23, 2018'de %21 olduğunu, tüm dünyada ÇİD'ye (kinolonlar, aminoglikozidler ve karbapenemler) sahip *Acinetobacter* oranının ise 2017'de %57, 2018 raporunda %62 olduğu bildirilmektedir. Türkiye'de ise ÇİD'ye sahip *Acinetobacter* oranının 2017 %76, 2018 %78 olarak belirtmiştir (6,7). ÇİD'ye sahip *A. baumannii* izolatlarının tedavisi için mevcut terapötik seçenekler kolistin ve tigesiklin ile sınırlıdır. Ancak, tigesiklinin farmakokinetik profili ve düşük serum konsantrasyonları nedeniyle bakteriyemi tedavisi için uygun bir seçenek değildir (8).

Ciddi nefrotoksik etkileri nedeniyle kullanılmayan polimiksinler, ÇİD Gram-negatif bakteriler (özellikle *A. baumannii*) ile oluşan enfeksiyonların sıklığında artış ve tedavilerinde yaşanan yetersizlikler nedeniyle son yıllarda, tekrar gündeme gelmişlerdir. Klinik olarak kullanılan en popüler polimiksin ailesi üyesi antimikrobiyal kolistindir. Kolistinin klinikte ÇİD bulunan *A. baumannii*'nin neden olduğu enfeksiyonlarda ve özellikle de kolistin dışındaki diğer antibiyotiklere direnç varlığında kullanılması önerilmektedir. Ancak, son raporlar kolistin direncinin tüm dünyada, sık kullanımına bağlı olarak arttığını göstermektedir (9-11).

Çalışmamızda YBÜ yatan hastaların kan kültürlerinden izole edilen ÇİD sahip *A. baumannii* izolatlarında kolistin direnç oranlarının, minimum inhibitör konsantrasyon (MİK) değerlerinin ve kolistin direncine neden olan plazmid aracılı yayılım gösteren direnç genlerinin araştırılması amaçlanmıştır.

Gereç ve Yöntem

Örnekler ve İdentifikasyon

Çalışmamıza Ocak 2017-Aralık 2018 tarihleri arasında tıbbi mikrobiyoloji laboratuvarında kan kültür örneklerinden izole edilen 97 *A. baumannii* izolatı alındı. Aynı hastaya ait tekrarlayan örnekler çalışma dışı tutuldu.

Kan kültür şişelerinde laboratuvarımıza gönderilen örnekler, BACT/ALERT 3D (BioMérieux, France) tam otomatize kan kültür sisteminde 5 gün inkübasyonda bırakıldı. Pozitif sinyal veren kan kültür örnekleri; %5 koyun kanlı agar, eozin metilen blue agar besiyerlerine ekimi yapıldı. On sekiz-24 saat inkübe edildi. İnkübasyon sonrası saf olarak üreyen izolatların identifikasyonu Matrix-Assisted Laser Desorption Ionization Time of Flight Mass Spectrometry (BioMérieux, France) ve konvansiyonel yöntemler ile yapıldı.

Broth Mikrodilüsyon

Broth mikrodilüsyon (BMD); Avrupa Antimikrobiyal Duyarlılık Testi Komitesi (EUCAST) kurallarına göre 96 kuyucuklu BMD panelleri kullanılarak gerçekleştirilmiştir. BMD MİK test aralığı 32 µg/mL-0,06 µg/mL olarak belirlenerek çalışıldı. EUCAST önerileri doğrultusunda BMD yöntemi ile MİK değeri 2 µg/mL ve altında bulunan izolatlar duyarlı, üstünde bulunan izolatlar dirençli olarak yorumlandı (12).

Kolistin dışında diğer antimikrobiyallerin duyarlılıkları otomatize sistem (MicroScan, Simens, USA) ve EUCAST önerileri doğrultusunda Kirby-Bauer disk diffüzyon yöntemi kullanılarak belirlendi.

Kolistin Direnç Genlerinin Moleküler Analizi

Kolistin için direnç gen bölgeleri mcr 1-5 Rebelo ve ark. (13) tarif ettiği şekilde multipleks polimeraz zincir reaksiyonu (PZR) ile çalışıldı. Çalışılan primer setlerine ait gen bölgeleri Tablo 1'de gösterilmektedir.

İstatistiksel Analiz

Çalışma verilerinin değerlendirilmesinde tanımlayıcı istatiksel analiz kullanıldı.

Bulgular

Altın standart olan BMD yöntemi ile 8 (%8,2) izolat dirençli, 89 (%91,8) izolat duyarlı saptandı. BMD ile *A. baumannii* kolistin $MİK_{50}$ 0,5 µg/mL, $MİK_{90}$ 2 µg/mL olarak belirlendi (Tablo 2). Kolistin direncinin horizontal yayılım tehlikesi açısından, plazmid aracılı mcr gen bölgelerinin varlığı araştırıldı. Ancak, plazmid aracılı kolistin direnci ile ilişkili mcr gen bölgeleri (1-5 mcr genleri) bulunamamıştır. Kolistin ve diğer antimikrobiyallerin direnç oranları Şekil 1'de gösterilmiştir.

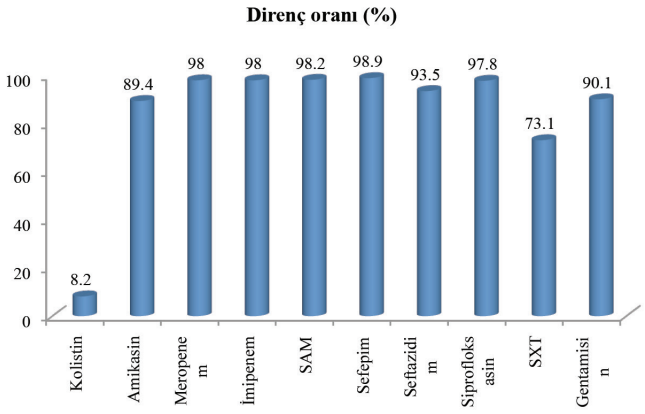
Tablo 1. Kolistin direnç gen bölgeleri primer setleri

Primer	Primer sekans	Gene	Primer boyut (bç)
mcr-1 (F)	5'-AGTCCGTTTGTTCTTGTGGC-3'	bla_{mcr-1}	320
mcr-1 (R)	5'-AGATCCTTGGTCTCGGCTTG-3'		
mcr-2 (F)	5'-CAAGTGTGTTGGTCGCAGTT-3'	bla_{mcr-2}	715
mcr-2 (R)	5'-TCTAGCCCGACAAGCATACC-3'		
mcr-3 (F)	5'-AAATAAAAATTGTTCCGCTTATG-3'	bla_{mcr-3}	929
mcr-3 (R)	5'-AATGGAGATCCCCGTTTTT-3'		
mcr-4 (F)	5'-TCACTTTCATCACTGCGTTG-3'	bla_{mcr-4}	1.116
mcr-4 (R)	5'-TTGGTCCATGACTACCAATG-3'		
mcr-5 (F)	5'-ATGCGGTTGTCTGCATTTATC-3'	bla_{mcr-5}	1.644
mcr-5 (R)	5'-TCATTGTGGTTGTCCTTTTCTG-3'		

Tartışma

İlk olarak 1939 yılında tanımlanan *A. baumannii* çevresel olarak toprak ve suda bulunan Gram-negatif kokobasildir. İnsanda ise derinin bakteriyel florasında özellikle aksilla, kasık, tırnak gibi nemli bölgelerde bulunabilmektedir (14). Ancak hastane ortamına kolonize olabilmekte, başta YBÜ olmak üzere cerrahi ve dahili ünitelerde yatan kritik hastalarda sağlık bakımı ilişkili enfeksiyonlara neden olduğundan, en önemli fırsatçı patojenler arasında yer almaktadır (1,5). Hastalık Kontrol ve Önleme Merkezleri verilerine göre, ÇİD'ye sahip *A. baumannii* izolatları YBÜ enfeksiyonlarının %20'sini, fiziksel olarak tıbbi ekipmana bağlı olan hastalarda enfeksiyonların %7'sini oluşturmaktadır (15).

A. baumannii özellikle altta yatan patolojileri olan bağışıklık sistemi baskılanmış hastalarda sağlık bakım ilişkili pnömoni ve kan dolaşımı enfeksiyonlarının önemli bir nedeni olarak karşımıza çıkmaktadır. ABD'de yılda yaklaşık 12.000 *A. baumannii* enfeksiyonu ve bu enfeksiyonlara bağlı 500 ölümle meydana geldiği tahmin edilmektedir (16). *A. baumannii* ile oluşan enfeksiyonlar için risk faktörleri arasında; ileri yaş, altta yatan ciddi hastalıkların varlığı, immün yetmezlik, majör travma veya yanık yaralanmaları, invaziv işlemler, kalıcı kateterlerin varlığı, mekanik ventilasyon, uzatılmış hastanede kalış ve daha önce antimikrobiyal tedavi özellikle üçüncü kuşak sefalosporinler,



Şekil 1. *Acinetobacter baumannii* izolatlarının antimikrobiyallere direnç oranları
SXT: Trimetoprim/sulfametoksazol, SAM: Ampicillin/sulbactam

Tablo 2. *Acinetobacter baumannii* izolatlarının kolistin inhibisyon ve %50, %90 MİK değerleri

	Kolistin MİK (µgr/mL) inhibisyon %										MİK (µgr/mL)	
	0,06	0,125	0,25	0,5	1	2	4	8	16	32	%50	%90
Acinetobacter baumannii	7,2	14,4	21,6	50,6	75,3	91,8	95,9	98	99	100	0,5	2

MİK: Minimum inhibitör konsantrasyon

florokinolonlar ve karbapenemler uygulanması yer almaktadır (2,6).

Son yıllarda destekleyici tedavilerin, invaziv girişimlerin artması ve hastanelerde irrasyonel ve uzun süreli antibiyotik tedavisi, özellikle *A. baumannii* izolatlarında antibiyotik direncinin yayılmasını ve ÇİD'ye sahip izolatların seleksiyonunu kolaylaştırmaktadır. *A. baumannii* birçok antimikrobiyale çeşitli mekanizmalar ile direnç geliştirmesi sonucu enfeksiyonlarının tedavisinde kullanılan ampisilin-sulbaktam, seftazidim, florokinolonlar, kotrimoksazol, amikasin ve tetrasiklin gibi antimikrobiyaller yetersiz kalmaktadır. Karbapenemler şu anda enfeksiyonlara karşı tercih edilen antibiyotiklerdir, ancak son yıllarda direnç oranları önemli ölçüde artmıştır (4,5). 2017 yılı CAESAR raporunda ülkemizde *A. baumannii* izolatlarında karbapenem direncinin %92, 2018 yılı raporunda %91 olarak bildirmektedir (6,7). Çalışmamızda karbapenem grubu antimikrobiyallerden imipenem ve meropeneme direnç oranını %98 olarak belirledik. Benzer şekilde aminoglikozidler, kinolonlar ve sefalosporinlere karşıda yüksek oranda direnç saptadık.

ÇİD'li *A. baumannii*, uygun enfeksiyon kontrol önlemleri alınmadığında hastane salgınlarına neden olabilir. Ayrıca bu izolatlar hastane ortamında kolonize olabilir ve kolonize olduktan sonra eredike edilmesi zordur. ÇİD'ye sahip *A. baumannii* oranları, Kuzey Avrupa ülkelerinde <%1, Güney ve Doğu Avrupa'daki birçok ülkede ise >%50 kadar değişmektedir. Bu yüksek ÇİD'ye sahip *A. baumannii* izolatlarının oranları, hastane ortamında dirençli klonların yayılımını yansıtmaktadır. Bu durum direnç oranları yüksek olan ülkelerde *A. baumannii*'nin neden olduğu enfeksiyonların tedavi seçeneklerinde ciddi kısıtlamalara neden olmaktadır (1,14). ÇİD'ye sahip *A. baumannii* izolatlarına bağlı enfeksiyonlarda son grup antimikrobiyal olarak kullanılan karbapenem ve kolistin gibi antibiyotiklere olan direncin her geçen gün artması, klinik olarak önemli endişe oluşturmaktadır (8). Lee ve ark. (17) 12 hastanın tedavisinde yalnız kolistin kullandıklarını ve kısa sürede kolistin MİK değerlerinde anlamlı bir artış tespit edildiğini ve 3 hastada kolistin direncinin geliştiğini bildirmiştir. Ülkemizde yapılan çeşitli çalışmalarda kolistin direncini; Yolbaş ve ark. (18) %6, Boral ve ark. (19) %1,2 belirlemiş, Çetinkol ve ark. (20) ise kolistine karşı direnç saptamadıklarını bildirmişlerdir. Talan ve ark. (5) ise 2015 yılında YBÜ izole edilen *A. baumannii* izolatlarında direnç oranını %27,2 olarak belirlemişler. Ayrıca kolistin dirençli izolat izole edilen hastaların YBÜ kalış sürelerinin iki kat uzun olduğu belirtmişlerdir. Yurt dışında yapılan çalışmalarda Maraki ve ark. (21) kolistin direncini %7,9, Gao ve ark. (22) ise %3, Bogiel ve ark. (23) %1,5 olarak bildirmişlerdir. Çalışmamızda, YBÜ yatan hastalarının kan kültürlerinden izole edilen *A. baumannii* izolatlarında $MİK_{50}$ değerini 0,5 µgr/mL, $MİK_{90}$ değerini 2 µgr/mL, direnç oranı ise %8,2 olarak saptadık. Ancak kolistin direncinin horizontal yayılım tehlikesi açısından araştırdığımız plazmid aracılı mcr gen bölgeleri (1-5 mcr genleri) bulamadık.

Sonuç

ÇİD sahip *A. baumannii* izolatları yoğu bakım ünitelerinde önemli bir sorundur ve neden olduğu enfeksiyonların morbidite ve mortalitesi yüksektir. Kolistine karşı her geçen gün artan direnç bu izolatlara bağlı enfeksiyonların tedavi seçeneklerini azaltmaktadır. Her ne olursa olsun, kolistine karşı direnç artışı korkunçtur. *A. baumannii*'nin neden olduğu enfeksiyonları tedavi etmek için yeni antibiyotik rejimlerine ihtiyaç vardır. Ayrıca özellikle YBÜ bu izolatların direnç oranlarının takip edilmesinin ve dirençli izolatların hastanelerde kolonizasyonunun önlenmesi için gerekli enfeksiyon kontrol önlemlerinin alınmasının önemli olduğu kanısındayız.

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ORIGINAL RESEARCH / *ÖZGÜN ARAŞTIRMA*

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The Turkish Adaptation, Validity and Reliability Study of the Intensive Care Unit-RESPECT Scale

Yoğun Bakım Ünitesi-Saygı Ölçeği'nin Türkçeye Uyarlama, Geçerlik ve Güvenirlik Çalışması

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ABSTRACT *Objective:* Intensive care units (ICUs) present patients and families with many challenges. Therefore, respecting them may contribute positively to their recovery. This study aims to determine the psychometric properties of the Turkish version of the ICU-RESPECT scale.
Materials and Methods: A methodological, cross-sectional study design was used. It was conducted in different types of ICUs between April and September 2019 with a hundred patients and family members. Data were collected with a socio-demographic form, The ICU-RESPECT scale, the Family Satisfaction in the ICU Survey, and The Newcastle Satisfaction with Nursing scales. The adaptation of the scale, language validity and content validity were studied. The construct validity of the scale was analysed by factor analysis. The reliability of the scale was evaluated with the reliability coefficient, and the scale was tested with similar measurement tools.
Results: The Kaiser-Meyer-Olkin coefficient and Bartlett's sphericity test results determined that the data were suitable for factor analysis. A single factor that had 73.56% of the total variance was found. The reliability coefficient for the scale was 0.95. A strong positive correlation between scales was determined.
Conclusion: The ICU-RESPECT scale is a valid and reliable instrument for the Turkish population.
Keywords: Intensive care units, patient, respect for life, reliability, validity

ÖZ *Amaç:* Yoğun bakım üniteleri (YBÜ), hastalar ve aileleri için birçok zorluk içermekte olup, hastalara ve ailelerine saygı duyulması iyileşmeye olumlu katkıda bulunabilir. Bu çalışmanın amacı YBÜ-SAYGI ölçeğini Türkçeye uyarlayarak psikometrik özelliklerini belirlemektir.
Gereç ve Yöntem: Çalışma, metodolojik ve kesitsel bir tasarım kullanılarak Nisan-Eylül 2019 tarihleri arasında bir eğitim ve araştırma hastanesinin farklı YBÜ'lerinde toplam yüz hasta ve aile üyesi ile gerçekleştirilmiştir. Veriler; Sosyo-Demografik Form, YBÜ-SAYGI ölçeği, Yoğun Bakım Ünitesi Memnuniyet Anketi ve Newcastle Hemşirelik Bakım Memnuniyet ölçeği ile toplanmıştır. Ölçeğin uyumuna ilişkin olarak, dil geçerliliği ve içerik geçerliliği çalışılmıştır. Ölçeğin yapı geçerliği faktör analizi ile analiz edilmiştir. Ölçeğin güvenirliği güvenirlik katsayısı ile değerlendirilmiş ve ölçek benzer ölçüm araçları ile test edilmiştir.
Bulgular: Kaiser-Meyer-Olkin katsayısı ve Bartlett'in küresellik testi sonuçları verilerin faktör analizi için uygun olduğunu belirlemiş olup toplam varyansın %73,56'sına sahip olan tek bir faktör bulunmuştur. Ölçeğin iç tutarlılık güvenirlik katsayısı 0,95 olarak hesaplanmıştır. Ölçekler arasında güçlü pozitif korelasyon saptanmıştır.
Sonuç: Bu çalışma YBÜ-SAYGI ölçeğinin Türk popülasyonu için geçerli ve güvenilir bir araç olduğunu göstermektedir.
Anahtar Kelimeler: Yoğun bakım üniteleri, hasta, yaşama saygı, geçerlik, güvenirlik

Introduction

Intensive care unit (ICU) provides a collaborative treatment and care with the participation of health professionals in problems related to a single organ of the patient or multiple organ failure (1,2). Although ICU is vital to the patient, critical care has many challenges for patients and their family members (3-6). These difficulties are different experiences such as prolonged bed rest, sedation, inactivity, loss of muscle tone, depression, delirium, poor quality of life, inadequate self-care, sleep disturbances, fatigue, anxiety and fear of death among ICU patients (6,7). Therefore, patients and their family members may experience stress in ICU. In addition to the traumatic experience of the patient and their families, there are difficulties in making decisions about patient-related issues (4).

As a result of developments in human rights and the protection of individual rights by law, respect for the patient's autonomy is accepted as an important patient right today (8,9). Ethical principles also emphasize respect for the protection of the integrity of the individual and prevent the physical and psychological harm of the individual by taking into consideration the individual characteristics of them (8). Autonomy is the capacity to make objective or rational decisions with ethical certainty (9). Since human beings are capable of making decisions and making judgments due to their intelligence, they have the right and ability to act with their emotions, attitudes, and desires. People are autonomous because they have autonomy, and it may be interpreted as an object that deserves respect (8). In ICU, patients are unable to speak due to illnesses, treatment interventions such as intubation, medications, etc., or do not have the ability to understand and make decisions when they are unconscious. The decisions of the patient's family members are important in patient-related decisions when a patient is not capable of making decisions (10). When deciding on behalf of the patient, in cases where the patients are inadequate to make decisions about themselves or are incapable of making this decision, it is important that the decision be as similar to the original decisions the patient can make while at will, or that the decision about the patient has been taken with due consideration of their superior benefit. Therefore, it is important to respect the ICU patient and family in this process.

There are not any studies on evaluating respect in ICU, and there is a need for further studies. Although it is important to protect the privacy of the patient, to create environments for the patient and their family members to feel safe, and to provide uninterrupted and understandable information for health institutions, there is no valid and reliable ICU-RESPECT scale for measuring the respect of the patient and their family members in ICU in Turkey.

Materials and Methods

Aim

This study was aimed to determine the psychometric properties of the Turkish version of the ICU-RESPECT scale which was developed by Geller et al. (11).

Study Design

This is a methodological and cross-sectional study.

Participants

This study was conducted with a total of 100 participants (50 patients and 50 patient's family members) for the 10-item scale by considering the number of scale items. The sample size for each scale item should be 5-10 people for validity and reliability studies (12). Inclusion criteria for patients were treated in the ICU, over 18, conscious, not sedated, not intubated and willing to participate in the study. Inclusion criteria for patients' family members were the family members of the patient who treated in the ICU, intubated, under sedation, unconscious and to be willing to participate in the study. Either the patient or one of the family members of the patient who were hospitalized in the ICU were included in the study.

Data Collection

The data were collected from patients or family members in different types of ICUs of an education and research hospital in Turkey between April-September 2019. For collecting data, the Socio-demographic form, The ICU-RESPECT scale, The Newcastle Satisfaction with Nursing scale, and The Family Satisfaction in The ICU Survey were used.

Socio-demographic Form: This form consists of the personal information of the patient and family member.

The ICU-RESPECT Scale: The scale was developed to purpose a brief index of patient and family member experiences of respect in the ICU by Geller et al. (11). The validity and reliability of the items of the scale were tested by Geller et al. (13). It is a 10-item and 4-point Likert-type (never-rarely/occasionally/most of the time/all of the time) self-reported index to assess patient and family perceptions of

respect in the ICU setting. Raw total scores ranged from 10 to 40 but, because of skewness, the original scale was ranged from 1 to 10 (13). High scores show high respect level. Factor analysis resulted in a unidimensional scale consisting of 10 items with an α of 0.85 and an eigenvalue of 11.3. Factor loadings ranged from 0.54 to 0.84, and item-test correlations ranged from 0.47 to 0.71 (11). The ICU-RESPECT scale covers "Introductions" (members of the care team introduce themselves to the patient/loved one when they first meet), "Courtesy" (members of the care team treat the patient/loved one with courtesy), "Understanding" (members of the care team make an effort to understand what matters to the patient/loved one most), "Responsiveness" (members of the care team are attentive to the patient/loved one's requests), "Engagement" (patient/loved one feel that the care team really listen to him or her), "Selfhood" (members of the care team make efforts to know patient/loved one as a unique individual), "Privacy" (members of the care team keep patient/loved one's body covered as best they could), "Equal" (members of the care team treat patient/loved one as their equal), "Comfort" (members of the care team do everything they could to manage patient/loved one's pain) and "Treated as human being" (members of the care team treat patient/loved one the way they would like to be treated if they were the patient). Cronbach's alpha for the scale in this study was 0.95.

The Newcastle Satisfaction with Nursing Scale: The scale was developed by Thomas et al. (14) and tested for validity and reliability in the Turkish language by Akin and Erdogan (15). It is a 19-item and 5-point Likert-type scale. The scale anchored from 1 (strongly disagree) to 5 (strongly agree). It is measured patients' experiences of and satisfaction with nursing, based on their perspective. Cronbach's alpha for the scale in this study was 0.85.

The Family Satisfaction in The Intensive Care Unit Survey: The survey was developed by Heyland and Tranmer (16) and tested for validity and reliability in the Turkish language by Tastan et al. (17). The survey consisted of 24 items-5 point Likert-type scale and two categories: satisfaction with care (14 items) and satisfaction with decision making (10 items). High scores show high satisfaction. Cronbach's alpha for the scale in this study was 0.90.

Ethical Considerations

Before starting the study, permission was obtained from the developer of the ICU-RESPECT scale. This study received necessary ethics approval from Bilecik Şeyh Edebali University's Ethics Committee (decision no: 7, date: 20.02.2019). In addition, permission was received from the study hospitals. The participating patients and family members were informed about the purpose of the study. The study was performed in accordance with the Declaration of Helsinki.

Statistical Analysis

SSPS 22.0 and Lisrel 8.8 statistical programs were used to analyze the data. Number, percentage, mean and standard deviation values were calculated in the definition of the data. In the adaptation process, language and content validity were studied. Skewness was measured. In the validation process, the suitability of the data for explanatory factor analysis was evaluated with Kaiser-Meyer-Olkin (KMO) and Bartlett's sphericity test and the reliability of the scale was evaluated with Cronbach's alpha. In addition, the Spearman-Rho correlation test was used to determine the relationship between the scale and the other scales. For statistical significance, $p<0.05$ was accepted. After the confirmatory factor analysis (CFA), normal theory weighted least squares chi-square (ΔX^2), degrees of freedom (df), root mean square error of approximation (RMSEA), normed fit index (NFI) and comparative fit index (CFI) were calculated. Structural Equation Modelling was also applied.

Results

Participant Characteristics

The socio-demographic characteristics of the participants are shown in Table 1. Fifty percent of the participants were patients, and most of them (85%) were hospitalized in surgical ICUs. The scores of the patients and family

Table 1. Socio-demographic characteristics of the participants

	Patient (n=50)		Patient's family members (n=50)	
	n	%	n	%
Gender of patient				
Male	29	58	18	36
Female	21	42	32	64
ICU of patient				
Medical ICU	11	22	4	8
Surgical ICU	39	78	46	92
Age of patients	59.70±15.86 (24-87)		63.88±21.11 (18-93)	

ICU: Intensive care unit

members on the ICU-RESPECT scale were 33.72±5.61 (13-40) and 33.20±6.60 (12-40), respectively, and there was no statistically significant difference between the scale mean scores (t=0.42, p≥0.05).

Adaptation Process

Language and Content Validity

ICU-RESPECT's language validity was determined according to the method proposed by the World Health Organization for translating and adapting instruments developed in different languages (18). The scale was translated from English to Turkish and then translated back from Turkish to English by five experts who live in Turkey and had a good command of English and Turkish to ensure the integrity of meaning. Then, the scale was administered to five ICU nurses, two ICU patients, two ICU patient's family members, and three experts to test the intelligibility and content validity of the items. These patients and the patient's family members were not included in the study.

Validation Process

Explanatory Factor Analysis

In the scale applied to patients and family members (n=100), the KMO coefficient was determined as 0.919 and Bartlett's sphericity test was determined as 1,047.379 in order to determine the suitability of the data for factor analysis (p<0.001). KMO coefficient indicating whether the sample size is sufficient varies between 0-1 and the lower limit is accepted as 0.50. The Bartlett's sphericity test shows whether there is a sufficient correlation between the data and being less than 0.05 of the p-value of this test means that there is a sufficient relationship between the data to perform factor analysis (19). KMO coefficient and Bartlett's sphericity test results determined in this study show that the data are suitable for factor analysis. As a result of the factor analysis of the data obtained from the scale, the only single factor was found that had 73.56% of the total variance and whose eigenvalue was higher than 1. Factor loads of the items on the scale ranged from 0.70 to 0.92 (Table 2).

Confirmatory Factor Analysis

The scale was confirmed using CFA. The ICU-RESPECT scale is 10 items totally and consisting of a single dimension. The confirmatory fit indexes obtained from the CFA were determined as $\Delta X^2/df=3.43$, RMSEA=0.15, NFI=0.95 and CFI=0.96 (Table 3). It is recommended as $2 \leq X^2/df \leq 3$; $0.05 \leq$ RMSEA≤ 1.0; $0.90 \leq$NFI≤ 0.95 and $0.90 \leq$CFI≤ 0.95 (19,20). These results show that the scale is well adapted to Turkish culture (Figure 1).

Internal Consistency Coefficient and Correlations Between Scales

For the reliability of the scale, internal consistency was evaluated with Cronbach's alpha coefficient. Cronbach's alpha for the scale in this study was 0.95. When the inter-item and item-total correlations of the scale were examined, the inter-item correlations were between 0.45-0.86, and the item-total correlations were between 0.65-0.91. The ICU-RESPECT scale was applied to patients with the Newcastle Satisfaction with Nursing scales, and the ICU-RESPECT scale was applied to families with the Family Satisfaction in the ICU Survey, and a strong positive correlation between scales was determined (r=0.64, r=0.64; p≤0.05).

Discussion

This study was conducted to determine the validity and reliability of the ICU-RESPECT scale which was developed to evaluate the perception of respect of ICU patients and family members.

Before performing factor analysis, evaluating KMO and Bartlett's test is recommended in the literature (19). In this study, the explanatory factor analysis was determined

Table 2. Exploratory factor analysis results of ICU-RESPECT

Factor	Item	Factor load values
ICU-RESPECT	1	0.92
	2	0. 91
	3	0. 91
	4	0. 90
	5	0. 90
	6	0. 86
	7	0. 83
	8	0. 81
	9	0. 77
	10	0. 70

Explained total variance =73.56%. ICU: intensive care unit

Table 3. Confirmatory factor analysis results

Scale	ΔX^2	df	$\Delta X^2/df$	RMSEA	NFI	CFI
ICU-RESPECT	116.27	35	3.43	0.15	0.95	0.96

ΔX^2: Normal theory weighted least squares chi-square, df: degrees of freedom, RMSEA: root mean square error of approximation, NFI: normed fit index, CFI: comparative fit index (p<0.001)

using KMO and Barlett's test. When the explanatory factor analysis results of the ICU-RESPECT scale were examined, the factor loads of the items were determined between 0.70-0.92. Geller et al. (13) found the factor loadings of the scale to be 0.50-0.86 in their study. The factor load value is the coefficient explaining the relationship of the items in the scale with the factors. It is stated in the literature that the scale item loads are above 0.30 (19). According to the data obtained from this study, it can be said that the factor load values of the scale are high for both patients and family members. In this study, as a result of factor analysis, a single factor structure was obtained similar to the original on the ICU-RESPECT scale. The items applied to patients and family members cover 73.56% of the total variance.

In the validity and reliability analysis, the most common method used in order to test the construct validity is factor analysis. It is associated with what the scale measures accurately (21). CFA was conducted to examine the validity of the scale's single-factor structure on the Turkish sample, and it was found that the single-factor structure of the scale was confirmed in Turkish culture.

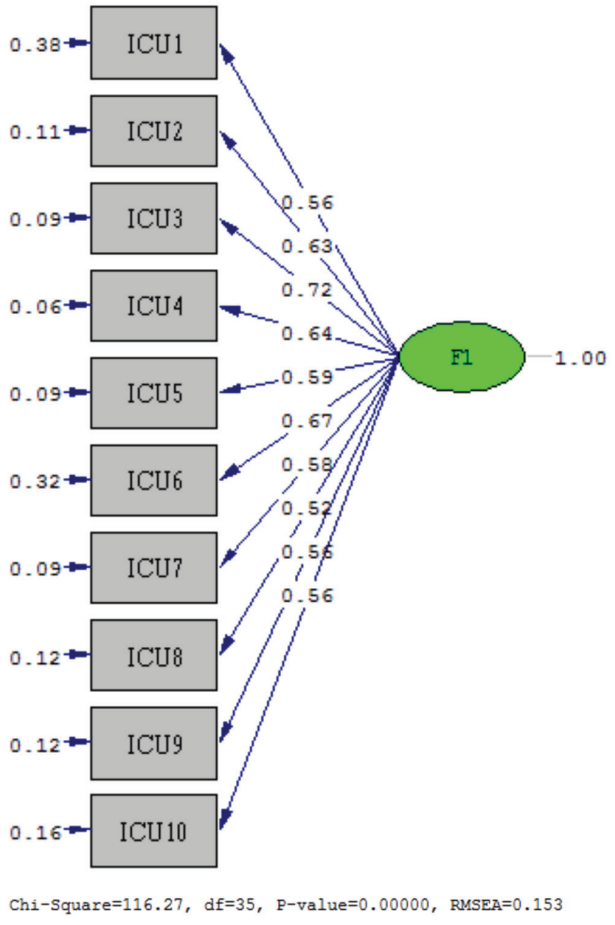

Figure 1. The standardized estimates of CFA
CFA: Confirmatory factor analysis, ICU: intensive care unit, RMSEA: root mean square error of approximation, df: degrees of freedom

The internal consistency of items was evaluated with Cronbach's alpha coefficient in scale development studies. A coefficient of '0.80-1.00' indicates that the scale is highly reliable (21). The Cronbach's alpha value of the scale was determined as 0.95. While Geller et al. (11) found the Cronbach's alpha value of the original scale as 0.85, Geller et al. (13) determined it as 0.90 in the validation study.

Although it was suggested in the literature to evaluate the time invariance of a scale with the same group at two-four week intervals (22), in this study, re-test was not performed because of the emotional and physical instability of the patients and family members in the ICU (23). This problem was solved using similar scales. The Newcastle Satisfaction with Nursing scale was used for patients and the Family Satisfaction in The ICU Survey was used for family members. As a result, the correlation between these scales was calculated and the accuracy of the scale was tested. When the relationship between the ICU-RESPECT and the Newcastle Satisfaction with Nursing scale of patients and between the ICU-RESPECT and the Family Satisfaction in the ICU Survey of patient's family members were examined, it was found that there was a statistically significant strong relationship between the ICU-RESPECT-the Newcastle Satisfaction with Nursing scale, the ICU-RESPECT- the Family Satisfaction in the ICU Survey ($r=0.64$, $r=0.64$; $p\leq0.05$). The correlation values were evaluated as 0-0.2= very week, 0.2-0.4= week, 0.4-0.6= moderate and 0.6-0.8= strong (19). Therefore, it can be said that the scale measures the respect perceived by ICU patients and family members.

The study was conducted at a single hospital in Turkey and the results of this study have social, cultural, religious and psychological dimensions. Therefore, it cannot be generalized for other regions and cultures. In addition, the study was conducted with patients and family members who agreed to participate in the study, and not all ICU patients and family members could be reached.

Conclusion

As a result of the validity and reliability analysis conducted in this study, it can be said that the Turkish version of the ICU-RESPECT scale is a valid and reliable tool that can be used to evaluate the level of respect perceived by ICU patients and family members. Especially in the accreditation of health institutions, ICUs are important indicators. Measuring the satisfaction of patients and family members from ICU and respectability which is one of the important factors affecting patient recovery will contribute to the solution of problems in the relations between patients and nurses. Demonstrating the applicability of the Turkish version of the ICU-RESPECT scale with this study may allow further studies to determine the level of respect that plays an important role in relationships with the ICU patient and family and can lead to problems when high or low. In addition, it can be an important measurement tool to evaluate the quality of nursing care in ICUs. It can also be compared with the results of other international studies.

Ethics

Ethics Committee Approval: This study received necessary ethics approval from Bilecik Şeyh Edebali University's Ethics Committee (decision no: 7, date: 20.02.2019).

Informed Consent: The participating patients and family members were informed about the purpose of the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: Ö.İ., S.M., E.A., Design: Ö.İ., S.M., E.A., Data Collection and Process: Ö.İ., S.M., E.A., Analysis or Interpretation: Ö.İ., S.M., E.A., Literature Search: Ö.İ., S.M., E.A., Writing: Ö.İ., S.M., E.A.

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ORIGINAL RESEARCH / *ÖZGÜN ARAŞTIRMA*

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Mortality Predictors in Sepsis: A Retrospective Study

Sepsiste Mortalite Prediktörleri: Retrospektif Bir Çalışma

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ABSTRACT *Objective:* This study aimed to assess the specificity and sensitivity of three predictors of mortality in patients with sepsis: the presence of infection-causing microorganisms, the severity of disease classifications, and biomarkers.
Materials and Methods: We retrospectively analyzed the records of 76 patients. All the patients were aged above 18 years, and were diagnosed with sepsis, admitted, treated, and followed-up in our hospital's reanimation unit between 01/01/2017 to 01/01/2018. Patients' demographic data, treatments in the intensive care unit, causes and durations, biochemical analyses, 24-hour Acute Physiology and Chronic Health Evaluation-II (APACHE-II) scores, Sequential Organ Failure Assessment (SOFA) scores, and microorganisms detected through culture analysis were analyzed in terms of their specificity and sensitivity in predicting mortality and morbidity.
Results: Of the patients analyzed, 46.05% were women and 53.95% were men. The average age was 62.67±18.1 years, and the mortality rate was 51.31%. While sepsis developed post-operatively in 60.53% of patients, 39.47% of patients developed sepsis due to an internal medical pathology. The average duration of treatment was 35±43.7 days. The most common infection-causing pathogen was *Klebsiella pneumoniae*, followed by *Staphylococcus aureus*. In terms of fungal infections, *Candida* spp. was found to be the most common. In the first 24 hours of treatment, high SOFA, APACHE-II, procalcitonin values, and infection with *Enterococcus faecalis* were all found to be independent risk factors for mortality (p<0.05).
Conclusion: In patients with sepsis, severity of disease classifications and *E. faecalis* infection are independent risk factors of high mortality rates, and should be considered in the evaluation of patients.
Keywords: Sepsis, biomarkers, APACHE-II, SOFA, mortality

ÖZ *Amaç:* Çalışmamızda, sepsis tanılı hastalarda enfeksiyona sebep olan mikroorganizmaların, hastalık ciddiyet skorlamalarının ve biyobelirteçlerin mortalite prediktörü olarak özgüllük ve duyarlılıklarını tespit etmeyi amaçladık.
Gereç ve Yöntem: Çalışmamızda hastanemiz reanimasyon ünitesinde 01.01.2017-01.01.2018 tarihleri arasında sepsis tanısı alarak takip ve tedavi edilen 18 yaşından büyük 76 hastanın kayıtları retrospektif olarak incelendi. Hastaların demografik verileri, yoğun bakım ünitesine yatış tedavileri, nedenleri ve süreleri, biyokimyasal analizleri, ilk yirmi dört saatinde hesaplanan Akut Fizyoloji ve Kronik Sağlık Değerlendirmesi-II (APACHE-II) skoru ve Ardışık Organ Yetersizliği Değerlendirme (SOFA) skoru ile kültür analizi sonucunda üreyen mikroorganizmalar mortalite ve morbidite prediksiyonu açısından duyarlılık ve özgüllükleri kıyaslandı.
Bulgular: Hastaların %46,05'i kadın,%53,95'i erkek, yaş ortalamaları 62,67±18,1 yıl, mortalite oranı %51,31 olarak tespit edildi. Hastaların %60,53 cerrahi operasyon sonrası, %39,47 dahili nedenler ile sepsis tanısı almış olup ortalama tedavi süresi 35±43,7 gündü. Enfeksiyona neden olan etken en sık *Klebsiella pneumoniae*, ikinci sıklıkta *Staphylococcus aureus*; fungal etken olarak ise *Candida* spp. olarak bulundu. Tedavilerin ilk 24 saatinde ölçülen yüksek SOFA, APACHE-II skorlarının, prokalsitonin değeri ve *Enterococcus faecalis* enfeksiyonu mortalite için bağımsız birer risk faktörü olarak belirlendi (p<0,05).
Sonuç: Sepsisli hastalarda mortalite prediksiyonunda, skorlama sistemlerinin yanında *E. faecalis* enfeksiyonun da bağımsız bir risk faktörü olması yüksek mortalite açısından dikkate alınmalıdır.
Anahtar Kelimeler: Sepsis, biyobelirteçler, APACHE-II, SOFA, mortalite

Introduction

Sepsis is syndrome characterised by an uncontrolled inflammatory response to infection that leads to physiological, biological, and biochemical abnormalities (1). Early diagnosis and appropriate treatment have a positive effect on prognosis. If early diagnosis and appropriate treatment are not carried out, the initial illness may progress to conditions such as septic shock and multiple organ failure, leading to a high mortality rates (2).

To predict the course of sepsis, it is important to know the organism that causes it. The most common pathogens causing sepsis are bacteria; however, viruses, fungi, and parasites can also lead to sepsis. The 2009 European Prevalence of Infection in Intensive Care II (EPIC II) study found Gram (-) microorganisms to be the more common cause of sepsis (62.2% vs 46.8%) (3). Alongside this, other studies have found that the incidence of Gram (+) microorganisms is increasing. Multi-center studies in recent years have shown that, in Turkey, the most commonly isolated pathogens are Gram (-) bacteria, while the second most common are Gram (+) bacteria (4). Following these, fungi and viruses are the most common pathogens (4). Nevertheless, sufficient epidemiological data on sepsis is as of yet unavailable in Turkey.

Prognostic insight into patients diagnosed with sepsis can be provided by evaluating basic biological parameters alongside various biomarkers and early disease severity classification scoring (5). Most common are the Acute Physiology and Chronic Health Evaluation-II (APACHE-II) and Sequential Organ Failure Assessment (SOFA) classification systems used in the intensive care unit (ICU). Internationally, varying results have been reported in terms of the effectiveness of these systems in predicting mortality. For this reason, these classification systems are used in combination with other biomarkers to determine prognosis. While a wide range of biomarkers have been studied in the past decade for their use in patients with sepsis, only a few of these have proven to be useful clinically. C-reactive protein (CRP) and procalcitonin (PCT) are the most widely used and well studied of these biomarkers. However, neither of these factors has been found to be sufficiently reliable in isolation.

In our study, patients diagnosed with sepsis and subsequently treated and followed up in the reanimation unit were evaluated in terms of causative microorganisms, APACHE-II and SOFA severity of disease classification scores, and biomarkers such as CRP and PCT. We aimed to investigate these parameters' sensitivity and specificity in predicting mortality.

Materials and Methods

This study was carried out in the Anaesthesiology and Reanimation Unit of İstanbul Bağcılar Training and Research Hospital, with approval from the İstanbul Bağcılar Training and Research Hospital ethics committee garnered on 17/08/2017 under number 2017/603. Seventy-six patients admitted and treated in the Reanimation Unit for sepsis between 01/01/2017 and 01/01/2018 were retrospectively included in the study through access to and evaluation of their patient files and electronically stored data.

Patients diagnosed with sepsis based on the Society of Critical Care Medicine and European Society of Intensive Care Medicine 2016 Sepsis-3 diagnosis criteria were included after an evaluation of patients' files (6). Patients that were younger than 18 years of age, pregnant, undergoing immunosuppressive therapy, were HIV (+), or had any diagnosed organ failure were excluded from the study.

Patients included in the study were evaluated with respect to their demographic data, reason for admission to the intensive care unit (either surgical or internal pathology), first day PCT, CRP, and white blood cell (WBC) values, and severity of disease classification scores (APACHE-II and SOFA). Furthermore, growth of microorganisms, microorganism locus (e.g. tracheal aspirate or blood), need for mechanical ventilation, inotropic and vasoactive agents used, need for renal replacement, and duration of inpatient treatment in the intensive care unit were each evaluated and recorded.

Recorded parameters were analyzed in terms of either their independent or combined value in predicting mortality in patients with sepsis. Results were evaluated for their sensitivity and specificity in predicting mortality in patients with sepsis and septic shock.

Statistical Analysis

Statistical analysis was carried out using Number Cruncher Statistical System 2007 Statistical Software Package (Utah, USA) in combination with the STATA 12 Statistics Package.

Analysis of data was carried out using descriptive statistical methods [average ± standard deviation (SD), median [minimum (min) - maximum (max)], interquartile range]. Pairs of normally distributed variables were compared using the independent t-test, while non-normally distributed

pairs were analyzed using the Mann-Whitney U test. Qualitative variables were evaluated using the chi-squared and Fisher's Exact test. Odds ratios were calculated using a 95% confidence interval. The factors affecting development of mortality were evaluated using logistic regression analysis.

The predicted results of the regression analysis were obtained using two separate software packages, and statistical significance was defined as $p<0.05$.

To determine APACHE and SOFA classifications' respective predictive values in terms of mortality, Area under receiver operating characteristic (AUROC) curve analysis was carried out and areas underneath the AUROC curve were evaluated. The larger test's area, which was located underneath the AUROC curve, was determined to be a parameter of greater value in predicting mortality.

Results

Seventy-six patients diagnosed with and treated for sepsis in the Anaesthesiology and Reanimation Unit of İstanbul Bağcılar Training and Research Hospital between 01/01/2017 and 01/01/2018 were analyzed in terms of their infectious agents causing sepsis, biomarkers, severity of disease classification scores, and the treatments they underwent. Each parameter's respective relationship to mortality was then evaluated.

Of the 76 patients included, 35 (46.05%) were women and 41 (53.95%) were men. The average age was 62.67±18.1 (20-93). Values were calculated as [average ± SD (min-max)] years. Of these patients, 60.53% were admitted to our ICU post-operatively, while 39.47% were admitted due to internal medical reasons (respiratory failure, pneumonia). Patients with sepsis underwent inpatient treatment for an average of 35±43.7 days (1-271). Of these patients, 51.31% died, while 48.68% recovered and were discharged. Table 1 shows the demographic data, inpatient treatment durations, and mortality rates of the patients.

Of the patients included in the study, median (min-max) SOFA score in the first 24 hours was 8 (2-17), and median (min-max) APACHE-II score was 20 (5-38). The average CRP value was 196.2±166.3 (0.74-1242.2) mg/dL, WBC average was 18.04±12.6 (1.2-69.8), and average PCT value was 17.8±30 (0.06-120) ng/mL (Table 2).

The microorganism responsible for infection was isolated in 96.05% of the 76 patients included in the study (n=73). Disease-causing microorganisms were most commonly isolated from blood (30.26%, n=23), followed by deep tracheal aspirate (DTA) (27.63%, n=21). Our analysis found no significant correlation between patients' infection loci and mortality.

Microorganisms causing infection were mostly Gram (-) (59.22%), followed by Gram (+) (33.76%) and fungal infections (7.89%). *Klebsiella pneumoniae* was the most commonly isolated bacterium (n=14, 18.42%), followed by *Staphylococcus aureus* (n=11, 14.47%). *Candida* spp. was the predominant microorganism in fungal infections (n=6, 7.89%) (Table 3).

Table 1. Patients' demographic data, inpatient treatment durations, and mortality rates

Sex (female/male) n (%)	35/41 (46.05%/53.95%)
Age (years) average ± SD (min-max)	62.67±18.1 (20-93)
Inpatient treatment duration (days) average ± SD (min-max)	35±43.7 (1-271)
Mortality n (%)	39 (51.31%)

SD: Standard deviation, Min: minimum, max: maximum

Table 2. Patients' Admission APACHE-II scores, SOFA scores, CRP, WBC, and PCT values

	n	Average ± SD	Median (min - max)
CRP mg/dL	76	196.2±166.3	176 (0.74-1242.2)
WBCx10^3/mm^3	76	18.0±12.6	15 (1.2-69.8)
PCT ng/mL	76	17.8±30.0	4 (0.06-120)
SOFA	76	8±3	8 (2-17)
APACHE-II	76	20±8	20 (5-38)

CRP: C-reactive protein, WBC: white blood cell, SD: standard deviation, min: minimum, max: maximum, APACHE: Acute Physiology and Chronic Health Evaluation, SOFA: Sequential Organ Failure Assessment, PCT: procalcitonin

Table 3. Distribution of isolated microorganisms

	n	%
Klebsiella pneumoniae	14	18.42
Staphylococcus aureus	11	14.47
Acinetobacter	10	13.16
Escherichia coli	10	13.16
Enterococcus faecalis	9	11.39
Pseudomonas aeruginosa	8	10.53
Candida spp.	6	7.89
Staphylococcus epidermidis	5	6.58
Haemophilus influenza	2	2.63
Streptococcus anginosus	1	1.32
Stenotrophomonas maltophilia	1	1.32

Our analysis of the effect of isolated microorganisms on mortality showed that *Enterococcus faecalis* was isolated from 19.51% of 39 patients that died. Of the 9 patients whose cultures exhibited growth of *E. faecalis*, 8 of them (88.8%) died. Statistical analysis showed that the presence of *E. faecalis* was positively correlated with mortality, and *E. faecalis* isolation was associated with an increased risk of mortality (p=0.017). Of the other isolated microorganisms, none were significantly associated with mortality rates (p>0.05) (Table 4).

SOFA and APACHE-II scores recorded within the first 24 hours of treatment were each found to be significantly positively correlated with mortality (p=0.006, p=0.0005, respectively) (Table 5).

Duration of treatment for included patients and laboratory biomarkers measured during inpatient treatment (CRP, WBC, PCT) were examined for their relationship with mortality (Table 6). Duration of inpatient treatment, as well as first 24-hour WBC and CRP values, was not found to be significantly related with mortality (p>0.05). High PCT values were shown to be independent risk factors for mortality (p=0.0078).

Of the patients who died, 94.87% (n=37) received some form of inotropic treatment, 48.72% (n=19) received renal replacement therapy (RRT), and 97.44% (n=38) received mechanical ventilation (MV) support. Analysis showed all of the aforementioned therapies (inotrope, RRT, and MV) to be significantly positively correlated with mortality rates (p=0.000, p=0.003, p=0.04, respectively).

To compare the predictive value of SOFA and APACHE scores with respect to mortality, AUROC curve analysis was carried out and the areas under the curve compared. The area under the AUROC curve was found to be larger in SOFA (AUROC curve =0.7449) compared to APACHE-II (AUROC curve =0.733). SOFA was determined to be a more successful parameter with regard to its value in predicting mortality (Figure 1, 2).

Table 4. Microorganisms' relationship with mortality

Microorganism	Growth	Survival n=37		Mortality n=39		p
		n	%	n	%	
Enterococcus faecalis	(-)	36	97.37	31	80.49	0.017
	(+)	1	2.63	8	19.51	
Staphylococcus aureus	(-)	30	81.08	35	89.74	0.441
	(+)	7	18.91	4	10.25	
Acinetobacter	(-)	32	86.84	34	87.80	0.597
	(+)	5	13.16	5	12.20	
Pseudomonas aeruginosa	(-)	33	89.47	35	90.24	0.614
	(+)	4	10.53	4	9.76	
Haemophilus influenza	(-)	36	97.37	38	97.56	0.74
	(+)	1	2.63	1	2.44	
Escherichia coli	(-)	30	81.58	36	92.68	0.134
	(+)	7	18.42	3	7.32	
Klebsiella pneumoniae	(-)	32	86.84	30	78.05	0.219
	(+)	5	13.16	9	21.95	
Streptococcus anginosus	(-)	36	97.37	39	100.00	0.487
	(+)	1	2.63	0	0.00	
Candida spp.	(-)	35	94.74	35	90.24	0.363
	(+)	2	5.26	4	9.76	
Stenotrophomonas maltophilia	(-)	36	97.37	39	100.00	0.487
	(+)	1	2.63	0	0.00	

The p values displayed are the results of Fisher's Exact test. P<0.05 was set as the threshold for statistical significance.

Logistic regression analysis was carried out for each of the variables that showed a positive correlation with mortality (PCT, age, SOFA, APACHE-II, inotropic therapy, RRT, MV, and *E. faecalis* growth). Age (p<0.01), *E. faecalis* growth (p<0.01) and inotropic therapy (p<0.01) were found to be the variables most valuable in predicting mortality (Table 6).

Discussion

Sepsis is an uncontrolled inflammatory response that can lead to organ failure. It is an increasingly common syndrome that affects millions of people every year (7). Due to sepsis' high mortality and morbidity, the prompt diagnosis and

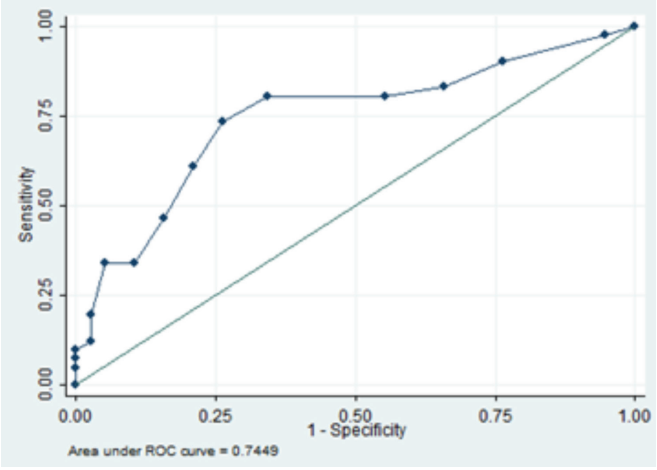

Figure 1. SOFA AUROC curve
AUROC: Area under receiver operating characteristic, SOFA: Sequential Organ Failure Assessment

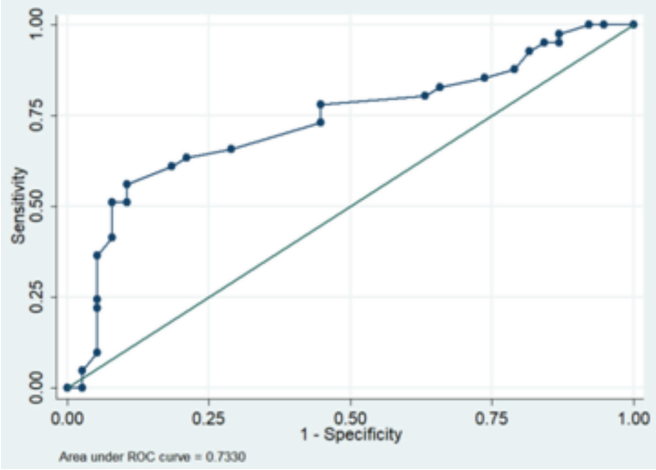

Figure 2. APACHE-II AUROC curve
AUROC: Area under receiver operating characteristic, APACHE: Acute Physiology and Chronic Health Evaluation

Table 5. Duration of treatment, severity of disease classification scores and biomarkers' relationship with mortality

	Mortality	Average ± SD	Median	(IQR)	p
Duration of Treatment (days)	(-)	34.32±41.49	14	(6.75-47.50)	0.482
	(+)	35.69±46.27	20	(6.5-46.5)	
CRP (mg/dL)	(-)	174.77±110.41	177.65	(77.88-235.23)	0.479
	(+)	216.57±205.37	179.4	(91-301.63)	
WBC (x10^3/mm^3)	(-)	15.43±10.61	13.65	(7.83-20.4)	0.057
	(+)	20.52±13.92	17.6	(11.25-25.5)	
PCT (ng/mL)	(-)	11.44±24.03	2.4	(1.06-5.88)	0.0078
	(+)	24.47±36.80	10.52	(1.96-29.35)	
SOFA	(-)	6.19±2.96	6	(3.75-8)	0.0006
	(+)	9.17±3.91	9	(7-12)	
APACHE-II	(-)	18.35±6.02	18	(14-22)	0.0005
	(+)	24.43±7.45	27	(19-30.5)	

The p values displayed are the results of the Mann-Whitney U test. p<0.05 was set as the threshold for statistical significance. CRP: C-reactive protein, WBC: white blood cell, SD: standard deviation, APACHE: Acute Physiology and Chronic Health Evaluation, SOFA: Sequential Organ Failure Assessment, PCT: procalcitonin, IQR: interquartile range

Table 6. Logistic regression analysis of factors correlating with mortality

Variable	PCT	SOFA	APACHE-II	Inotrope	RRT	MV	Age	*E. faecalis*
Mortality	0.0244*	0.0740	0.00648	3.088**	1.029	0.232	0.0618**	2.274**
	(0.0146)	(0.125)	(0.0564)	(1.053)	(0.711)	(1.469)	(0.0217)	(0.813)

**p<0.01, *p<0.1. PCT: Procalcitonin, SOFA: Sequential Organ Failure Assessment, APACHE: Acute Physiology and Chronic Health Evaluation, RRT: renal replacement therapy, MV: mechanical ventilation, *E. faecalis: Enterococcus faecalis*

appropriate provision of treatment according to the severity and prognosis of the disease is of utmost importance. In order to provide an early prediction of the prognosis of septic patients, we investigated proven infectious agents, biomarkers (CRP, WBC, and PCT), and the severity of disease classification scores (SOFA, APACHE-II). Each factor was analyzed for their relationship with mortality to assess their sensitivity, specificity, and predictive value. Furthermore, patients' demographic data as well as treatments (inotropic therapy, RRT, MV support) were analyzed with respect to mortality.

A retrospective study involving 6,621,559 patients diagnosed with sepsis found that yearly sepsis incidence was 3/1,000 for the general population but 26.2/1,000 for patients 85 years and older (7). This study determined that aging was an independent risk factor for both development of sepsis and death due to sepsis (7). In the same study, total mortality rates for sepsis were found to be 28.2%, while this figure was 38.4% for patients 85 years and older (7). A different study found that sepsis mortality rates were 24.4%, with mortality steadily increasing with age (8). Patients under 65 years old had a 17.7% chance of dying if diagnosed with sepsis, while patients 65 years and older had a 27.7% mortality rate (8). Logistic regression analysis in the same study showed that being over the age of 65 independently increased risk of mortality due to sepsis by a factor of 2.26 (8). In our study, patients included had a mortality rate of 51.31%. When patients' mortality rates were compared with respect to their age, 20-34 year olds, 35-49 year olds, 50-64 year olds, 65-74 year olds, and patients aged 75 and older were found to have mortality rates of 25%, 37.5%, 47.4%, 57.2%, and 65%, respectively. Thus, sepsis incidence and mortality were found to be positively correlated with advancing age.

Two important prognostic factors in sepsis are the infection locus and the causative microorganism. In several different publications, the most common infection locus was found to be the respiratory tract, followed by the intra-abdominal region, and subsequently the urinary system, blood, and soft tissues (4,9-12). In terms of microbiological environment, bacteria were most often isolated on blood culture (4,9-12). In our patients, the most common infection locus was the respiratory system, followed by the digestive system and the urinary system, respectively. Microbiological infectious agents were most frequently isolated from blood samples (30.26%), followed by DTA, and finally from soft tissue / lesion cultures. In our study, no significant association was found between infection locus and mortality.

The specific causative microorganisms associated with sepsis were not found to be of importance for prognosis. Other publications have identified the relevant infectious agents, which include, in order of commonality, Gram (-) bacilli, Gram (+) cocci, and fungal agents (4,10,11). For specific microorganisms, the most common include, in order of frequency, *Acinetobacter* spp., *Pseudomonas* spp., *Klebsiella* spp., *S. aureus*, *Enterococcus* spp., *E. coli*, and *Candida* spp. (4,10,11). Though patients with sepsis are most commonly infected with Gram (-) bacteria, in recent years the increase of nosocomial infections has caused Gram (+) related bacterial sepsis to occur increasingly often (9). In our study, 59.22% of cases were associated with Gram (-) bacteria, 33.76% with Gram (+) bacteria, and 7.89% with fungal infections. Examining the incidence of microorganisms revealed the most common to be *K. pneumoniae* (18.42%), followed by *S. aureus* (14.47%), *Acinetobacter* spp. (13.14%), *E. coli* (13.16%), *E. faecalis* (11.39%), *P. aeruginosa* (10.53%), and *Candida* spp. (7.89%). While Gram (-) bacteria were observed more frequently in our study, the distribution of infectious agents was found to be different from those described in the literature. This may be caused by the variation in flora between our ICU and centers where other studies were conducted.

In a study assessing mortality rates in patients with sepsis according to microorganisms, 28-day mortality rates were found to be 40.5% in patients infected with Gram (-) bacilli, 42.9% for Gram (+) cocci, and 52.4% for sepsis associated with fungal infections (11). In the last ten years, the third most common species isolated in nosocomial infections is *Enterococcus* spp., which has appeared with increasing frequency (13). A retrospective study on mortality rates of 196 patients with growth of *Enterococcus* spp. on blood cultures found that inappropriate use of antibiotics was an independent risk factor associated with mortality, while mortality rates were 26% in cases with appropriate antibiotic therapy (14). In a prospective study analyzing 398 patients infected with *Enterococcus* spp., 14-day mortality rates were found to be 19% and vancomycin resistance was found to be an independent risk factor for mortality. While assessing infectious agents' relationship with mortality in our study, *E. faecalis* was found to be associated with a higher risk

of mortality compared to other microorganisms that we isolated. Presence of *Enterococcus* spp. was also found to be an independent risk factor for mortality (15).

In studies carried out on patients diagnosed with sepsis, promptly measured PCT levels are known to be of predictive value for mortality rates (16,17). Another study analyzing response to antibiotic therapy found that CRP is a potentially preferable biomarker over PCT. Despite this, PCT has been determined to be of greater prognostic value than CRP in evaluating organ failure and mortality risk in patients with sepsis (18). In our study, patients' PCT values as measured in the first 24 hours were found to be positively correlated with mortality. While high PCT values were found to be independent risk factors for mortality, we found no such relationship for high CRP values.

Across the globe, the most commonly used scoring systems in ICUs are SOFA and APACHE-II. These systems contain multiple parameters and are not specific to sepsis. Various studies have investigated whether they can predict mortality in isolation or when combined. In one prospective study, inpatients with a SOFA score ≥11 in the first 24 hours were found to have higher mortality rates while, in 48 hourly followups, SOFA scores ≥50% were similarly associated with high mortality (19). Consequently, SOFA scores have been found to be valuable parameters in determining mortality risk (19). In a study conducted by Fang et al. (20), patients were divided into three groups: all infected patients, patients without preexisting organ dysfunction, and patients with existing organ dysfunction. In terms of predicting 21 day mortality, SOFA scores of 2 and more were found to be 94.2%, 91%, and 97.6% sensitive, respectively, while specificity was 16.9%, 21.9%, and 7.2%, respectively.

A retrospective study of 415 patients undergoing treatment in the ICU assessed the relationship between APACHE-II scores and mortality. It found that APACHE-II scores of 27 and over were associated with increased mortality (21). In our study, both SOFA and APACHE-II scores as recorded in the first 24 hours were found to be significantly associated with mortality. Mortality in patients with high SOFA and APACHE-II scores as calculated at diagnosis had significantly higher mortality rates. In AUROC analysis, which was carried out in order to assess these scoring systems' sensitivity and specificity in predicting mortality, the SOFA AUROC curve value was 0.7449 and the APACHE-II AUROC curve value was 0.733. According to these results, the SOFA scoring system was a better parameter in terms of its value as a predictor of mortality.

The study was subject to several limitations due to a number of factors: the patient population was relatively small, the patients' reasons for admissions were varied, it was carried out retrospectively, and it was a single center study. The study's single-center nature means that the variance in microbial flora between centers may have had an effect on the data.

Conclusion

The locus of the infection leading to sepsis was found not to have a significant effect on mortality. However, the infective microorganism was found to potentially increase mortality. Specifically, *Enterococcus* spp. infection was found to be an independent risk factor for infection. Furthermore, in place of CRP or WBC values, PCT was found to be a more specific biomarker in terms of predicting patients' prognosis.

Ethics

Ethics Committee Approval: İstanbul Bağcılar Training and Research Hospital Ethics Committee garnered on 17/08/2017 under number 2017/603.

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: U.D.H., F.G.Ö., Design: M.S.S., U.D.H., Data Collection and Process: U.D.H., K.E., Analysis or Interpretation: A.S., U.D.H., F.G.Ö., Literature Search: A.S., K.E., Writing: U.D.H., F.G.Ö.

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CASE REPORT / *OLGU SUNUMU*

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Human Metapneumovirus Infection in Adults as the Differential Diagnosis of COVID-19

COVID-19 Ayırıcı Tanısı Olarak Yetişkinlerde İnsan Metapnömovirüs Enfeksiyonu

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ABSTRACT Human metapneumovirus (HMPV) is a respiratory tract virus identified 18 years prior to severe acute respiratory syndrome coronavirus-2. Both viruses cause acute respiratory failure characterised by a rapid onset of widespread inflammation in the lungs with clinical symptoms similar to those reported for other viral respiratory lung infections. HMPV, more generally known as childhood viral infection, causes mild and self-limiting infections in the majority of adults, but clinical courses can be complicated in risky groups and associated morbidity and mortality are considerable. Moreover, adults are not regularly screened for HMPV and the prevalence of adult HMPV infections in Turkey is unknown, with previous reports in the paediatric population. This should always be kept in mind during the coronavirus disease-2019 pandemic, particularly when neurological complications are added to respiratory findings. In our study, two adult cases of HMPV pneumonia and encephalitis have been recorded.
Keywords: Metapneumovirus infection, acute respiratory infections, neurological involvement, wide respiratory screening

ÖZ İnsan metapnömovirus (HMPV), şiddetli akut solunum sendromu koronavirüs-2'den 18 yıl önce tanımlanan yeni solunum yolu virüsüdür. Bilinen diğer viral solunum yolu enfeksiyonlarına benzer klinik semptomlarla sahip olup, her iki virüs de akut solunum yetersizliğine neden olabilir. HMPV çocukluk çağı solunum yolu enfeksiyonu olarak bilinse de, yetişkinlerin çoğunda hafif ve kendini sınırlayan enfeksiyonlara neden olur, hatta riskli hastalarda klinik seyir komplike olup ciddi morbidite ve mortaliteye neden olabilir. Yetişkinler viral enfeksiyon durumunda rutin olarak HMPV için taranmadığından Türkiye'de HMPV enfeksiyonlarının prevalansı bilinmemektedir ve önceki rapor edilen olgular pediatrik popülasyonda yer almaktadır. Koronavirüs hastalığı-2019 pandemisi sırasında özellikle solunum bulgularına nörolojik komplikasyonlar eklendiğinde akılda tutulmalıdır. Bu raporda HMPV pnömonisi ve ensefaliti olan iki yetişkin olguyu sunmaktayız.
Anahtar Kelimeler: Metapnömovirüs enfeksiyonu, akut solunum yolu enfeksiyonları, nörolojik tutulum, geniş respiratuvar tarama

Introduction

Human metapneumovirus (HMPV) is a respiratory tract virus identified 18 years before severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). Both viruses cause acute respiratory failure characterized by rapid onset of widespread inflammation in the lungs with clinical symptoms similar to those reported for other viral respiratory lung infections (1). HMPV is known as childhood infection, but can cause life-threatening infections especially in the frail elderly and the immunocompromised patients (2,3). Adults are not routinely screened for HMPV and prevalence of adult HMPV infections in Turkey is unknown, previous reports were in the pediatric population. However, it should always be kept in mind during coronavirus disease-2019 (COVID-19) pandemic especially when neurological complications are added to respiratory findings. We report two adult cases with HMPV pneumonia and encephalitis.

Case Reports

A first case was a 69-year-old woman with hypertension and Addison's disease. She was admitted to a hospital with fever and dyspnea during SARS-CoV-2 pandemic. At hospital admission, her level of consciousness and the neurological examination was normal. She was transferred directly to our intensive care unit (ICU) due to respiratory failure and non-invasive mechanical ventilation (NIMV) support with a helmet mask was started. Reverse real-time transcriptase polymerase chain reaction (PCR) for COVID-19 was negative and chest computed tomography (CT) was compatible with viral pneumonia. During COVID-19 outbreak because of the situations where the first PCR for COVID-19 can be negative, we initially started treatment against SARS-CoV-2. However, as the respiratory failure progressed she was intubated on the 3th ICU day. Antibiotherapy was changed to piperacillin/tazobactam + vancomycin. Mechanical ventilation was started with pressure-controlled ventilation mode, pressure controlled level (PC): 16 cmH_2O, positive end-expiratory pressure (PEEP): 10 cmH_2O, FiO_2: 70%, but respiratory acidosis and hypoxia persisted and prone ventilation has been used. She was prescribed 5 mg prednisolone due to Addison's disease, steroid treatment of stress dose was arranged by consulting endocrinology. Laboratory tests showed lymphopenia and elevated inflammatory markers. A nasopharyngeal swab specimen was identified as positive for HMPV using duplex reverse transcription PCR. On the 11th day the inflammatory markers were almost normalized and chest X-ray was better, so sedoanalgesia was gradually reduced. However, 48 h following cessation of all sedation the patient did not regain consciousness and neurology consultation was performed. Cranial magnetic resonance imaging (MRI), including diffusion-weighted and contrast-enhanced series showed bilateral frontal signal changes compatible with meningoencephalitis. MRI findings were suggestive of acute encephalitis with a concomitant acute demyelinating process. Lumbar puncture revealed normal glucose and high protein levels, cell count, IgG index and albumin were within normal limits and no viruses could be isolated in the cerebrospinal fluid (CSF). Oligoclonal bands were negative. Intravenous corticosteroid treatment (1 mg/kg/24 h) followed by plasmapheresis with albumin was initiated and performed on alternate days for five cycles. The patient developed generalized tonic-clonic seizure, so sedation was deepened with thiopental, midazolam and fentanyl. General condition of the patient worsened, lymphopenia and inflammatory marker elevation persisted with refractory fever around 40 °C. All potential infectious sources were ruled out, antibiotherapy was escalated and inotropic support has been increased significantly. However, cardiac arrest developed on the 16th ICU day, and cardiopulmonary resuscitation was unsuccessful.

The second case was an 82-year-old woman with atrial fibrillation and hypertension. She presented fever and worsening dyspnea, a diagnosis of viral pneumonia was confirmed by chest CT. Reverse real-time transcriptase PCR for SARS-CoV-2 was negative. She was hospitalized directly in the ICU and started NIMV support with a helmet mask. During coronavirus pandemic we started treatment accepting patients as PCR positive for COVID-19 without waiting for the result. Laboratory tests showed lymphopenia and elevated inflammatory markers. On the third day of admission, her respiratory failure required endotracheal intubation and mechanical ventilation (PC mode, PC: 20 cmH_2O, PEEP: 14 cmH_2O, FiO_2 50%). A nasopharyngeal swab specimen was identified as negative for COVID-19 and positive for HMPV. On the 12th of ICU day with the normalization of infectious markers and improvement of chest X-ray, sedation was gradually reduced and stopped. She was awake with delirium which couldn't be explained by any metabolic occurrence, and was extubated under maximum doses of haloperidol and dexmedetomidine. Neurology consultation was performed, but MRI or lumbar puncture (LP) wasn't performed due to

the lessening of symptoms. The patient was discharged to a ward on the 14th day of ICU treatment. Agitation decreased but persisted despite treatment even after discharged to a ward. The patients remained physically and cognitively impaired despite rehabilitation. The neuropsychological assessment showed mild difficulties on social abilities.

Discussion

To the best of our knowledge, this is the first case report of HMPV infection in adults from Turkey. Our first case support consideration of HMPV as a causative agent of acute central nervous system (CNS) involvement after respiratory tract infection in adults. The clinical presentation, laboratory and CSF results, and radiologic findings supported the diagnosis of encephalitis. CSF examinations showed elevated protein with no marked pleocytosis typically seen in viral encephalitis and similar to cases of COVID-19-related CNS involvement (4). The presence of severe agitation in the second case suggests CNS involvement, but we do not have MR and LP evidence to support this hypothesis.

HMPV infection can not be distinguished from other respiratory viruses on clinical and laboratory findings only (5). Compared to other respiratory viruses it has similar rates of ICU admission, mechanical ventilation, and length of stay for hospitalization (6). Neurotropic potential of HMPV seems to be one of the main pathologic mechanisms of these infections. CNS involvement is documented in both children and adults (7-9). Moreover, in many cases of encephalitis of unknown etiology, HMPV has been simultaneously detected in the respiratory tract. The mechanism by which the CNS is affected by the virus is unclear, and treatment approaches are not well defined (10). The fact that we could not demonstrate the virus from CSF may point toward the role of autoimmune inflammatory response as the pathogenic factor in CNS involvement or the timing of viral isolation from CSF had passed.

HMPV at present is still without specific antiviral therapy and managing HMPV-encephalitis is a challenge for intensivists (11). Current clinical management as with COVID-19 includes infection prevention and control measures and supportive care, including supplemental oxygen or mechanical ventilatory support, and advanced supportive therapy like plasmapheresis and steroid therapy when indicated.

The presented cases emphasize the importance of a wider respiratory screening in viral pneumonias. HMPV should be kept in mind when no other etiological agent can be found in the presence of viral pneumonia and CNS involvement findings. Determination of the etiological agent may prevent the use of unnecessary antibiotics. Further studies and treatment strategies are necessary to augment the therapeutic approach in these patients.

Ethics

Informed Consent: Due to pandemic conditions consent was taken by phone from patient relatives.

Peer-review: Internally peer-reviewed.

Authorship Contributions

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

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CASE REPORT / *OLGU SUNUMU*

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Neuroleptic Malignant Syndrome Requires Intensive Care Monitoring: A Review with Three Cases

Yoğun Bakımda Takibi Gerektiren Üç Nöroleptik Malign Sendrom Olgusu ve Literatür Taraması

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ABSTRACT Neuroleptic malignant syndrome (NMS) is a rare, idiosyncratic and potentially fatal side effect of antipsychotics. The syndrome is characterised by hyperthermia (fever), muscle rigidity, autonomic disturbances and alterations of mental state. Psychotropic medications, such as typical and atypical antipsychotics, certain dopamine receptor-blocking drugs used in the treatment of nausea and gastroparesis (e.g. promethazine, metoclopramide and prochlorperazine) and antidepressants, such as amoxapine, have all been implicated in the aetiology of NMS. Herein, we report three cases of NMS and discuss their possible aetiology with reference to the existing literature.
Keywords: Fever, antipsychotics, mental state alterations

ÖZ Nöroleptik malign sendrom (NMS), antipsikotik ilaçların nadir görülen, idiyosenkratik, potansiyel olarak ölümcül bir yan etkisidir. Sendrom, hipertermi (ateş), rijidite, otonomik bozukluklar ve zihinsel değişiklikler ile karakterizedir. Tipik ve atipik antipsikotikler gibi psikotropik ilaçlar, bulantı ve gastroparezi tedavisinde kullanılan bazı dopamin reseptör antagonisti ilaçlar (örneğin; prometazin, metoklopramid, proklorperazin) ve amoksapin gibi antidepresanların tümü NMS etiyolojisinde yer almıştır. Bu olgu serisinde üç NMS olgusu bildirdik ve mevcut literatürler eşliğinde olası etiyolojileri tartışmayı amaçladık.
Anahtar Kelimeler: Ateş, antipsikotikler, mental durum değişikliği

Introduction

Neuroleptic malignant syndrome (NMS) is a rare, idiosyncratic and potentially fatal side effect of antipsychotic medications (1). First described in 1968 (2,3), shortly after the introduction of neuroleptics, it occurs in about 0.2% of patients (4) treated with the medications. The prevalence of NMS is found to be variable, ranging from 0.02 to 2.4% (1). Syndrome is characterized by hyperthermia (fever), muscle rigidity, autonomic disturbances and mental state alterations.

Psychotropic medications such as the typical and atypical (5,6) antipsychotics, certain dopamine receptor-blocking drugs used in the treatment of nausea and gastroparesis (e.g., promethazine, metoclopramide, prochlorperazine), and antidepressants like amoxapine have all been implicated in the aetiology of NMS (7). Another precipitant is the abrupt discontinuation of anti-Parkinsonian agents (8). Some cases have been reported after the use of cocaine (5) and lysergic acid diethylamide (9). Despite being a well-recognised condition, the pathogenesis of NMS is not fully understood. Although many risk factors have been identified, predicting which patients will develop NMS and when, remains extremely difficult (10). We report three cases of NMS and discuss possible etiologies with reference to the existing literature.

Case Reports

Two of the three patients were male and one were female. None of the patients had a previous diagnosis of NMS. All patients had a previously known psychiatric disorder. Two of the patients were using a combination of typical and atypical antipsychotics and the other was using lithium and antipsychotics. All patients had high fever and blurred consciousness, but rigidity was not seen in any patient. Creatine kinase (CK) was elevated in all patients. One of the patients died during the follow-up. Necessary consents were obtained from all patients.

Case 1

A seventy-one-year-old male patient was brought to the emergency department by his relatives due to blurred consciousness, unresponsiveness, and speech impairment. Patient was started risperidone, quetiapine and sodium valproate five days ago. Three days after started the medications, his complaints have appeared. In physical examination; Glasgow coma score (GCS): $E_1M_4V_3$, blood pressure: 128/77 mmHg, heart rate: 103/min, saturation: 96%, respiratory rate: 23/min, no rigidity. The patient had fever of 38.9 °C and white blood cell (WBC) count: 10,140/mm^3, and CK: 3,026 U/L were detected in the laboratory. Patient was admitted to intensive care unit with a preliminary diagnosis of NMS. Patient was consulted to the neurology and psychiatry. Only hydration was recommended. Patient's general condition gradually deteriorated during follow-up and was intubated on the fifth day of hospitalization. The patient died on the 8th day of hospitalization.

Case 2

A nineteen-year-old female patient were following up with congenital mental developmental delay and psychotic disorder for 10 years. She was brought to the emergency department by her relatives due to blurred consciousness, tremors and fever. It was learned that, due to the deterioration in oral intake during the last ten days; she has not been used the medication; quetiapine, clonazepam and biperiden. In physical examination; GCS: $E_4M_3V_1$, blood pressure: 98/63 mmHg, heart rate: 82/min, saturation: 94%, respiratory rate: 12/min, no rigidity. The patient had fever of 38.5 °C and WBC: 10,000/mm^3, and CK: 3,803 U/L were detected in the laboratory. Patient was admitted to intensive care unit with a preliminary diagnosis of NMS. Patient was consulted to the neurology and psychiatry. Hydration and supportive treatment recommended. CK decreased to 300 U/L and vitals were stable, he was transferred to the neurology department. The patient was hospitalized for 15 days. He was discharged on 25th day.

Case 3

Sixty-one years old male patient were using risperidone, lithium and quetiapine for psychosis. He was brought to the emergency department by his relatives due to deterioration in his communication with relatives, inability to sleep, confusion and fever. It was learned from the relatives that the patient voluntarily discontinued his medication. In physical examination; GCS: $E_2M_4V_3$, blood pressure: 118/69 mmHg, heart rate: 77/min, saturation: 100%, respiratory rate: 15/min, no rigidity. The patient had fever of 39,2 °C and WBC: 6,720/mm^3, and CK: 4,545 U/L were detected in the laboratory. The patient was hospitalized with a pre-diagnosis of NMS. Hydration and supportive treatment was started. The patient's CK value regressed to normal limits. The patient treatment was regulated and discharged with recommendations.

Discussion

NMS is a rare clinical entity characterized by mental status change, motor abnormalities such as, rigidity and bradykinesia, autonomic dysfunction (such as blood pressure changes, diaphoresis and tachycardia) and fever. Although rare, it can lead to life-threatening complications that require immediate intervention. Laboratory findings such as leukocytosis, CK and elevation in liver function tests frequently accompany the clinical picture (6,11-14). Clinical findings of NMS include; changes in consciousness, hyperthermia, diaphoresis, elevated or labile blood pressure, dysphagia, incontinence, lead-tube rigidity, akinesia or dystonia, rhabdomyolysis, myoclonus. Not all NMS findings may be present at the same time (15). None of our cases had rigidity. Leukocytosis and CK elevation were observed in all of our cases. We lost one of our patients despite all the treatments.

Normal oral temperature of a man is 35.7-37.7 degrees (96.3-99.9 °F). Hyperpyrexia (temperature above 38 °C) was encountered in almost all cases. All of our patients had fever.

Central dopaminergic hypoactivity due to sudden discontinuation of dopaminergic agents or antipsychotics, or the use of dopamine antagonists is the main cause of NMS (6,13-16). Although NMS is mostly associated with the use of typical and high potency antipsychotics (such as

haloperidol), there are also cases identified with other low potency antipsychotics and new atypical antipsychotics (17). Few cases have been reported either due to the use of lithium and other antipsychotics or due to the combination of anticonvulsants such as carbamazepine and tricyclic antidepressants (18,19). All of our cases had a history of antipsychotic use. The most frequently encountered drugs in our patients were risperidone, an atypical antipsychotic, and quetiapine, a combination of other antipsychotics.

The main predisposing factors to facilitate the development of NMS include male sex, young age, dehydration, hyponatremia, agitation, intramuscular or parenteral administration of antipsychotic medication, or use of depot formulas, high dose neuroleptic uptake and rapid dose titration, concomitant use of lithium and reuptake inhibitors, mental retardation, extrapyramidal syndromes, psychomotor agitation, malnutrition, emotional stress, infections and previous history of NMS (6,12,14,16,20,21). Two of our cases were male and one was female. One of our patients did not take their medication due to oral intake disorder and the other was stopped because of their own will; it was thought NMS might have developed.

Laboratory changes that we frequently see in NMS include; increased serum CK level (>1,000 IU/L), elevation in liver, kidney and coagulation tests, leukocytosis, electrolyte changes, proteinuria and rhabdomyolysis (16). All of our patients had a high CK value and decreased to normal limits after treatment. Rhabdomyolysis is one of the major complications that may occur during the course of NMS. Increased CK value with deterioration of renal function and darkening of urine color but no hematuria detected on urine microscopy should be a warning for rhabdomyolysis. No pathology related to liver or kidney was detected in any of our patients. Rhabdomyolysis was not seen in any our patients.

Discontinuation of the medicatio is the most important step in the treatment. Dehydration, electrolyte imbalance, protection from infection and thrombosis, supportive therapies for hyperthermia and acute renal failure are important in reducing morbidity and mortality (20). Dopaminergic agents such as bromocriptine and amantadine, dantrolene, and lorazepam and diazepam which are effective over the GABA'ergic system are the most commonly used pharmacological treatment methods. Drug therapy should be continued for at least two to three weeks until symptoms disappear and are completely healed (20,22). If the use of antipsychotic medication is to be initiated after complete treatment of NMS, it should be performed at low doses, by slow titration, avoiding dehydration and the use of lithium together (14,16).

As a result, NMS is a serious and life-threatening condition. Early diagnosis and appropriate treatment are of great importance in reducing mortality and morbidity. Although NMS is a psychiatric diagnosis, its treatment requires a very complicated and systematic approach. In this regard, after any neuroleptic intake, patients with suspicious symptoms and signs should be carefully monitored and the most appropriate treatment should be given at the right time.

Ethics

Informed Consent: Necessary consents were obtained from all patients.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: İ.A.Ş., Design: İ.A.Ş., Data Collection or Processing: İ.A.Ş., Analysis or Interpretation: İ.A.Ş., M.K., C.Ş., H.S., Literature Search: İ.A.Ş., M.K., C.Ş., H.S., Writing: İ.A.Ş.

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CASE REPORT / *OLGU SUNUMU*

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A Novel Therapeutic Approach for Renal Transplant Recipient with Septic Shock and Acute Kidney Injury: A Case Report

Septik Şok ve Akut Böbrek Hasarı Olan Böbrek Nakil Alıcısında Yeni Bir Terapötik Yaklaşım: Bir Olgu ile

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ABSTRACT Extracorporeal blood purification (EBP) therapies, using oXiris® haemofilter, are popular and used globally in intensive care units for management of patients with septic acute kidney injury (AKI). Herein, we present a case of an immunocompromised renal transplant recipient with sepsis and AKI who was treated with continuous renal replacement therapy (CRRT) using oXiris® haemofilter. A 45-year-old female who underwent cadaveric renal transplantation in 2015 was admitted due to septic shock secondary to *Escherichia coli* urinary tract infection (bacteraemia) and acute respiratory distress syndrome (ARDS). Her acute physiology and chronic health assessment score was 23, sepsis-related organ failure score was 11 and Glasgow coma scale was 15. She was intubated because of moderate ARDS and administered vasopressors due to hemodynamic instability. For immunosuppressive therapy, methylprednisolone (40 mg q12h) was administered. Antimicrobial therapies, including intravenous meropenem, linezolid, trimethoprim-sulfamethoxazole, voriconazole and oseltamivir, were administered. She exhibited metabolic acidosis and septic AKI and was classified as Kidney Disease Improving Global Outcomes stage 3. Therefore, CRRT with oXiris® haemofilter was administered at the 11th hour after admission. A full recovery of transplant renal function and diuresis was observed 7 days after admission. She was transferred to ward after 9 days and discharged after 2 weeks, without the requirement of RRT. EBP is proposed as an adjuvant therapy for sepsis and AKI. Solid organ transplant recipients with septic AKI may benefit from early usage of oXiris® haemofilter with CRRT as a novel approach for improving survival and clinical outcomes.
Keywords: Sepsis, acute kidney injury, renal replacement therapy, renal transplant recipient, extracorporeal blood purification

ÖZ oXiris® hemofiltre gibi ekstrakorporeal tedavi (ET) yöntemlerinin kullanımı, özellikle yoğun bakım ünitelerinde septik akut böbrek hasarı (ABH) olan hastaların yönetiminde giderek artmaktadır. Sepsis ve ABH olan immünosüprese böbrek nakil alıcısında oXiris® hemofiltre ile sürekli renal replasman tedavisinin (SRRT) etkin kullanımını göstermeyi amaçladık. 2015 yılında kadavradan böbrek transplantasyonu yapılan 45 yaşında kadın hasta, akut solunum sıkıntısı sendromu (ARDS) ve *Escherichia coli*'ye bağlı idrar yolu enfeksiyonu nedeniyle septik şok ile yoğun bakım ünitesine kabul edildi. Akut fizyoloji ve kronik sağlık değerlendirme skoru 23, sepsise bağlı organ yetersizliği skoru 11 ve Glasgow koma skalası 15 idi. Orta derecede ARDS nedeniyle entübe edildi ve hemodinamik disfonksiyon nedeniyle vazopresör desteği başlandı. İmmünosüpresif tedavi için metilprednizolon 2x40 mg uygulandı. İntravenöz meropenem, linezolid, trimetoprim-sülfametoksazol, vorikonazol ve oseltamivir ile çoklu antimikrobiyal tedavi uygulandı. Septik ABH ve metabolik asidozu mevcuttu. Böbrek hastalığı; Küresel Sonuçları İyileştirilmesi Çalışma Grubu'na göre evre 3 olarak sınıflandırıldı ve yoğun bakım ünitesine kabulden sonraki 11. saatte oXiris® hemofiltre ile SRRT başlandı. Kabulden 7 gün sonra transplante böbrek fonksiyonunda ve diürezde tam bir iyileşme gözlendi. Dokuz gün sonra servise devredildi ve 2 hafta sonra RRT ihtiyacı olmadan taburcu edildi. ET, sepsis ve ABH için adjuvan bir tedavi olarak önerilmektedir. Yeni bir tedavi yöntemi olarak oXiris® hemofiltre ile SRRT'nin erken kullanımı, septik ABH olan solid organ nakil alıcılarında sağkalımı ve klinik sonuçları iyileştirebilir.
Anahtar Kelimeler: Sepsis, akut böbrek hasarı, renal replasman tedavisi, böbrek nakil alıcısı, ekstrakorporeal tedavi

Introduction

Sepsis is one of the most important causes of acute kidney injury (AKI) in intensive care unit (ICU). It can be seen in approximately 50% of critically ill patients with severe AKI (1,2). If a patient with septic AKI has hemodynamic instability and/or fluid overload, continuous renal replacement therapy (CRRT) is recommended for treatment (3).

Extracorporeal blood purification (EBP) is suggested as an adjuvant therapy for sepsis aimed at correcting organ dysfunctions associated with the dysregulated immune system (4). The oXiris® hemofilter has a high permeability polyacrylonitrile (AN69) based membrane (1,5). It is a next-generation EBP device that has high adsorption capacity for CRRT and both endotoxins and cytokine removal (5-7).

Several cytokines such as interleukin-1 (IL-1), IL-6 and tumor necrosis factor-alpha (TNF-α) increase in sepsis. There is a significant relationship between increased levels of these cytokines and morbidity and mortality. oXiris® hemofilter purifies the majority of immune system mediators. There are *in vitro* filtration and observational studies showing that all IL-10 and 90% of IL-6 and TNF-α are removed from the blood (8). Endotoxin adsorption is an innovative approach involved in management of sepsis. It controls the systemic inflammatory response that causes acute tissue and organ damage in sepsis (9).

The use of EBP therapies such as oXiris® hemofilter for management of septic AKI patients are popular worldwide in intensive care settings. Mondhe et al. (10) presented a poster describing the use of oXiris® hemofilter in a liver transplant recipient with sepsis and AKI. We present a successful clinical report of an immunocompromised renal transplant recipient with sepsis and AKI treated with CRRT using a oXiris® hemofilter.

Case Report

A 45-year-old female was hospitalized with nausea, vomiting and dysuria. Empirical antibiotic treatment was started with ertapenem due to urinary tract infection. The patient was admitted to ICU from the ward due to rapid deterioration of her clinical status. She had metabolic acidosis, respiratory distress and severe hemodynamic instability with need for vasopressor support. In the medical history, she had hypertension, diabetes mellitus type 2 and she underwent cadaveric renal transplantation 4 years ago. The patient has given her written informed consent to publish her case (including publication of images).

On physical examination, she was awake at ICU admission. Her vitals were as follows: Heart rate: 125/minute, respiratory rate: 32/min, and blood pressure: 69/43 mmHg and body temperature (axillary measurement): 36.5 ˚C. In lung auscultation, coarse rales were present in the middle-lower areas of both hemithorax. Acute Physiology and Chronic Health Assessment-II (APACHE-II) score was 23, Sequential Organ Failure Assessment (SOFA) score was 11 and Glasgow coma score (GCS) was 15. Arterial blood gas (ABG) was pH: 7.22, partial oxygen pressure (PaO_2): 62.3 mmHG, partial carbon dioxide pressure ($PaCO_2$): 26.3 mmHg, bicarbonate (HCO_3): 9.8 mmol/L, lactate: 1.7 mmol/L, oxygen saturation (SaO_2): 90.8% under nasal oxygen therapy of 6 lt/min at ICU admission. PaO_2/FiO_2 (inspired oxygen fraction) ratio was 141.5 in accordance with moderate acute respiratory distress syndrome (ARDS). Chest X-ray showed bilateral patchy infiltrates on the middle-lower areas of both hemithorax and computerized tomography of the thorax confirmed bilateral patchy alveolar infiltrates, ground-glasses and consolidations (Figure 1).

The hemodynamic status was instable so, norepinephrine infusion was started at 0.1 µg/kg/min and rapidly increased to 1.5 µg/kg/min, in combination with dobutamine infusion at 5 µg/kg/min. An advanced hemodynamic monitoring system (Most Care® powered by Pressure Recording Analytical Method, PRAM; Vytech Health®, Padova, Italy) was applied. She was treated according to the sepsis bundle guidelines, including administration of hydrocortisone dosages (200 mg/day on 4 days) for septic shock. Then, methylprednisolone

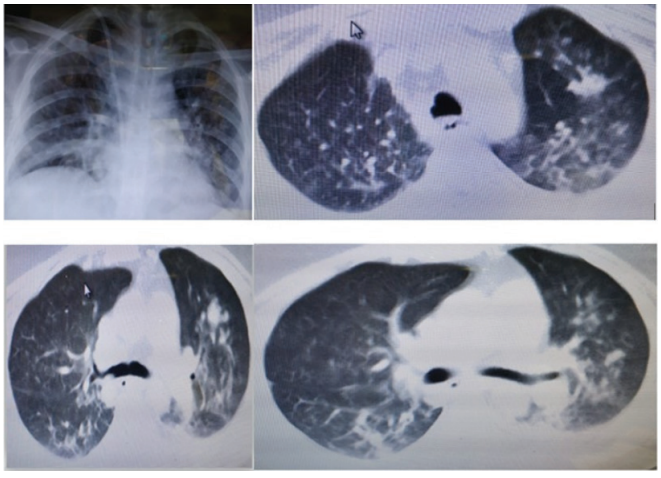

Figure 1. Chest X-ray and computerized tomography of the thorax

was administered 40 gm q12h for 9 days. She was intubated 5th hour after ICU admission because of moderate ARDS and ventilated by intellivent adaptive support ventilation mode for 6 days.

Laboratory parameters were presented in Table 1. There were elevated inflammatory marker plasma levels, increased blood urea nitrogen and serum creatinine. ABG analysis revealed metabolic acidosis on ICU admission (pH: 7.22, pCO_2: 24.4 mmHg, base excess: -16.3 mmol/L, HCO_3: 9.8mmol/L, lactate: 1.7 mmol/L). Renal biopsy was performed, and infection-associated acute tubulointerstitial nephritis was diagnosed.

Due to a further increase in retention parameters and metabolic acidosis, she was classified as Kidney Disease Improving Global Outcomes (KDIGO) stage 3, so she received CRRT for the following 7 days. Continuous venovenous hemodiafiltration (CVVHDF) using Prismaflex CRRT machine (Baxter, Deerfield, IL, USA and Gambro Hospal, Stockholm, Sweden) and the oXiris® hemofilter with citrate anticoagulant was initiated at 11th hour of admission to the ICU and it was stopped at 96th hour of treatment. Due to volume overload, ultrafiltration was attempted and was successfully established at 50-250 mL/h in order to reduce the positive fluid balance. Blood flows was set at 100 mL/min and dialysis maintained in the range of 25-30 mL/kg/h (Table 2). The CVVHDF was stopped after 168 hours because of renal recovery. The therapy ensured a progressive improvement in her hemodynamic status and a reduction vasopressor requirements (Table 3).

Escherichia coli was isolated in the blood and the urine culture. Antimicrobial therapy with intravenously meropenem (2 gram every 8 h) for 13 days, linezolid (600 mg every 12 h) for 8 days, trimethoprim-sulfamethoxazole (400 mg every 8 h-dosing is based upon the trimethoprim component) for 14 days, oral voriconazole (200 mg every 12 h) 14 days and oral oseltamivir (75 mg every 12 h) for 5 days were administered. Polymerase chain reaction tests of influenza type A-B,

Table 1. Laboratory parameters of inflammation and organ dysfunction throughout the treatment period

Day	1st day	2nd day	3rd day	4th day	5th day	6th day	7th day	8th day	9th day
Hgb (g/dL)	10.2	8.8	9.9	10	10.2	9.5	8.7	7.9	9.3
Hct (%)	30.7	27.9	31	32.1	29	30.2	27.4	25.5	28.5
Platelet (10^3/µl)	69	65	69	63	88	68	64	53	72
WBC (10^3/µl)	10.8	17.1	16.7	13.8	17.2	16.3	10.8	5.36	5.98
PT (sec.)	20.5	19.2	15	13.8	13	13.3	13.6	13.6	13.5
INR	1.8	1.69	1.32	1.2	1.14	1.16	1.19	1.19	1.18
BUN (mg/dL)	59.3	42	43	57	56	43	32	33	43
Cr (mg/dL)	3.88	3.03	2.11	2.07	1.78	1.62	1.22	1.39	2.11
Na (mg/dL)	138	133	133	130	130	133	130	135	136
K (mg/dL)	3	3.6	3.9	3.6	4	3.5	3.9	3.9	3.7
Cl (mg/dL)	103	99	98	96	95	98	97	102	104
P (mg/dL)	4.78	3.2	3.7	3.4	4.3	4.3	2.6	1.9	3
Albumin (g/dL)	2.9	2.9	3	2.9	3	2.8	2.7	2.5	2.5
AST (U/L)	42	43	40	38	29	25	23	26	27
ALT (U/L)	8	19	19	15	14	11	11	13	16
T. bil (mg/dL)	0.57	0.7	0.7	0.6	0.4	0.5	0.5	0.6	0.5
D. bil (mg/dL)	0.42	0.3	0.4	0.4	0.2	0.3	0.5	0.2	0.2
Lactate (mmol/L)	2.7		1.2	1.2	1.9	1.4	0.9	1.3	
CRP (mg/L)	337	525	361.1	242	141	77	70.7	43.4	28.3
PCT (µg/L)	59	-	15	-	5.5	-	2.8	-	0.25

Hgb: Hemoglobin, Hct: hematocrit, WBC: white blood cell, PT: prothrombin time, INR: international normalized ratio, BUN: blood urea nitrogen, Cr: creatinine, Na: sodium, K: potassium, Cl: chloride, P: phosphate, AST: aspartate aminotransferase, ALT: alanin aminotransferase, T. bil: total bilirubin, D. bil: direct bilirubin, CRP: C-reactive protein, PCT: procalcitonin, sec: second

respiratory syncytial virus and cytomegalovirus DNA were negative. Pneumocystis pneumonia was not detected in bronchoalveolar lavage.

She was extubated after 6 days. A recovery of transplant renal function and diuresis was observed evidenced by increasing urine output and decreasing serum creatinine, which resulted in the discontinuation of CVVHDF after 7 days from the admission. Her glomerular filtration rate was 37 mL/min by the Cockcroft-Gault formula and 26.9 mL/min/1.73 m^2 by the Modification of Diet in Renal Diseases Study formula. She was transferred to ward after 9 days and discharged after 2 weeks without requirement for renal replacement therapy.

Discussion

Sepsis is a combination of organ dysfunctions that occur with infection. This dysregulated host response has physiologic, pathologic, and biochemical abnormalities. One of the most important recommendations in the management of sepsis is the urgent application of antibiotics within the first 3 hours of suspected sepsis (9). The first approach in the management of sepsis to control the source of infection by early and targeted intervention. The importance of endotoxin and cytokine removal in criticaly ill patients is increasing to improve outcomes (11). This case presented that the clinical situation improved with rapid infection source control, effective antibiotic administration, and early use of the oXiris® hemofilter with CRRT due to AKI within 6-24 hours of suspected sepsis.

oXiris® hemofilter is a combination of AN69-based membrane hemofilter, surface treatment with polyethyleneimine and grafted with heparin. It removes cytokines and endotoxins from blood circulation (12,13). Case series demonstrated that oXiris® hemofilter therapy reduced especially IL-6 level and improved hemodynamics

Table 2. Setting changes of CRRT with oXiris® hemofilter

Day	1st day	2nd day	3rd day	4th day	5th day	6th day	7th day	8th day
Q_b, mL/min	100	100	100	100	100	100	100	100
Q_d mL/h	250	250	250	100-250	250-500	500	500	500
Predilution, mL/h	1,500	1,500	1,500	1,500	1,500	1,500	1,500	1,500
Postdilution, mL/h	250	250	250	100-250	250	250	250	250
Q_r mL/h	1,750	1,750	1,750	1,600-1,750	1,750	1,750	1,750	1,750
UF, mL/h	0	50-250	250	100	100-200	50-70	70	0
UO, mL/24 h	10	40	20	40	5	1,180	1,510	4,200

Q_b: Blood flow rate, Q_d: dialysate flow rate, Q_r: replacement fluid rate, UF: ultrafiltration rate, UO: urine output, CRRT: continuous renal replacement therapy

Table 3. Hemodynamic and arterial blood gas analysis during CRRT with oXiris® hemofilter

	0th hour	1st hour	6th hour	12th hour	24th hour	48th hour	72nd hour	96th hour	120th hour	144th hour	168th hour
pH	7.4	7.41	7.4	7.38	7.43	7.42	7.39	7.4	7.49	7.53	7.51
paO_2 (mmHg)	89.5	86.1	111	176	45.2	86.3	83	113	93.6	126	124
$paCO_2$ (mmHg)	28.6	31.4	32.7	36.6	34.1	31.1	29.7	27.3	27.2	23.8	26.3
HCO_3 (mmol/L)	17.6	19.7	20.1	21.6	22.7	20.1	17.9	16.9	20.9	19.9	21.3
BE (mmol/L)	-6.2	-4.1	-3.8	-2.6	-0.9	-3.5	-6	-6.8	-1.9	-2.5	-1.3
Lactate (mmol/L)	3.3	2.6	2	1.5	1.3	1.3	1.7	2	1.4	1.4	1.1
Urine output (mL/h)	0	0	0	0.4	0	0	0	0	0	58	70
N (mcg/kg/min)	1	1	1.5	1.4	0.9	0.25	0.25	0.18	0.08	0.03	-
D (mcg/kg/min)	5	5	5	5	5	4	4	4	3	3	1
CVP	8	8	7	6	10	7	6	7	7	6	4
SOFA score	11	-	-	-	11	10	9	9	8	8	5

PaO_2: partial oxygen pressure, $PaCO_2$: partial carbon dioxide pressure, HCO_3: bicarbonate, BE: base excess, N: norepinephrine, D: dobutamine, CVP: central venous pressure, SOFA: Sequential Organ Failure Assessment, min: minute, CRRT: continuous renal replacement therapy

(7). So, oXiris® hemofilter can be considered as a supportive therapy in the treatment of sepsis.

We presented a patient with *E. coli* bacteremia who had decrease in SOFA score, improved hemodynamics and reduction of vasopressor requirements with oXiris® hemofilter therapy (Table 3). Our results were similar to most studies researching the oXiris® hemofilter (14-16). Schwindenhammer et al. (17) reported their experiences with 31 septic shock patients using CRRT and the oXiris® hemofilter. They found that the most severe patients who received CRRT therapy with the oXiris® hemofilter also had higher observed survival than predicted by a severity score (SAPS II). There are studies showing that it improves hemodynamic status and hyperlactathemia in Gram negative bacilli-induced intra-abdominal sepsis. In the study of Shum et al. (14), oXiris® hemofilter and continuous venovenous hemofiltration (CVVH) were performed in 6 patients with septic AKI caused by Gram negative bacteria. The SOFA score decreased significantly after 48 hours in the oXiris® group. A significant decrease in the SOFA score at 72 hours was also observed in the study of Adamik et al. (15). In our case, we reported a 3-point decrease in the SOFA score 72 hours after the treatment. Also, Shum et al. (14) presented that *E. coli* accounted for 100% (6 patients) in the oXiris-CVVH group. The same bacteria from the blood and the urine culture of our patient was identified. Like our case, 4 patients with septic AKI who were applied renal replacement therapy with oXiris® hemofilter in China, were presented in the study of Zhang et al. (18). These cases in the literature and our case showed that the clinical condition of patients improved with rapid infection source control and the usage of oXiris® hemofilter within 6-24 hours in the management of suspected sepsis. Furthermore, 2 patients had gram negative sepsis as our patient.

Broman and Bodelsson (11) presented reduction of endotoxin levels after usage oXiris® hemofilter in 2 patients with Gram negative bacteria-induced septic shock including endotoxemia. KDIGO class 3 AKI was detected in both patients, and CRRT was started using an oXiris® hemofilter. Likewise, we presented a successful clinical report of an immunocompromised renal transplant recipient with gram negative septic shock and KDIGO grade 3-AKI treated with CRRT using a oXiris® hemofilter.

Determining the best time to start EBP with devices such as the oXiris® hemofilter is difficult and controversial. If a patient with septic AKI has a hyperinflammatory state and/or hemodynamic instability, early usage of EBP with the oXiris® hemofilter may be considered without waiting for diagnostic confirmation of abnormal biomarker levels. Of course, it should be done together with the source of infection and standard sepsis care (19).

The timing of EBP with the oXiris® hemofilter is an important key factor. In the study of Govil et al. (20), a significant difference was observed in the SOFA score and vasopressor decrease in the group that used early Oxiris hemofilter. oXiris® hemofilter inception time was shorter in survivors than non-survivors (7.2 vs 12.5 hours) in the study of Tang et al. (21). A clinical trial involving 15 septic patients who were applied CRRT with the oXiris® hemofilter reported that the early inception of therapy improved outcomes before the organ damage started (22). In this case, oXiris® hemofilter was used on 11th hour after admission similar to literature.

oXiris® hemofilter improve hemodynamic status and lactate metabolism and increases respiratory capacity. The improvement is thought to be due to purification of cytokines, inflammatory mediators, endotoxin adsorption and the maintenance of fluid balance. In a clinical trial involving 40 septic patients who were applied CRRT with the oXiris® membrane, levels of procalcitonin, IL-6, endotoxin, norepinephrine and creatinine decreased after 24 hours of therapy (7). The dosage of noradrenaline is also decreased, as shown by Shum et al. (14) and Turani et al. (7). In our case, lactate level decreased in 6th hour of therapy, creatine and norepinephrine levels decreased 24 hours after treatment, procalcitonin decreased 48 hours later and she was extubated after 6 days.

Normally, it is recommended to change the filter set every 24 hours to ensure the filter performance. The product label includes the replacement of the hemofilter to an upper limit of 72 hours and/or a maximum through put of 780 L of blood (5). However, we used the filter continuously for 96 hours with citrate anticoagulation.

Immunoparalysis is observed in immunocompromised patients. So, the use of EBP therapies may also represent a good adjunctive therapy option in these patients with sepsis and multiple organ failure. Keles et al. (23) reported the a successful administration of CytoSorb® hemadsorption in an immunocompromised pediatric patient with collapsing glomerulopathy, ARDS, and sepsis. There is limited data about the usage of oXiris® hemofilter in immunocompromised adult patients in the literature.

The case report has some limitations. There is no clinical study in which loss of antibiotics and micronutrients with CRRT using a highly adsorptive hemofilter like oXiris® hemofilter was reported. A close drug-monitoring should be performed to ensure appropriate antibiotic concentrations. But, the monitoring could not be done because the antibiotic levels are not studied comprehensively in our hospital. One of our limitations was that we could not measure endotoxin and cytokine levels, so we could not detect the decrease due to treatment. This presentation is only a case report. Randomised controlled trials about this therapy will provide more useful information.

This is a case report that includes the successful use of oXiris® hemofilter in a renal transplant recipient with septic AKI. The use of EBP therapies in acute phase of septic shock and septic AKI may be beneficial for early improvement, decreasing vasopressor requirment, need for organ supports, the length of ICU stay and mortality. So, EBP is proposed as an adjuvant therapy for sepsis and AKI. Solid organ transplant recipients with septic AKI may benefit from early usage of oXiris® hemofilter with CRRT as a novel approach to improve survival and clinical outcomes. Further randomized control trials are recommended to prove the potential benefits of this treatment.

Ethics

Informed Consent: The patient has given her written informed consent to publish her case (including publication of images).

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.H., Concept: E.G., P.Z., M.H., Design: E.G., P.Z., M.H., Data Collection or Processing: F.İ.Y., B.M.Y., Analysis or Interpretation: F.İ.Y., E.G., P.Z., Literature Search: F.İ.Y., B.M.Y., Writing: F.İ.Y., B.M.Y., E.G.

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