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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.

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

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YAZARLARA BİLGİ

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

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

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

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

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

2) Özet (Sayfa 2)

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

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

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

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

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

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

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

Bulgular bölümü de çalışmanın tekrar edilebilmesine yetecek ayrıntıları içermelidir.

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

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

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

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

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REVIEW / *DERLEME*

Lee Goeddel,
Ozan Akça

Perioperative Acute Kidney Injury

Perioperatif Akut Böbrek Hasarı

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ABSTRACT Acute kidney injury (AKI) is one of the important complications of the perioperative period, and associated with increased risk of chronic kidney disease, renal replacement therapy requirements, increased cost, and risk of mortality. In this overview, we summarized baseline confounders and surgical procedure related risk factors contributing to the perioperative AKI, which may serve as risk scores, improve early diagnosis, contribute to prevention, and early management of AKI. There are immediate needs for context specific clinical prediction scores and novel biomarkers to very early diagnose AKI. Preventive guidance provided by Kidney Disease: Improving Global Outcomes is a helpful practical tool for clinicians. Potential roles of novel biomarkers and their context specific contributions require further exploration and close attention. Perioperative hemodynamics and oxygenation appear to contribute to AKI. Therefore, while their optimization can be recommended, their detailed and context specific roles need further explored. Overall, decreased exposure to nephrotoxic agents is recommended to further decrease the impact of perioperative AKI.

Keywords: Perfusion, oxygen, oxygenation, hypoxia, oxygen delivery, blood pressure, hypotension, hemoglobin, acute kidney injury, creatinine, lipocalin (NGAL), hypoxia inducible factor, Kidney Disease: Improving Global Outcomes

ÖZ Akut böbrek hasarı (ABH), perioperatif dönemin önemli komplikasyonlarından birisidir. Perioperatif ABH kronik böbrek hastalığı riskini, diyaliz gereksinimini, periopeartif maliyeti ve mortalite şansını artırır. Hastalarımızın ameliyat öncesi riskleri ve cerrahi prosedürlerin ağırlığına bağlı risk faktörleri ABH oluşumuna katkıda bulunur. ABH'yi çok erken teşhis edebilecek yeni biyobelirteçlere ihtiyaç duyulmaktadır. Yeni biyobelirteçlerin potansiyel rolleri ve bunların tanıya ve prognostik değerlendirmeye katkıları detaylı araştırmalar gerektirmektedir. Böbrek Hastalığı: Küresel Sonuçların İyileştirilmesi tarafından sağlanan ABH'yi önlemeye yönelik öneriler klinisyenler için yararlı ve pratik bir rehber oluşturmaktadır. Perioperatif hemodinami ve oksijenasyonun ABH'yi önlemeye katkıda bulunduğu görülmektedir. Genel olarak, nefrotoksik ajanlara maruz kalmanın azaltılması, tedavinin etkisini daha da azaltmak için tavsiye edilir. Bu derlemede perioperatif dönemde ABH'ye yol açan risk faktörlerini özetlemeyi amaçladık. Ayrıca, erken tanının avantajlarını, ABH'nin önlenmesine katkısı olacak girişimleri ve erken yönetimini özetlemeye gayret ettik.

Anahtar Kelimeler: Perfüzyon, oksijen, oksijenasyon, hipoksi, oxygen delivery, kan basıncı, hipotansiyon, hemoglobin, akut böbrek hasarı, kreatinin, lipokalin (NGAL), hipoksi indükleyen faktör, Böbrek Hastalığı: Küresel Sonuçların İyileştirilmesi

Introduction

Perioperative management of surgical patients has been constantly improving within the past few decades. Improvements in safe anesthesia practices decreased intraoperative and immediate postoperative mortality to negligible levels, but when the perioperative focus expands to 30-day range, there's about a 2% mean mortality rate in non-cardiac and non-obstetric surgery (1). Interestingly, this relatively high mortality rate is strongly associated with end organ injuries, and myocardial and acute kidney injuries (AKIs) (1).

In this overview, we will focus on perioperative AKI. Although the importance of immediate perioperative factors in AKI formation is obvious, patients' age and baseline confounding factors play very significant roles as well (2,3).

Baseline Risk Factors for AKI

There are a few validated prediction scores for perioperative AKI including the frequently utilized "Dialysis

Risk After Cardiac Surgery" (Cleveland Clinic Score by Thakar) (4), "AKI risk after surgery" (Postop-MAKE by Woo) (5), and "Simple Postoperative AKI Risk Classification before Non-cardiac Surgery" (SPARK by Park) (Table 1a, b, c) (6). These scores were built from multicentric clinical databases including data from thousands of perioperative patients. Although there are specific confounders depending on the type of surgery and the environment, the following factors are commonly found in most of the risk scores: age, gender, baseline kidney functions, hypertension, congestive heart failure, type of surgery and acuity level of surgery, baseline laboratory values [specifically hemoglobin (Hb), sodium, albumin levels], history of diabetes (insulin dependent vs. non-dependent). Calculated value of each of these confounding factors are different depending on the context. Unfortunately, most of these risk factors are ever non-modifiable in the immediate perioperative period (e.g., age, baseline kidney functions, congestive heart failure), some of them are potentially modifiable within the immediate preoperative period (e.g., Hb, sodium levels, hypertension, duration of surgery).

Preventive role of modifiability of these factors is a good question on its own and requires testing in prospective interventional trials. On the other hand, confounding roles of these factors cannot be underestimated. Therefore, we strongly recommend using above mentioned perioperative AKI risk scores or any other institute-specific prediction system when approaching perioperative patients.

Table 1a. AKI risk prediction scores. Cleveland Clinic score (Thakar)

Risk factors	Points
Female gender	1
Congestive heart failure	1
Left ventricular ejection fraction <35%	1
Preoperative use of IABP	2
COPD	1
Insulin-requiring diabetes	1
Previous cardiac surgery	1
Emergency surgery	2
Valve surgery only (reference to CABG)	1
CABG + valve (reference to CABG)	2
Other cardiac surgeries	2
Preoperative creatinine 1.2 to <2.1 mg/dL (reference to 1.2)	2
Preoperative creatinine ≥2.1 (reference to 1.2)	5

[1a]Minimum score, 0; maximum score, 17. AKI: Acute kidney injury, IABP: intra-aortic balloon pump, COPD: chronic obstructive pulmonary disease, CABG: coronary artery bypass graft

Definition of Acute Kidney Injury

There are multiple clinical definitions of AKI Kidney Disease: Improving Global Outcomes (KDIGO), Risk Injury Failure, Loss, End-stage, and Acute Kidney Injury Network. All 3 of these established criteria use changes in creatinine levels and urine output to assess and level the disease process of AKI (Table 2).

Within the definitions provided, KDIGO gained more interest, which may help in the means of communication of a common medical language.

Role of Perioperative Hypotension

Intraoperative hypotension is one of the factors which has recently gained a lot of interest due to its strong associations with perioperative AKI. Cumulative evidence suggests that on a population basis, intraoperative mean arterial pressures (MAP) less than 60 to 70 mmHg are associated with myocardial injury, AKI, and death in adults having non-cardiac surgery (7-10). The risk was moderately increased with exposures to MAP less than 65 to 60 mmHg for at least 5 min, or any exposure to MAP less than 55 to 50 mmHg (11). High risk of any end-organ injury was reported for exposures to MAP less than 65 mmHg for at least 20 min, MAP less than 50 mmHg for at least 5 min, or any exposure to MAP less than 40 mmHg (11).

Perioperative hypotension is a modifiable factor, one can test the hypothesis that whether optimization of perioperative blood pressure (BP) with various approaches prevent organ injuries and accordingly decrease perioperative mortality (12,13). Hypotension during and after non-cardiac surgery is multifactorial in origin, including baseline patient-specific confounders, anesthetic pharmacological effects, and surgical procedural factors (14,15). In non-cardiac and non-obstetric surgeries of adult patients, intraoperative hypotension is associated with >10% of AKI, which ~2% of these become persistent AKI extending beyond 90-day period (16). Postoperative hypotension is also common and may also impact organ injury. Mild vs. profound hypotension can be prolonged in the postoperative phase, but largely can be missed due to the conventional intermittent low-frequency vital sign monitoring (meaning hourly to once in every 8 hours) (12).

Table 1b. Postop-MAKE by Woo et al (5). Predictors of postoperative AKI requiring dialysis					
Characteristics	**Coefficient**	**SEM**	**p-value**	**Adjusted odds ratio (95% confidence interval)**	
Intercept	-9.228	0.122	<0.001		
Age, per yr	0.012	0.001	<0.001	1.01 (1.01 to 1.02)	
Ascites	0.971	0.089	<0.001	2.64 (2.22 to 3.14)	
Congestive heart failure	0.832	0.059	<0.001	2.30 (2.05 to 2.58)	
Emergency surgery	0.773	0.042	<0.001	2.17 (2.00 to 2.35)	
Hypertension requiring medication	0.440	0.038	<0.001	1.55 (1.44 to 1.67)	
Diabetes, reference: no diabetes					
Insulin dependent		0.667	0.04	<0.001	1.95 (1.79 to 2.12)
Non-insulin dependent		0.219	0.05	<0.001	1.25 (1.14 to 1.36)
Serum sodium, reference: 135.1-145, mEq/L					
0-130		0.328	0.07	<0.001	1.39 (1.21 to 1.60)
130.1-135		0.193	0.04	<0.001	1.21 (1.12 to 1.31)
>145		0.390	0.09	<0.001	1.48 (1.24 to 1.76)
Missing		-0.165	0.18	0.36	0.85 (0.59 to 1.21)
Serum hematocrit, reference: >30, %					
0-24		0.802	0.07	<0.001	2.23 (1.93 to 2.57)
24.1-30		0.688	0.04	<0.001	1.99 (1.83 to 2.16)
Missing		-0.582	0.16	<0.001	0.56 (0.40 to 0.78)
Preoperative sepsis, reference: no					
SIRS		0.959	0.06	<0.001	2.61 (2.34 to 2.91)
Sepsis		1.238	0.06	<0.001	3.5 (3.09 to 3.85)
Septic shock		2.116	0.06	<0.001	8.30 (7.35 to 9.38)
Surgery type, reference: anorectal, appendix					
ENT		0.255	0.37	0.49	1.29 (0.62 to 2.68)
Bariatric, stomach, esophagus		1.425	0.12	<0.001	4.16 (3.24 to 5.33)
Brain		0.872	0.21	<0.001	2.39 (1.58 to 3.61)
Cardiac		2.864	0.14	<0.001	17.53 (13.30 to 23.09)
Endocrine, thyroid, parathyroid, adrenal, breast		-0.427	0.20	0.04	0.65 (0.44 to 0.97)
Gallbladder, biliary tract		0.555	0.14	<0.001	1.74 (1.33 to 2.29)
Hernia, peritoneum, omentum, diverticul		0.920	0.12	<0.001	2.51 (1.98 to 3.18)
Intestine (not rectum)		1.690	0.11	<0.001	5.42 (4.36 to 6.73)
Liver, pancreas, spleen		2.565	0.13	<0.001	13.00 (10.16 to 16.64)
OBGYN		0.203	0.17	0.24	1.23 (0.87 to 1.72)
Orthopedic lower extremity, pelvis		0.732	0.11	<0.001	2.08 (1.7 to 2.62)
Orthopedic upper extremity, shoulder		0.020	0.26	0.94	1.02 (0.61 to 1.70)
Skin, subcutaneous, other musculoskeletal		0.909	0.12	<0.001	2.48 (1.93 to 3.20)
Spine		0.593	0.14	<0.001	1.81 (1.35 to 2.42)
Thoracic (non-esophageal)		1.913	0.15	<0.001	6.77 (5.06 to 9.07)
Urology		1.590	0.12	<0.001	4.90 (3.85 to 6.25)
Vascular (endovascular aneurysm repair)		2.310	0.15	<0.001	10.07 (7.50 to 13.53)
Vascular (open aorta surgery)		3.993	0.13	<0.001	54.20 (42.19 to 69.64)
Vascular (other)		1.709	0.12	<0.001	5.53 (4.37 to 6.98)
Preoperative serum creatinine per 1 mg/dL		0.449	0.01	<0.001	1.57 (1.54 to 1.59)

SIRS: Systemic inflammatory response syndrome, ENT: ear, nose, throat, OBGYN: obstetrics and gynecology, SEM: scanning electron microscopy, AKI: Acute kidney injury

Table 1c. SPARK by Park et al. (6)			
Perioperative risk factors		**Scores**	
Age (years)			
<40 y		0	
≥40 and <60 y		6	
≥60 and <80 y		9	
≥80 y		13	
eGFR (mL/min per 1.73 m^2)			
≥60		0	
≥45 and <60		8	
≥30 and <45		15	
≥15 and <30		22	
Dipstick albuminuria (urine alb ≥1+)		6	
Sex			
Female		0	
Male		8	
Expected surgical duration (hours)			
Expected duration		x5	
Emergency procedure		7	
Baseline confounders			
Diabetes mellitus		4	
RAAS blockade use		6	
Hypoalbuminemia (<3.5 g/dL)		8	
Anemia (<12 g/dL for female, <13 g/dL for male)		4	
Hyponatremia (<135 mEq/L)		3	
SPARK class	**Total score**	**AKI**	**Critical AKI**
A	<20	Less likely (<2%)	Less likely (<2%)
B	≥20 and <40	Possible (≥2%)	Less likely (<2%)
C	≥40 and <60	At risk (≥10%)	Possible (≥2%)
D	≥60	Definite risk (≥20%)	At risk (≥10%)

eGFR: Estimated glomerular filtration rate, RAAS: renin-angiotensin-aldosterone system, alb: albumin, AKI: Acute kidney injury

Perioperative Oxygen Delivery & Impact on Organ Injury

BP which is a product of cardiac output (CO) and systemic vascular resistance (SVR) is only one of the factors altering organ-tissue perfusion [BP = CO x SVR]. When considering tissue and organ oxygenation and perfusion, the first thing comes to mind is oxygen delivery.

The two components of oxygen delivery are 1) availability and transportability of oxygen (main substrate & carrier; oxygen & Hb), and 2) the flow needed to deliver oxygen (CO) (Table 3). Great majority of oxygen is being carried by Hb. In addition to oxygen's availability, its delivery also depends upon cardiac functionality. CO is the product of stroke volume and heart rate, and BP/SVR. When we adopt global oxygen delivery physiology to the tissue level, we realize that we need to stick with the same principles. In short, availability of oxygen to the tissues and blood flow which helps transportation of that oxygen. Therefore, tissue oxygenation and perfusion together assure the delivery of oxygen to the peripheral tissues and end organs.

We may consider giving a new spin to ischemia-based AKI. If ischemia can be explained by decreased DO_2 and

Table 2. AKI stages-KDIGO, RIFLE, and AKIN				
AKI stage	**KDIGO**	**RIFLE**	**AKIN**	**Urine output**
1. Risk	Increase ≥0.3 mg/dL within 48 h or ≥1.5- to 2x from baseline	Increase ×1.5 baseline or GFR decrease >25%	Increase 1.5-1.9x from baseline or ≥0.3 mg/dL increase within 48 h	<0.5 mL/kg/h for 6-12 h
2. Injury	2.0-2.9x from baseline	Increase ×2 from baseline or GFR decreased >50%	Increase >2- to 3-x from baseline	<0.5 mL/kg/h for 12 h
3. Failure	3.0x from baseline or increase in creatinine to ≥4.0 mg/dL or initiation of RRT or, in patients <18 years, decrease in eGFR to <35 mL/min per 1.73 m^2	Increase ×3 from baseline, or creatinine >4 mg/dL) with an acute rise >0.5 mg/dL or GFR decreased >75%	Increased >300% (>3x) from baseline, or ≥4.0 mg/dL with an acute increase of ≥0.5 mg/dL or on RRT	<0.3 mL/kg/h for 24 h or anuria for 12 h

KDIGO: Kidney Disease: Improving Global Outcomes, RIFLE: The Risk, Injury, Failure, Loss, End-Stage, AKIN: Acute Kidney Injury Network, RRT: renal replacement therapy, GFR: glomerular filtration rate, eGFR: estimated glomerular filtration rate, AKI: acute kidney injury

Table 3. Blood pressure, cardiac output, & oxygen delivery
BP = CO x SVR
CO = BP / SVR
$DO_2 = CO \times CaO_2$
CO = HR x SV
$CaO_2 = (SO_2 \times 1.34 \times Hb) + (PaO_2 \times 0.003)$
If we adjust the relevant components of DO_2 and ignore the very small contribution of PaO_2 component, then we will end up with the following formula:
$DO_2 = [BP / SVR] \times [SO_2 \times 1.34 \times Hb]$

BP: Blood pressure, SVR: systemic vascular resistance, CO: cardiac output, SV: stroke volume, Hb: hemoglobin

if the main components of DO_2 are BP, SO_2, and Hb (also reversely by SVR), then we can extrapolate that directly positive effects of BP, SO_2, and Hb, and negative effects of SVR impacts oxygen delivery. In a recent post-hoc analysis, from these components, von Groote and Zarbock showed that hypotension and low CO contributed to 2-2.5x more AKI (17).

Another important component to consider in MINS is the total Hb level and decrease in Hb level in the perioperative period. MINS was associated with a hazard ratio of 1.29 [95% confidence interval (CI), 1.17-1.42] with each unit reduction of postoperative Hb after adjusting for iron deficiency anemia and anemia of chronic disease in the time-varying Cox model (18).

Role of Nephrotoxic Agents

Agent-induced nephropathy is a type of renal dysfunction, which occurs after exposure to nephrotoxic drugs. It is a relatively common pathology for patients with underlying renal dysfunction, or confounding cardiovascular disease, diabetes mellitus, and increased inflammatory diseases like sepsis. Nephrotoxic drugs can cause mild to moderate organ injury such as intrarenal obstruction, interstitial nephritis, acid-base changes, fluid-electrolyte disturbances, changes in intraglomerular hemodynamics, renal tubular inflammation, and persistent renal tissue injury leading to AKI and chronic kidney injury.

There are many nephrotoxic drugs and drug combinations: Beta-lactam antibiotics such as piperacillin-tazobactam (especially in combination with vancomycin), cephalosporin-aminoglycoside combinations, rifampin, polymyxins/colistin, non-steroidal anti-inflammatory drugs, acetaminophen, interferon, proton pump inhibitors, bisphosphonates, lithium, various chemotherapeutic agents (e.g. mitomycin, gemcitabine), cisplatin, cyclosporin A, methotrexate, ACE inhibitors, anabolic androgenic steroids, TNF-alpha inhibitors, amphotericin B, dextrans, and contrast dyes.

Following the early signs of adverse effects of drugs and reviewing a patient's baseline renal function, drug-related risk factors, and nephrotoxic drug combinations need to

be closely addressed to prevent nephrotoxicity and the progression of AKI.

Biomarkers of Organ Injury

In perioperative AKI, mechanisms of short-term volume depletion-triggered and ischemia-triggered injuries are likely different, but their clinical phenotypes are similar (i.e., creatinine increase and urine output decrease). Ischemic insult provokes cell injury and repair (which upregulates ERB, MAPK) and inflammatory genes (such as TLR, NFKB, JAK/STAT, chemokines) (19). Macrophages and CD4 T-cells' overexpression of Lcn2 could induce intrinsic resistance to ischemia, causing protection from kidney ischemia-reperfusion (I/R) injury (20,21). Lipocalin (NGAL), despite being a potential biomarker for renal injury, has been shown to have protective effects in ischemic AKI by inhibition of tubular cell death and induction of antioxidant genes (22).

Tissue inhibitor of metalloproteinases-2 (TIMP-2) and insulin-like growth factor binding protein-7 (IGFBP-7) are released during cell cycle arrest, which makes them potentially sensitive and specific biomarker molecules for diagnosing AKI (23). During cell damage, cell cycle arrest serves as a protective mechanism to get around the replication of damaged DNA (24). Renal cells' cell cycle arrest is possibly an adaptive response due to tissue damage mediated by surrounding cells through the release of TIMP-2 and IGFBP-7 (24). Combined presence of TIMP-2 and IGFBP-7, along with a change in creatinine, could potentially predict renal adverse events with better sensitivity and specificity. NephroCheck (Astute Medical, USA), which tests presence of both TIMP-2 and IGFBP-7 was authorized by Food and Drug Administration in 2014 as a point-of-care urinary biomarker assay to evaluate AKI development (25). In spite of NephroCheck's predictive role in critically ill patients' AKI, it's role in distinguishing temporary injury from persistent AKI or acute kidney disease (AKD) is unclear (26).

Compared to ischemia or ischemic tissue damage triggered AKI, volume depletion-triggered AKI promotes adaptive appearing metabolic pathways (i.e. TCA, gluconeogenesis, oxidative phosphorylation, respiratory electron transport) (27). In volume depletion-triggered AKI, upregulated genes are typically localized to the cortex and inner stripe of the outer medulla, and this type of injury appears to cause more transient triggers such as *PAPPA2* gene (metalloproteinase secreted by the thick ascending loop of Henle) expression. However, in theory, an extended duration of volume depletion stimulus with or without a secondary injury (e.g., nephrotoxins) may impact the volume depletion injury to progress to ischemia-based injury, meaning temporary AKI to persistent AKI vs. AKD. Also, it's noteworthy that NGAL rapidly stimulated by ischemic injury, is in fact not responsive to the volume depletion injury despite the similar elevations in creatinine levels (28,29).

It looks like the absence of permanent injury in most AKI is due to volume depletion mechanisms and renal protective factors such as prostaglandins, NO, NGAL, and hypoxia inducible factor, but instead of being conclusive statements, these are likely testable hypotheses at this point. In the light of current evidence, NGAL and TIMP-2 & IGFBP-7 combination appears to be only available and somewhat guiding biomarkers.

Kidney Disease: Improving Global Outcomes Guidelines

These guidelines aimed to provide a bundle of potentially preventive strategies for the patients who are at high risk for developing AKI. The bundle includes avoidance of nephrotoxic agents, contrast dyes, maintenance of intravascular volume status and perfusion pressure, maintenance of normoglycemia, monitoring of creatinine and urine output, and functional hemodynamic monitoring (Table 4) (30).

A recent randomized controlled clinical trial (PrevAKI) showed that biomarker-guided implementation of the KDIGO guidelines as compared with standard care significantly reduced the occurrence of AKI in cardiac surgery patients [absolute risk reduction, 16.6% (95 CI, 5.5-27.9%)]; p=0.004 (31).

Other Preventive Measures of Perioperative AKI

As previously mentioned, the application of nephrotoxic agents is associated with AKI. Surgical patients are frequently exposed to contrast agents or anti-inflammatory drugs. Avoidance of these agents are recommended. As stated before, prevention of hypotension and related blood flow decreases in kidneys need to be prevented, and intravascular volume status needs to be optimized. The choice of intravenous fluids plays an important role in the development of AKI. Isotonic saline 0.9% has high chloride content, which may cause hyperchloremic acidosis and renal vasoconstriction, resulting in a reduced glomerular filtration rate (32) and a higher incidence of AKI (33). Therefore, balanced crystalloid solutions with electrolyte compositions compared with plasma should be preferred for volume resuscitation.

Table 4. Summary of KDIGO guidelines
Recommendations of the KDIGO guidelines can be summarized as follows:
1) Discontinuation of nephrotoxic agents
2) Optimization of volume status and hemodynamics [stroke volume (SV), SV based cardiac output monitor use suggested)
a) If stroke volume variation (SVV) ≥11, then give 500 to 1000 mL of crystalloid
b) If SVV <11, but cardiac index (CI) <3 L/min/m^2, then consider starting dobutamine (or epinephrine)
c) If SVV <11, CI >3 L/min/m^2, but MAP <65 mmHg, then consider starting norepinephrine
d) Repeat following above volume state and hemodynamic parameters in frequent intervals
3) Consideration of functional hemodynamic monitoring
4) Close monitoring of serum creatinine and urine output
5) Avoidance of hyperglycemia
6) Consideration of alternatives of radiocontrastagents
KDIGO: Kidney Disease: Improving Global Outcomes, MAP: mean arterial pressures

Arterial hypotension is a frequent result of hypovolemia, but also occurs in association with multiple other etiologies. AKI is associated with intraoperative hypotension in a graded fashion. Therefore, all efforts needed to prevent decreasing MAP levels <65 mmHg, and if/when BP drops treated depending on the cause is strongly recommended.

Tight glycemic control has been shown to significantly reduce AKI in critically ill patients (34). Subsequently, it has been ruled out in cardiac surgery patients that tight glycemic control is superior to continuous perioperative insulin therapy in terms of AKI incidence and mortality. This has been underlined by several well-conducted clinical trials (35,36).

Active Areas for Future Research

In this review we have highlighted the risk factors that appear to be both unmodifiable and potentially modifiable. Much of the work highlighting the association of these confounding risk factors has been done in retrospective fashion. Their prospective can be graded and assessed prospectively.

Given the perioperative importance of AKI, there appear to be multiple areas for future research. Hemodynamic management to prevent hypotension and improve perfusion & oxygen delivery appear to be important in prior studies and these are potentially modifiable factors. This would be one important target of priority, especially given the recent advances in bioinformatics that make new studies possible that before were not.

Additionally, plasma and urinary biomarkers of renal injury overcome the limitations of the current gold standard definitions of serum creatinine and may offer significant future clinical utility to diagnose and treat kidney injury. Perioperative diagnostic, mechanistic, and even therapeutic potentials of biomarkers require further attention.

Conclusion

AKI is a relatively common complication of the perioperative period. It is associated with increased risk of chronic kidney disease, hemodialysis requirements after discharge, increased cost, and risk of mortality. Better understanding of baseline and procedure related risk factors, which contribute to perioperative AKI may improve early diagnosis, prevention, and early management of AKI. There are still needs for detailed context specific clinical prediction scores and novel biomarkers to improve the chances of early diagnosis. Improved imaging techniques with decreased exposure to contrast dyes, avoiding nephrotoxic agents, and improved perioperative care focusing on prevention of hypotension, diminished CO and oxygen delivery will further decrease the impact of perioperative AKI.

Ethics

Peer-review: Internally peer-reviewed.

Authorship Contributions

Concept: L.G., O.A., Analysis or Interpretation: L.G., O.A., Literature Search: L.G., O.A., Writing: L.G., O.A.

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References

1. Nepogodiev D, Martin J, Biccard B, Makupe A, Bhangu A; National Institute for Health Research Global Health Research Unit on Global Surgery. Global burden of postoperative death. Lancet 2019;393:401.
2. Mathis MR, Naik BI, Freundlich RE, Shanks AM, Heung M, Kim M, et al. Preoperative Risk and the Association between Hypotension and Postoperative Acute Kidney Injury. Anesthesiology 2020;132:461-75.
3. Ahuja S, Mascha EJ, Yang D, Maheshwari K, Cohen B, Khanna AK, et al. Associations of Intraoperative Radial Arterial Systolic, Diastolic, Mean, and Pulse Pressures with Myocardial and Acute Kidney Injury after Noncardiac Surgery: A Retrospective Cohort Analysis. Anesthesiology 2020;132:291-306.
4. Thakar CV, Arrigain S, Worley S, Yared JP, Paganini EP. A clinical score to predict acute renal failure after cardiac surgery. J Am Soc Nephrol 2005;16:162-8.
5. Woo SH, Zavodnick J, Ackermann L, Maarouf OH, Zhang J, Cowan SW. Development and Validation of a Web-Based Prediction Model for AKI after Surgery. Kidney360 2021;2:215-23.
6. Park S, Cho H, Park S, Lee S, Kim K, Yoon HJ, et al. Simple Postoperative AKI Risk (SPARK) Classification before Noncardiac Surgery: A Prediction Index Development Study with External Validation. J Am Soc Nephrol 2019;30:170-81.
7. Salmasi V, Maheshwari K, Yang D, Mascha EJ, Singh A, Sessler DI, et al. Relationship between Intraoperative Hypotension, Defined by Either Reduction from Baseline or Absolute Thresholds, and Acute Kidney and Myocardial Injury after Noncardiac Surgery: A Retrospective Cohort Analysis. Anesthesiology 2017;126:47-65.
8. Sun LY, Wijeysundera DN, Tait GA, Beattie WS. Association of intraoperative hypotension with acute kidney injury after elective noncardiac surgery. Anesthesiology 2015;123:515-23.
9. Sessler DI, Meyhoff CS, Zimmerman NM, Mao G, Leslie K, Vásquez SM, et al. Period-dependent Associations between Hypotension during and for Four Days after Noncardiac Surgery and a Composite of Myocardial Infarction and Death: A Substudy of the POISE-2 Trial. Anesthesiology 2018;128:317-27.
10. Monk TG, Bronsert MR, Henderson WG, Mangione MP, Sum-Ping ST, Bentt DR, et al. Association between Intraoperative Hypotension and Hypertension and 30-day Postoperative Mortality in Noncardiac Surgery. Anesthesiology 2015;123:307-19.
11. Wesselink EM, Kappen TH, Torn HM, Slooter AJC, van Klei WA. Intraoperative hypotension and the risk of postoperative adverse outcomes: a systematic review. Br J Anaesth 2018;121:706-21.
12. Turan A, Chang C, Cohen B, Saasouh W, Essber H, Yang D, et al. Incidence, Severity, and Detection of Blood Pressure Perturbations after Abdominal Surgery: A Prospective Blinded Observational Study. Anesthesiology 2019;130:550-9.
13. Saugel B, Sessler DI. Perioperative Blood Pressure Management. Anesthesiology 2021;134:250-61.
14. Reich DL, Hossain S, Krol M, Baez B, Patel P, Bernstein A, et al. Predictors of hypotension after induction of general anesthesia. Anesth Analg 2005;101:622-8.
15. Cheung CC, Martyn A, Campbell N, Frost S, Gilbert K, Michota F, et al. Predictors of intraoperative hypotension and bradycardia. Am J Med 2015;128:532-8.
16. Shaw AD, Khanna AK, Smischney NJ, Shenoy AV, Boero IJ, Bershad M, et al. Intraoperative hypotension is associated with persistent acute kidney disease after noncardiac surgery: a multicentre cohort study. Br J Anaesth 2022;129:13-21.
17. von Groote TC, Ostermann M, Forni LG, Meersch-Dini M, Zarbock A; PrevAKI Investigators. The AKI care bundle: all bundle components are created equal-are they? Intensive Care Med 2022;48:242-5.
18. Turan A, Cohen B, Rivas E, Liu L, Pu X, Maheshwari K, et al. Association between postoperative haemoglobin and myocardial injury after noncardiac surgery: a retrospective cohort analysis. Br J Anaesth 2021;126:94-101.
19. Xu K, Rosenstiel P, Paragas N, Hinze C, Gao X, Huai Shen T, et al. Unique Transcriptional Programs Identify Subtypes of AKI. J Am Soc Nephrol 2017;28:1729-40.
20. Jung M, Brüne B, Hotter G, Sola A. Macrophage-derived Lipocalin-2 contributes to ischemic resistance mechanisms by protecting from renal injury. Sci Rep 2016;6:21950.
21. Lee SA, Noel S, Kurzhagen JT, Sadasivam M, Pierorazio PM, Arend LJ, et al. CD4(+) T Cell-Derived NGAL Modifies the Outcome of Ischemic Acute Kidney Injury. J Immunol 2020;204:586-95.
22. Mishra J, Mori K, Ma Q, Kelly C, Yang J, Mitsnefes M, et al. Amelioration of ischemic acute renal injury by neutrophil gelatinase-associated lipocalin. J Am Soc Nephrol 2004;15:3073-82.
23. Koyner JL, Shaw AD, Chawla LS, Hoste EA, Bihorac A, Kashani K, et al. Tissue Inhibitor Metalloproteinase-2 (TIMP-2) IGF-Binding Protein-7 (IGFBP7) Levels Are Associated with Adverse Long-Term Outcomes in Patients with AKI. J Am Soc Nephrol 2015;26:1747-54.
24. Kashani K, Al-Khafaji A, Ardiles T, Artigas A, Bagshaw SM, Bell M, et al. Discovery and validation of cell cycle arrest biomarkers in human acute kidney injury. Crit Care 2013;17:25.
25. Lameire N, Vanmassenhove J, Van Biesen W, Vanholder R. The cell cycle biomarkers: promising research, but do not oversell them. Clin Kidney J 2016;9:353-8.
26. Daubin D, Cristol JP, Dupuy AM, Kuster N, Besnard N, Platon L, et al. Urinary Biomarkers IGFBP7 and TIMP-2 for the Diagnostic Assessment of Transient and Persistent Acute Kidney Injury in Critically Ill Patients. PLoS One 2017;12:e0169674
27. Neuhofer W, Beck FX. Response of renal medullary cells to osmotic stress. Contrib Nephrol 2005;148:21-34.
28. Belcher JM, Sanyal AJ, Peixoto AJ, Perazella MA, Lim J, Thiessen-Philbrook H, et al. Kidney biomarkers and differential diagnosis of patients with cirrhosis and acute kidney injury. Hepatology 2014;60:622-32.
29. Paragas N, Qiu A, Zhang Q, Samstein B, Deng SX, Schmidt-Ott KM, et al. The Ngal reporter mouse detects the response of the kidney to injury in real time. Nat Med 2011;17:216-22.
30. Nephrology ISo: KDIGO Clinical Practice Guideline for Acute Kidney Injury. Available at: https://kdigo.org/wp-content/uploads/2016/10/KDIGO-2012-AKI-Guideline-English.pdf. Accessed 08/22/2022
31. Meersch M, Schmidt C, Hoffmeier A, Van Aken H, Wempe C, Gerss J, et al. Prevention of cardiac surgery-associated AKI by implementing the KDIGO guidelines in high risk patients identified by biomarkers: the PrevAKI randomized controlled trial. Intensive Care Med 2017;43:1749.
32. Bullivant EM, Wilcox CS, Welch WJ. Intrarenal vasoconstriction during

hyperchloremia: role of thromboxane. Am J Physiol 1989;256:152-7.
33. McCluskey SA, Karkouti K, Wijeysundera D, Minkovich L, Tait G, Beattie WS. Hyperchloremia after noncardiac surgery is independently associated with increased morbidity and mortality: a propensity-matched cohort study. Anesth Analg 2013;117:412-21.
34. van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, et al. Intensive insulin therapy in critically ill patients. N Engl J Med 2001;345:1359-67.
35. Gandhi GY, Nuttall GA, Abel MD, Mullany CJ, Schaff HV, O'Brien PC, et al. Intensive intraoperative insulin therapy versus conventional glucose management during cardiac surgery: a randomized trial. Ann Intern Med 2007;146:233-43.
36. Bhamidipati CM, LaPar DJ, Stukenborg GJ, Morrison CC, Kern JA, Kron IL, et al. Superiority of moderate control of hyperglycemia to tight control in patients undergoing coronary artery bypass grafting. J Thorac Cardiovasc Surg 2011;141:543-51.

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ORIGINAL RESEARCH / *ÖZGÜN ARAŞTIRMA*

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An Evaluation of the PRE-DELIRIC (PREdiction of DELIRium in ICu Patients) Delirium Prediction Model in Intensive Care Units in Türkiye

PRE-DELIRIC (PREdiction of DELIRium in ICU Patients) Deliryum Öngörme Modelinin Türkiye'de Yoğun Bakım Ünitelerinde Kullanılabilirliğinin Değerlendirilmesi

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ABSTRACT *Objective:* This methodological study was conducted in order to carry out the adaptation and validation of the "PRE-DELIRIC score" prediction of delirium model in Türkiye among patients hospitalized in the intensive care unit (ICU).

Materials and Methods: The research involved 172 patients treated in the intensive care units of a training and research hospital between October 2019 and April 2020. The study data were collected using (1) a data collection form to determine the participants' descriptive characteristics, (2) the PRE-DELIRIC score, and (3) the Confusion Assessment Method for the ICU (CAM-ICU). Receiver operating characteristic (ROC) analysis and diagnostic screening tests were applied for the purpose of determining cut-off points for the groups. The scores' sensitivity and specificity were calculated. Significance was evaluated at the $p<0.05$ level.

Results: A statistically significant association was determined between the cut-off point obtained for the PRE-DELIRIC score (≥7.58%) and the study groups ($p=0.003$). Patients with PRE-DELIRIC scores of 7.58 or higher exhibited a 7.404-fold greater risk of being CAM-ICU-positive [odds ratio: 7.404; 95% confidence interval (CI): 1.638-33.469]. The area under the ROC curve was 64.9% (95% CI: 0.538-0.760), and the standard error was 5.6% ($p=0.044$).

Conclusion: The PRE-DELIRIC score yielded reliable results in this study. It appears significant for patients with a likelihood of developing delirium within the ICU, and its use is recommended as a functional score that is easily applied and calculated.

Keywords: Critical care, PRE-DELIRIC, delirium, model

ÖZ *Amaç:* Metodolojik tipteki bu çalışma, yoğun bakım ünitesinde (YBÜ) yatan hastalarda "PRE-DELIRIC skoru" deliryum tahmin modelinin Türkiye'ye uyarlanması ve geçerliliğinin sağlanması amacıyla yapılmıştır.

Gereç ve Yöntem: Araştırma, Ekim 2019-Nisan 2020 tarihleri arasında bir eğitim ve araştırma hastanesinin YBÜ'sünde tedavi gören 172 hasta ile yapılmıştır. Veriler, (1) katılımcıların tanımlayıcı özelliklerine yönelik bilgi formu, (2) PRE-DELIRIC skoru ve (3) YBÜ'de Konfüzyon Değerlendirme Formu (CAM-ICU) ile toplanmıştır. Gruplara göre kesme noktasını saptamada alıcı işletim karakteristik (ROC) analizi ve tanı tarama testleri kullanıldı. Skorun duyarlılık ve özgüllük özelliği hesaplandı. Anlamlılık $p<0,05$ düzeyinde değerlendirildi.

Bulgular: PRE-DELIRIC skoru için elde edilen kesme noktası (≥%7,58) ile gruplar arasında istatistiksel olarak anlamlı ilişki saptanmıştır ($p=0,003$). PRE-DELIRIC skoru 7,58 ve üzerinde olan olgularda CAM-ICU pozitif olma riski 7,404 kat fazladır [(OR: 7,404; %95 güven aralığı (GA): 1,638-33,469)]. ROC eğrisi altında kalan alan ise, %64,9 (%95 GA: 0,538-0,760) ve standart hata %5,6 ($p=0,044$) olarak saptanmıştır.

Sonuç: Bu çalışmada, PRE-DELIRIC skorunun güvenilir sonuçlara sahip olduğu bulundu. YBÜ'lerde deliryum gelişmesi olası olan hastalar için önemli olduğu görülmekte, uygulaması ve hesaplaması kolay kullanışlı bir skor olarak kullanımı önerilmektedir.

Anahtar Kelimeler: Yoğun bakım, PRE-DELIRIC, deliryum, model

Introduction

Delirium is a neuropsychiatric disorder characterized by impaired consciousness, distraction, and disorganized thinking (1). It can be seen at rates of up to 80% in intensive care patients and causes increased morbidity and mortality, prolongation of mechanical ventilation and intensive care unit (ICU) stays, and long-term cognitive impairment (2,3).

A number of organic factors can result in delirium (4). Final diagnosis is based on the assessment of findings elicited by means of interviews. Several different scales have been developed for the screening, diagnosis and grading of symptoms. Proper diagnosis requires periodic evaluation of the diagnostic criteria and a knowledge of the patient's initial mental state (5). The most common methods used for the evaluation of delirium are the Confusion Assessment Method for the intensive care unit (CAM-ICU) (6) and the Intensive Care Delirium Screening Checklist (7). Delirium has been detected at a rate of 30-70% in intensive care patients using these methods (8).

Appropriate interventions are extremely important in preventing delirium. Guidelines on pain, agitation and delirium management (9) strongly recommend the application of non-pharmacological methods for preventing delirium, but the evidence supporting pharmacological approaches is inadequate. The applications of such procedures is also time-consuming and entails a significantly increased workload. A number of prediction models that may be of assistance in identifying high-risk individuals have therefore been produced (4). One of these models, the PREdiction of DELIRium in ICu patients (PRE-DELIRIC), has been validated in various ICUs and described as useful (10). This model emerged from the findings of a systematic review study investigating risk factors for delirium (11). It predicts the development of the condition in the first 24 hours following admission to the ICU. This relies on a calculation containing 10 known risk factors for the development of delirium that are capable of being both objectively and precisely defined. This model used for estimating the risk of delirium (4,12,13) was also employed in a recent study from Turkey, although its predictive ability for dementia was not assessed (14).

This methodological study was conducted for the purpose of establishing the applicability of the "PRE-DELIRIC score" delirium prediction model in general ICU patients.

- Is the PRE-DELIRIC score confidential?
- Can it be used in the ICU?

Materials and Methods

This methodological study was conducted in order to carry out the adaptation and validation of the "PRE-DELIRIC score" prediction of delirium model in Turkey among patients hospitalized in the ICU.

Patients treated in the ICU of a training and research hospital between October 2019 and April 2020 were included in the research.

Participants

Patients who were hospitalized and treated for more than 24 hours in the general ICU, aged 18 years or older, with no history of chronic alcoholism, dementia, or delirium, who were not pregnant or breastfeeding, who had no communication problems, with Richmond Agitation Sedation scale (RASS) values of +4 to -2, and for whom consent to participate was obtained from a relative were included in the study. One hundred eighty-nine 189 cases were initially included, although the study was eventually conducted with 172 patients since eight cases were excluded due to dementia, three due to history of delirium, one due to history of alcoholism, and five for being aged under 18.

Study Procedure

A data collection form was applied to elicit the participants' descriptive characteristics, together with the PRE-DELIRIC score, and the CAM-ICU as collection tools. Data collection took place during the study period and was performed by a physician and a nurse, who were also involved as researchers. In this study, the patient who was delirium negative at admission should have been included. The general data were collected in the first 24 hours. Data on the diagnostic and clinical characteristics were obtained from the patients' relatives and patient charts. Data on the clinical course were also collected within the first 24 hours.

The data collection form was produced by the authors following a review of the literature in the field (9,15-17). It consists of 19 questions investigating sociodemographic and clinical characteristics.

Measures

PRE-DELIRIC Score

The PRE-DELIRIC Scoring System developed by van den Boogaard et al. (10) considers the patient's age, Acute Physiology and Chronic Health Evaluation-II (APACHE-II) score, blood urea level, amount of morphine used, sedation

use, metabolic acidosis, coma state, infection, planned/emergency intensive care admission, and the reason for hospitalization to provide a score. A pre-delirium score ≥50 is reported to be associated with a high incidence of delirium. The scoring system is used within the first 24 hours after admission to the ICU. The blood results were obtained from the patient's medical chart by the researchers and recorded in the questionnaire. The PRE-DELIRIC score was determined within the first 24 hours after admission to the ICU in this study.

Once the scale had been independently translated into Turkish by three translators consisting of an English teacher, an English language linguistic specialist, and a medical doctor proficient in English language, the translators agreed on a common text in terms of the appropriateness and comprehensibility of translations. The scale thus obtained was then translated back into English by three English teachers. No change in meaning was determined in the backtranslated scale compared to the original English document and the form was finalized after preliminary administration to five intensive care nurses and 10 patients. The PRE-DELIRIC Scoring System does not include intercultural differences since it is based on objective criteria and not on patient statements or interpretation. The risk factors including these objective data have the same meaning in all languages and cultures. Determining content validity by eliciting an expert opinion was therefore not required for the PRE-DELIRIC score.

CAM-ICU

This scale is in common use and is reported to provide the best compliance with DSM IV criteria (16). It was developed by Ely et al. (6). The reliability and validity of the Turkish-language version were confirmed by Akıncı et al. (18) and the scale was found to have an acceptable level of sensitivity (65-69%), together with perfect specificity (97%) and reliability (Kappa =0.96). The scale has four domains, consisting of changes in the patient's state of consciousness, attention disorder, impaired thought process, and level of consciousness. Sub-categories are not taken into account and a conclusion is reached in the form of the "presence" or "absence" of delirium according to the answers to the scale questions. All the first and second category answers must be negative, and one of the third and fourth categories must be present as a condition for the "presence" of delirium. This scale can be applied to all intensive care patients aged over 18 who are not comatose and who are able to communicate. It is recommended that the scale be completed within the first 24 hours following admission to the ICU. A repeat evaluation is performed during the day in case of any change in the patient's condition. Otherwise evaluation once a day is appropriate. CAM-ICU was measured within the first 24 hours following admission to the ICU in this study.

Kırklareli University Institute of Health Sciences Ethics Committee approval (decision no: 3, date: 11.10.2019) was obtained from the institution in which the study was carried out, in addition to consent from the patients who were included in the study with the permission of the relevant institution. Written permission for the use of the PRE-DELIRIC score was obtained by e-mail from van den Boogaard.

Statistical Analysis

All statistical analyses were conducted on NCSS (Number Cruncher Statistical System) 2007 (Kaysville, Utah, USA) software. The study data were analyzed using mean, standard deviation, median, frequency, ratio, minimum, and maximum values. Normality of distribution was evaluated by means of the Shapiro-Wilk test and graphical assessments. Student's t-test was applied to compare normally distributed variables between the two groups, and the Mann-Whitney U test in case of non-normal distribution. ROC analysis and diagnosis screening tests were employed to calculate cut-off points by the groups. The score's sensitivity and specificity characteristics were also calculated. P values <0.05 were considered statistically significant.

Results

One hundred seventy-two patients were enrolled in the study. CAM-ICU measurement revealed that 90.1% (n=155) of the patients were negative and 9.9% (n=17) positive for delirium. The age range of the subjects was 35-94 years, and the mean age was 72.94±13.99 years. The mean age (p=0.036) and the cerebrovascular event (CVE) incidence rate (p=0.036) of the patients who were positive on CAM-ICU were statistically significantly higher than those who were negative. No statistically significant difference was found between the groups in terms of the other variables (p>0.05) (Table 1).

Patients who were positive on the CAM-ICU required statistically significantly more physical restriction (p=0.07) and developed more pressure ulcers (p=0.001) than those who were negative. Statistically significantly larger amounts

Table 1. Evaluation of descriptive features according to CAM-ICU status					
		Total	CAM-ICU		p-value
			Negative (n=155)	Positive (n=17)	
Age (years)	Min-max (median)	35-94 (77)	35-94 (74)	66-94 (84)	[a]0.006**
	Mean ± SD	72.94±13.99	71.98±14.18	81.65±8.12	
Gender	Female	90 (52.3)	80 (51.6)	10 (58.8)	[c]0.572
	Male	82 (47.7)	75 (48.4)	7 (41.2)	
BMI (kg/m²)	Min-max (median)	17.2-40 (25)	17.2-40 (25)	19.5-28.3 (24.6)	[a]0.595
	Mean ± SD	24.88±3.64	24.93±3.74	24.44±2.59	
Chronic disease status		149 (86.6)	133 (85.8)	16 (94.1)	[d]0.475
Chronic disease type[†]					
Hypertension		95 (55.2)	88 (56.8)	7 (41.2)	[c]0.220
Diabetes		42 (24.4)	39 (25.2)	3 (17.6)	[d]0.766
Chronic heart failure		50 (29.1)	47 (30.3)	3 (17.6)	[d]0.401
Chronic arterial failure		8 (4.7)	8 (5.2)	0 (0)	[d]1.000
COPD		24 (14.0)	22 (14.2)	2 (11.8)	[d]1.000
Asthma		2 (1.2)	1 (0.6)	1 (5.9)	[d]0.188
Alzheimer disease		2 (1.2)	1 (0.6)	1 (5.9)	[d]0.188
Cerebrovascular attack		14 (8.1)	10 (6.5)	4 (23.5)	[d]0.036*
Use cigarette-alcohol		18 (10.5)	18 (11.6)	0 (0)	[d]0.222

BMI: Body mass index, COPD: chronic obstructive pulmonary disease, SD: standard deviation, CAM-ICU: Confusion Assessment Method for the intensive care unit, min-max: minimum-maximum
[a]Student t-test, [b]Mann-Whitney U test, [c]Pearson chi-square test, [d]Fisher's exact test, *p<0.05, **p<0.01, [†]more than one chronic disease

of sedatives were required for patients who were negative on the CAM-ICU than those who were positive (p=0.017). A statistically significant difference was found between the groups in terms of the form of discharge from intensive care (p=0.047) and those who died were usually negative while those who were transferred were usually positive. No statistically significant difference was found between the groups in terms of the other variables (p>0.05) (Table 2).

The 1st PRE-DELIRIC score of the patients who were negative on CAM-ICU was 3.9-11.9 with a mean value of 7.85±1.91. The 1st PRE-DELIRIC score of the patients who were positive for CAM-ICU was 6.7-14.9 with a mean value of 9.04±2.09 (Figure 1). A statistically significant difference was found between the 1st PRE-DELIRIC scores of the CAM-ICU negative and positive groups (p=0.017), and the scores of the positive patients were higher than the negative patients. An increase of one unit in the PRE-DELIRIC scores increased the risk of CAM-ICU positivity 1.358 times [odds ratio (OR): 1.358; 95% confidence interval (CI): 1.047-1.761] (Table 3).

Determining the Cut-off Point for PRE-DELIRIC Scores Based on CAM-ICU Status

A statistically significant difference was found between the 1st PRE-DELIRIC scores of the CAM-ICU negative and positive patients (p=0.017), with the CAM-ICU positive patients having higher scores (Table 3). Based on this significance, the cut-off point for the PRE-DELIRIC score was calculated. ROC analysis and diagnostic screening tests were used to determine this cut-off point by group. The cut-off point for the PRE-DELIRIC score was 7.58. This PRE-DELIRIC score cut-off value exhibited sensitivity of 88.24%, specificity of 49.68%, a positive predictive value of 16.13%, a negative predictive value of 97.47%, and accuracy of 53.49% (Table 4). The area under the ROC curve was 64.9% (95% CI: 0.538-0.760) and the standard error was 5.6% (p=0.044) (Figure 2).

The cut-off point determined for the PRE-DELIRIC score (≥7.58%) was significantly associated with the groups (p=0.003). The risk of CAM-ICU positivity was 7.404 times higher among individuals with PRE-DELIRIC scores of 7.58

Table 2. Distribution of some descriptive characteristics of patients according to CAM-ICU status					
		Total n (%)	CAM-ICU		p-value
			Negative (n=155)	Positive (n=17)	
Coming to intensive care	Emergency room	147 (85.5)	131 (84.5)	16 (94.1)	[d]0.473
	Clinic	25 (14.5)	24 (15.5)	1 (5.9)	
Reason for hospitalization	Surgery	19 (11.0)	18 (11.6)	1 (5.9)	[e]0.977
	Medical	134 (77.9)	118 (76.1)	16 (94.1)	
	Trauma	11 (6.4)	11 (7.1)	0 (0)	
	Neurosurgery	8 (4.7)	8 (5.2)	0 (0)	
Feeding type	Enteral	97 (56.4)	86 (55.5)	11 (64.7)	[e]0.668
	Parenteral	48 (27.9)	43 (27.7)	5 (29.4)	
	Oral	17 (9.9)	16 (10.3)	1 (5.9)	
	Enteral + parenteral	4 (2.3)	4 (2.6)	0 (0)	
	Parenteral + oral	6 (3.5)	6 (3.9)	0 (0)	
Physical restriction status		70 (40.7)	58 (37.4)	12 (70.6)	[c]0.017*
Drain-tube-ostomy status		117 (68.0)	104 (67.1)	13 (76.5)	[c]0.431
Drain-tube-ostomy type (n=117)	Drain	13 (11.1)	13 (12.5)	0 (0)	[e]0.671
	Tube	84 (71.8)	72 (69.2)	12 (92.3)	
	Ostomy	6 (5.1)	6 (5.8)	0 (0)	
	Drain + tube	8 (6.8)	7 (6.7)	1 (7.7)	
	Tube + ostomy	5 (4.3)	5 (4.8)	0 (0)	
	Drain + tube + ostomy	1 (0.9)	1 (1.0)	0 (0)	
Catheter status		171 (99.4)	154 (99.4)	17 (100)	[d]1.000
Catheter type (n=171)	CVC	3 (1.8)	3 (1.9)	0 (0)	[e]0.868
	CVC + foley	24 (14.0)	21 (13.6)	3 (17.6)	
	PVC + foley	100 (58.5)	91 (59.1)	9 (52.9)	
	CVC + PVC + foley	44 (25.7)	39 (25.3)	5 (29.4)	
Pressure ulcer status		45 (26.2)	34 (21.9)	11 (64.7)	[d]0.001**
Pressure ulcer phase (n=45)	Phase 1	8 (17.8)	5 (14.7)	3 (27.3)	[e]0.540
	Phase 2	33 (73.3)	26 (76.5)	7 (63.6)	
	Phase 3	3 (6.7)	2 (5.9)	1 (9.1)	
	Phase 4	1 (2.2)	1 (2.9)	0 (0)	
MV status		68 (39.5)	64 (41.3)	4 (23.5)	[c]0.155
MV type (n=68)	Invasive	59 (86.8)	57 (89.1)	2 (50.0)	[d]0.082
	Non-invasive	9 (13.2)	7 (10.9)	2 (50.0)	
Invasive MV time (day) (n=59)	Min-max (median)	1-24 (6)	1-24 (6)	3-4 (3.5)	[b]0.164
	Mean ± SD	8.54±6.30	8.72±6.34	3.50±0.71	
Non-invasive MV time (day) (n=9)	Min-max (median)	2-12 (3)	2-12 (2)	3-3 (3)	[b]0.533
	Mean ± SD	3.78±3.23	4.00±3.70	3.00±0	
Sedation status		54 (31.4)	53 (34.2)	1 (5.9)	[c]0.017*
Sedation time (day) (n=54)	Min-max (median)	1-30 (6)	1-30 (6)	3-3 (3)	[b]0.332
	Mean ± SD	8.78±7.62	8.89±7.65	3.00±0	
CAM-ICU 2nd measurement	Negative	91 (52.9)	85 (54.8)	6 (35.3)	[c]0.125
	Positive	81 (47.1)	70 (45.2)	11 (64.7)	
Discharge type in intensive care	Exitus	76 (44.2)	71 (45.8)	5 (29.4)	[e]0.047*
	Referral	95 (55.2)	84 (54.2)	11 (64.7)	
	Discharge	1 (0.6)	0 (0)	1 (5.9)	
Length of stay in intensive care (day)	Min-max (median)	1-49 (5)	1-49 (5)	2-13 (4)	[b]0.393
	Mean ± SD	6.60±6.39	6.79±6.64	4.82±2.86	
Length of stay in the hospital (day)	Min-max (median)	2-49 (5)	2-49 (5)	2-13 (4)	[b]0.218
	Mean ± SD	8.56±8.71	8.89±9.04	5.53±3.45	

Min-max: Minimum-maximum, SD: standard deviation, CAM-ICU: Confusion Assessment Method for the intensive care unit, MV: mechanical ventilation, CVC: central venous catheter, PVC: peripheral venous catheter

[b]Mann-Whitney U test, [c]Pearson chi-square test, [d]Fisher's Exact test, [e]Fisher-Freeman-Halton test, *p<0.05, **p<0.01

or above (OR: 7.404; 95% CI: 1.638-33.469). An increase of 5% or more in the PRE-DELIRIC score exhibited sensitivity of 100%, a specificity of 6.45%, a positive predictive value of 10.49%, a negative predictive value of 100%, and accuracy of 15.70%. An increase of 10% of more in the PRE-DELIRIC score exhibited sensitivity of 29.41%, a specificity of 29.41%, a positive predictive value of 17.85%, a negative predictive value of 91.67%, and accuracy of 79.65%.

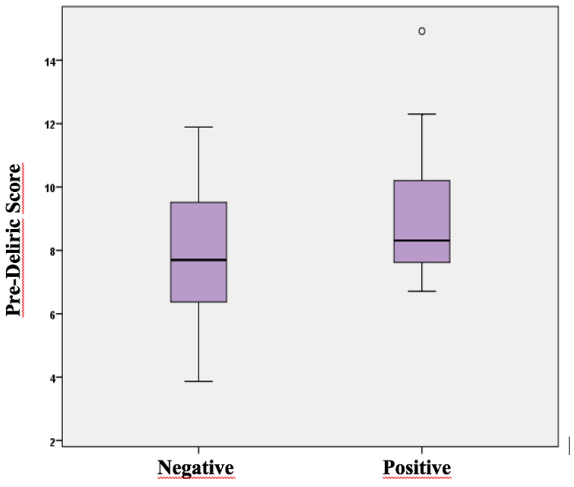

Figure 1. PRE-DELIRIC scores of the cases with negative and positive CAM-ICU in the 1st measurement
CAM-ICU: Confusion Assessment Method for the intensive care unit

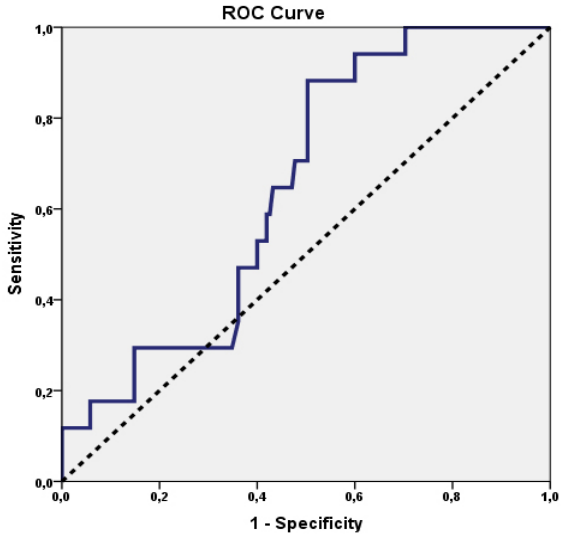

Figure 2. ROC curve for PRE-DELIRIC score by groups
ROC: Receiver operating characteristic

Table 3. Evaluation of PRE-DELIRIC scores according to CAM-ICU status

		Total	CAM-ICU		p-value
			Negative (n=155)	Positive (n=17)	
1st measurement PRE-DELIRIC score	Min-max (median)	3.9-14.9 (7.9)	3.9-11.9 (7.7)	6.7-14.9 (8.3)	[a]0.017*
	Mean ± SD	7.97±1.95	7.85±1.91	9.04±2.09	
2nd* measurement PRE-DELIRIC score	Min-max (median)	2.9-15.8 (8.3)	2.9-15.8 (8.2)	6.4-10.0 (9.2)	[a]0.053
	Mean ± SD	8.28±2.04	8.21±2.11	8.87±1.15	

Min-max: Minimum-maximum, SD: standard deviation, CAM-ICU: Confusion Assessment Method for the intensive care unit
[a]Student t-test, *p<0.05, *24 h later

Table 4. Diagnostic screening tests and ROC curve results for PRE-DELIRIC scores

PRE-DELIRIC (%)	Diagnostic scan				
	Cut-off	Sensitivity	Specificity	Positive predictive value	Negative predictive value
Low risk	≥7.58	88.24	49.68	16.13	97.47
Medium risk	≥8.06	64.71	52.90	13.10	93.18
High risk	≥8.32	47.06	60.00	11.43	91.18
Very high risk	≥9.32	29.41	72.90	10.64	90.40
PRE-DELIRIC >5		100	6.45	10.49	100
PRE-DELIRIC >10		29.41	85.16	17.85	91.67

ROC: Receiver operating characteristic

Discussion

We investigated the applicability of the PRE-DELIRIC model in intensive care, and the sensitivity of the model in predicting delirium with various physical and medical parameters compared with the CAM-ICU, the current gold standard.

The rate of development of delirium in this study was 9.9%. The reported delirium rate in ICUs ranges widely, from 10% to 80%, and it is important to obtain a measurement that can easily detect delirium, since this is vital for follow-up, treatment, and care (19-21). Delirium development is affected by many factors, and its prediction and prevention will make it possible to reduce the rate of disorders capable of leading to mortality and morbidity (14). There is evidence that delirium increases the length of hospital stay, exacerbates the risk of transmission of in-hospital infections, and puts the patient at risk of pressure ulcers and injuries (22-24).

CAM-ICU exhibited sensitivity of 88.24% (95% CI: 0.538-0.760) in this study and specificity of 85.16%. In their prospective, observational study, Guenther et al. (25) determined a risk of delirium of 19.8%, with CAM-ICU exhibiting sensitivity of 71% [(CI) 44-90%] and specificity of 100%, while another study reported a risk of delirium development of 25.2%, and CAM-ICU sensitivity of 100% [(CI) 92-99%] and specificity of 98% (6). A meta-analysis of nine separate studies concluded that CAM-ICU exhibited 80.0% sensitivity (95% CI: 77.1% and 82.6%) and 95.9% specificity (95% CI: 94.8% and 96.8%) (26). These inconsistencies may be due to variations in sampling and patient diagnoses.

CAM-ICU-positive cases exhibited higher scores than negative cases in this study. Patients with PRE-DELIRIC scores of 7.58 or more were 7.404 times more at risk of CAM-ICU-positivity (OR: 7.404; 95% CI:1.638-33.469). Studies elsewhere in the literature have also noted that PRE-DELIRIC and CAM-ICU scores are superior in identifying delirium, and that PRE-DELIRIC scores are particularly important on account of their simplicity, reliability, and rapid calculation (10,27). Studies have also observed high PRE-DELIRIC scores among individuals with positive CAM-ICU values (28,29). Similarly in the present study, a positive correlation was determined between CAM-ICU and PRE-DELIRIC.

The relevant factors in patients developing delirium according to the CAM-ICU in the present study were age, previous CVE, being physically restrained, presence of a pressure ulcer, and the form of intensive care discharge. Delirium was found to develop more commonly in elderly patients, those under physical restraint, in patients with a history of CVE, and in those with pressure ulcers. The predisposing factors reported to be related to delirium in the literature are similar to those found in the present study (12,30,31). Alcohol abuse, a history of dementia, hypertension, sedation, a high APACHE-II score, mechanical ventilation, and metabolic acidosis have also been described as factors exacerbating the risk of development of delirium in other studies (4,12,30,31). Since we only included intensive care patients with no history of chronic alcohol abuse, delirium or dementia, and no communication problems, and with a RASS score of +4 to -2 in this study, we may have been unable to detect all predisposing factors. However, the question of whether the PRE-DELIRIC model should not be taken into account in individuals with histories of dementia or misuse of alcohol and those who may have significant risk factors for delirium is a controversial one. van den Boogaard et al. (10) excluded groups of patients with a history of alcohol abuse and dementia from their PRE-DELIRIC regression model due to the low prevalence rate and reported that preventive measures can be taken directly instead of predicting the delirium risk, since the present evidence shows that these patients are already at a high risk of delirium. This has been criticized as a deficiency of the PRE-DELIRIC model by many researchers (4,31-33).

The PRE-DELIRIC score is easily applied and uses objective data, without the need for the patient to be conscious. This score can also be used as an important screening tool in detecting delirium in patients who are unable to communicate. Based on the findings of this study, we suggest that the PRE-DELIRIC score can be usefully employed in determining the risk of development delirium among patients in the ICU since it is easy to use and calculate and can make a useful contribution to clinical practice.

This study cannot be generalized to the general population since it was conducted at a single center within a limited time frame. The number of patients included in the study was also quite low. In addition, the inclusion of only conscious and communicating patients in the ICU, in which delirium evaluation was not routinely performed, may have resulted in a lower incidence than usual in this study in which we observed an incidence rate at the lower limit of the range reported in the literature.

Conclusion

Routine use of the PRE-DELIRIC score will make it possible to safely and easily predicting the risk of delirium within the first 24 hours after admission to the ICU. Evidence-based literature support of whether the model provides a fully valid and reliable risk estimate will require its common use in intensive care patients in addition to further interventional and observational studies to decrease the risk of delirium. In addition, CAM-ICU can predict the presence of delirium, and the PRE-DELIRIC model is beneficial when making a preliminary prediction and evaluation. The PRE-DELIRIC score is convenient for determining the risk of delirium development in patients hospitalized in the ICU and connected to a mechanical ventilator. There is currently no suitable screening test for delirium diagnosis, especially in disorientated patients. The present delirium screening tests require evaluation using a subjective method, in other words by means of answers to questions put to conscious and communicating patients.

Ethics

Ethics Committee Approval: Kırklareli University Institute of Health Sciences Ethics Committee approval (decision no: 3, date: 11.10.2019) was obtained from the institution in which the study was carried out, in addition to consent from the patients who were included in the study with the permission of the relevant institution. Written permission for the use of the PRE-DELIRIC score was obtained by e-mail from van den Boogaard.

Informed Consent: Consent was obtained from the patients included in the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.S., Concept: S.S., V.Ö., Design: S.S., V.Ö., B.T., Data Collection and Process: S.S., A.A.S., Analysis or Interpretation: B.T., N.Ö., Literature Search: S.S., V.Ö., B.T., A.A.S., N.Ö., Writing: S.S., V.Ö., B.T., A.A.S., N.Ö.

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References

1. European Delirium Association; American Delirium Society. The DSM-5 criteria, level of arousal and delirium diagnosis: inclusiveness is safer. BMC Med 2014;12:141.
2. Brummel NE, Girard TD, Ely EW, Pandharipande PP, Morandi A, Hughes CG, et al. Feasibility and safety of early combined cognitive and physical therapy for critically ill medical and surgical patients: the Activity and Cognitive Therapy in ICU (ACT-ICU) trial. Intensive Care Med 2014;40:370-9.
3. Salluh JI, Wang H, Schneider EB, Nagaraja N, Yenokyan G, Damluji A, et al. Outcome of delirium in critically ill patients: systematic review and meta-analysis. BMJ 2015;350:h2538.
4. Linkaitė G, Riauka M, Bunevičiūtė I, Vosylius S. Evaluation of PRE-DELIRIC (PREdiction of DELIRium in ICu patients) delirium prediction model for the patients in the intensive care unit. Acta Med Litu 2018;25:14-22.
5. Kırkpınar İ. Assessing and Managing Delirium in Surgical and Internal Medicine: an Overview. Bezmialem Science 2016;3:113-22.
6. Ely EW, Inouye SK, Bernard GR, Gordon S, Francis J, May L, et al. Delirium in mechanically ventilated patients: validity and reliability of the confusion assessment method for the intensive care unit (CAM-ICU). JAMA 2001;286:2703-10.
7. Bergeron N, Dubois MJ, Dumont M, Dial S, Skrobik Y. Intensive Care Delirium Screening Checklist: evaluation of a new screening tool. Intensive Care Med 2001;27:859-64.
8. Sutter R. Predicting the Unpredictable-How to Score the Risk of Delirium in Critically Ill Patients. Crit Care Med 2019;47:484-6.
9. Barr J, Fraser GL, Puntillo K, Ely EW, Gélinas C, Dasta JF, et al. American College of Critical Care Medicine. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. Crit Care Med 2013;41:263-306.
10. van den Boogaard M, Schoonhoven L, Maseda E, Plowright C, Jones C, Luetz A, et al. Recalibration of the delirium prediction model for ICU patients (PRE-DELIRIC): a multinational observational study. Intensive Care Med 2014;40:361-9.
11. Van Rompaey B, Schuurmans MJ, Shortridge-Baggett LM, Truijen S, Bossaert L. Risk factors for intensive care delirium: a systematic review. Intensive Crit Care Nurs 2008;24:98-107.
12. Lee A, Mu JL, Joynt GM, Chiu CH, Lai VKW, Gin T, et al. Risk prediction models for delirium in the intensive care unit after cardiac surgery: a systematic review and independent external validation. Br J Anaesth 2017;118:391-9.
13. Green C, Bonavia W, Toh C, Tiruvoipati R. Prediction of ICU Delirium: Validation of Current Delirium Predictive Models in Routine Clinical Practice. Crit Care Med 2019;47:428-35.
14. İnal MT, Memiş D, İnal V, Uyar AŞ, Tek ŞÇ, Çiftçi T, et al. Yoğun bakım hastalarında Predeliryum Skorunun değerlendirilmesi. Turk J Intense Care 2018;16:26-9.
15. Balas MC, Vasilevskis EE, Burke WJ, Boehm L, Pun BT, Olsen KM, et al. Critical care nurses' role in implementing the "ABCDE bundle" into practice. Crit Care Nurse 2012;32:35-8, 40-7; quiz 48.
16. Grover S, Kate N. Assessment scales for delirium: A review. World J Psychiatry 2012;2:58-70.
17. Yaşayacak A, Eker F. Kalp damar cerrahisi yoğun bakım ünitesinde yatan hastalarda deliryum ve risk faktörlerinin belirlenmesi. Türk Göğüs Kalp Damar Cerrahisi Dergisi 2012;20:265-74.
18. Akıncı SB, Rezaki M, Özdemir H, Çelikcan A, Kanbak M, Yorgancı K et al. Yoğun bakım ünitesinde Konfüzyon Değerlendirme Ölçeği'nin geçerlik güvenilirlik çalışması. Türk Anesteziyoloji ve Reanimasyon Dergisi 2005;33:333-3341.
19. Sosa FA, Roberti J, Franco MT, Kleinert MM, Patrón AR, Osatnik J. Assessment of delirium using the PRE-DELIRIC model in an intensive care unit in Argentina. Rev Bras Ter Intensiva 2018;30:50-6.
20. Lin WL, Chen WF, Wang J. Factors associated with the development of delirium in elderly patients in intensive care units. JNR 2015;4:322-9.
21. Kalabalik J, Brunetti L, El-Srougy R. Intensive care unit delirium: a review of the literature. J Pharm Pract 2014;27:195-207.
22. Aliberti S, Bellelli G, Belotti M, Morandi A, Messinesi G, Annoni G, et al. Delirium symptoms during hospitalization predict long-term mortality in patients with severe pneumonia. Aging Clin Exp Res 2015;27:523-31.
23. Pauley E, Lishmanov A, Schumann S, Gala GJ, van Diepen S, Katz JN. Delirium is a robust predictor of morbidity and mortality among critically ill patients treated in the cardiac intensive care unit. Am Heart J 2015;170:79-86
24. Wolters AE, van Dijk D, Pasma W, Cremer OL, Looije MF, de Lange DW, et al. Long-term outcome of delirium during intensive care unit stay in survivors of critical illness: a prospective cohort study. Crit Care 2014:18;18:R125.
25. Guenther U, Wolke M, Hansen HC, Feldman N, Diers A, Dewald O, et al. Bedeutung der Desorientierung bei der Delireinschätzung : Sekundäranalyse einer prospektiven, observationellen Studie [Disorientation and delirium assessment: A secondary analysis of a prospective, observational study]. Med Klin Intensivmed Notfmed 2022;117:419-27.
26. Gusmao-Flores D, Salluh JI, Chalhub RÁ, Quarantini LC. The confusion assessment method for the intensive care unit (CAM-ICU) and intensive care delirium screening checklist (ICDSC) for the diagnosis of delirium: a systematic review and meta-analysis of clinical studies. Crit Care 2012;16:R115.
27. Wassenaar A, Schoonhoven L, Devlin JW, van Haren FMP, Slooter AJC, Jorens PG, et al. Delirium prediction in the intensive care unit: comparison of two delirium prediction models. Crit Care 2018;22:114.
28. Heesakkers H, Devlin JW, Slooter AJC, van den Boogaard M. Association between delirium prediction scores and days spent with delirium. J Crit Care 2020;58:6-9.
29. Liang S, Chau JPC, Lo SHS, Bai L, Yao L, Choi KC. Validation of PREdiction of DELIRium in ICu patients (PRE-DELIRIC) among patients in intensive care units: A retrospective cohort study. Nurs Crit Care 2021;26:176-82.
30. Huai J, Ye X. A meta-analysis of critically ill patients reveals several potential risk factors for delirium. Gen Hosp Psychiatry 2014;36:488-96.
31. Zaal IJ, Devlin JW, Peelen LM, Slooter AJ. A systematic review of risk factors for delirium in the ICU. Crit Care Med 2015;43:40-7.
32. Ho MH, Chen KH, Montayre J, Liu MF, Chang CC, Traynor V, et al. Diagnostic test accuracy meta-analysis of PRE-DELIRIC (PREdiction of DELIRium in ICu patients): A delirium prediction model in intensive care practice. Intensive Crit Care Nurs 2020;57:102784.
33. Paton L, Elliott S, Chohan S. Utility of the PRE-DELIRIC delirium prediction model in a Scottish ICU cohort. J Intensive Care Soc 2016;17:202-206.

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ORIGINAL RESEARCH / *ÖZGÜN ARAŞTIRMA*

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COVID-19 Experiences of Turkish Intensive Care Nurses: A Qualitative Study

Türk Yoğun Bakım Hemşirelerinin COVİD-19 Deneyimleri: Nitel Araştırma

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ABSTRACT *Objective:* Nurses are at the forefront of the fight against the pandemic. This study was conducted to reveal the experiences, problems, motivation and support resources of intensive care nurses in the first period of the coronavirus disease-2019 (COVID-19) pandemic.
Materials and Methods: The research is a descriptive qualitative study. The sample of the study consisted of 12 intensive care nurses working in the intensive care unit of a state hospital in İzmir and caring for patients infected with COVID-19 virus.
Results: Main themes (sub-themes); emotions (worry/anxiety), difficulties in patient care (aspiration, intubation), measures taken by nurses (internal isolation), effects of the pandemic on intensive care nurses (physical; back pain, psychological; sleep problems, social; exclusion), support and motivation sources of nurses (teammates support), positive contributions of the pandemic process (crisis management).
Conclusion: Intensive care nurses experienced physical, psychological and social problems during the pandemic period. In this process, it was determined that they tried to strengthen with support resources and gained skills in crisis management.
Keywords: COVID-19, pandemic, intensive care nurse, experiences

ÖZ *Amaç:* Hemşireler, pandemi ile mücadelenin ön saflarında görev almaktadır. Bu çalışma, yoğun bakım hemşirelerinin koronavirüs hastalığı-2019 (COVİD-19) pandemisinin ilk döneminde yaşadıkları deneyimleri, sorunları, motivasyon ve destek kaynaklarını ortaya çıkarmak amacıyla yapılmıştır.
Gereç ve Yöntem: Araştırma tanımlayıcı nitel bir çalışmadır. Araştırmanın örneklemini İzmir ilinde bir devlet hastanesinin yoğun bakım ünitesinde görev yapan ve COVİD-19 virüsü ile enfekte hastalara bakım veren 12 yoğun bakım hemşiresi oluşturmuştur.
Bulgular: Ana temalar (alt temalar); duygular (endişe/kaygı), hasta bakımındaki zorluklar (aspirasyon, entübasyon), hemşirelerin aldığı önlemler (iç izolasyon), pandeminin yoğun bakım hemşireleri üzerindeki etkileri (fiziksel; sırt ağrısı, psikolojik; uyku sorunları, sosyal; dışlama), hemşirelerinin destek ve motivasyon kaynakları (ekip arkadaşları desteği), pandemi sürecinin olumlu katkıları (kriz yönetimi) olarak belirlenmiştir.
Sonuç: Yoğun bakım hemşireleri pandemi döneminde fiziksel, psikolojik ve sosyal sorunlar yaşamıştır. Bu süreçte destek kaynakları ile güçlenmeye çalıştıkları ve kriz yönetiminde beceri kazandıkları belirlenmiştir.
Anahtar Kelimeler: COVİD-19, pandemi, yoğun bakım hemşireliği, deneyimler

Introduction

An unexpected virus, severe symptoms seen in people infected with the virus, and the rapidly increasing number of cases worldwide have caused a rapid change in intensive care activities (1). The coronavirus disease-2019 (COVID-19) outbreak was declared as a pandemic by the World Health Organization due to the high spread rate of the virus, its serious effects on public health and the deaths of thousands of people (2). The first COVID-19 case in Turkey was announced on March 10, 2020, and this number has gradually increased. COVID-19 infection has become a universal problem with widespread respiratory symptoms causing pneumonia, severe acute respiratory infection,

kidney failure, and death in severe cases (2). COVID-19 infection is a highly contagious disease and the virus poses a huge threat to healthcare workers. There has been a sudden increase in the number of intensive care beds due to COVID-19 worldwide. In this sudden increase, additional intensive care units were opened with the support of nurses in the healthcare system, and the number of beds was increased (3). This increase has seriously increased the workload of nurses (1). The main reason for the increase in the workload per patient is more intensive hygiene practices, difficult mobilization, support programs for patient relatives, maintenance of respiratory function, and an increase in the number of deaths (1). Nurses provide care to patients with close physical contact and are therefore in a risky group in terms of COVID-19 (4-8). Individuals who need intensive care treatment in the pandemic are generally elderly individuals with a history of comorbid diseases. Severe pneumonia resulting in breathing difficulties in COVID-19 infection has resulted in the hospitalization of thousands of people. Two-thirds of the individuals in need of intensive care met the criteria for acute respiratory distress syndrome and respiratory support was required (9). Intensive care nurses have undertaken important duties in meeting the care needs of individuals experiencing advanced symptoms of the disease during the COVID-19 global epidemic.

In the pandemic, intensive care units have become the most important units for patients. Since patients need a mechanical ventilator when COVID-19 symptoms worsen, intensive care nurses have many more responsibilities such as monitoring and maintenance of the patient's respiratory functions, aspiration of secretions, oral care, giving the patient a prone position, monitoring early sepsis symptoms, regular administration of supportive therapies determined by the physician at appropriate doses, maintaining the patient's enteral nutrition, ensuring hygiene requirements, blood gas analyses and informing the physician when necessary (10,11). In these treatment and care practices, the distance between the intensive care nurse and COVID-19 (+) or suspected (+) individuals can be maximum 10 cm. Due to the care and treatment needs of the patient, it is very rarely possible for the intensive care nurse to leave the patient's room, to enter and exit the patient's room less, or to stay away or behind. Many international scientific associations, especially the World Federation of Intensive Care Nurses; emphasize that the patient: a nurse ratio should be 2:1 for the care of critically ill (not mechanically ventilated) patients who require complex care, but 1:1 for critically ill patients who are mechanically ventilated and highly dependent. Although there is no evidence in the literature yet, China and the United States, etc., where the pandemic spread before Turkey. The practice made and recommended by countries is that one intensive care nurse takes care of a patient with COVID (+) due to the high risk of transmission, as well as the critical patient is connected to a mechanical ventilator (10,12).

Therefore, providing care to infected patients for a long time poses a high risk in terms of transmission of the disease to intensive care nurses (10). The anxiety experienced by nurses while caring for infected patients is related to their risk of infection, being carriers of the source of infection and death anxiety (13-18).

Nurses are especially concerned about the spread of the virus to family members in the risk group such as the elderly, immunocompromised persons and children. To protect family members from the virus, nurses isolated themselves from their relatives (13,16,19). It is reported that nurses experience fear and anxiety despite taking protective measures (5). To date, a limited number of studies have been conducted on the pandemic experiences of nurses (13,16,20,21). During the pandemic, the effects of caregiving on nurses should be made visible.

Addition to, it is vital to understand the effects of the pandemic process on nurses and to determine the nurses' experiences to ensure the quality of health services. In this study, the experiences of intensive care nurses who have managed the COVID-19 pandemic with close follow-up, observation, and successful attempts will be reported.

Materials and Methods

This research was carried out in phenomenological type to determine both physical and psychological problems experienced by intensive care nurses during the COVID-19 pandemic process. The research focused on the problems experienced by intensive care nurses in combating a pandemic they had not experienced before, difficulties in patient care, difficulties in using equipment, being away from their families, and psychological difficulties they experienced in social isolation.

Research Questions

1. What are the feelings of intensive care nurses providing care in the COVID-19 pandemic?

2. What are the difficulties faced by intensive care nurses in patient care during the COVID-19 pandemic?

3. What are the precautions taken by the intensive care nurses during care in the COVID-19 pandemic?

4. What are the effects (physical, psychological, social) of the COVID-19 pandemic on intensive care nurses?

5. What are the sources of support and motivation for intensive care nurses during the COVID-19 pandemic?

Population and Sample of the Research

The population of the study consisted of intensive care nurses who gave care to patients with a diagnosis of COVID-19 who were working in a state hospital in İzmir. The sample consisted of nurses who agreed to participate in the study voluntarily. Due to qualitative research and data collection, the sample size was determined according to the saturation of the data, and in-depth interviews were conducted with 12 nurses.

Inclusion Criteria

Intensive care nurses who care for patients over the age of 18 with a diagnosis of COVID-19 were included. Nurses who did not agree to participate in the study were excluded from the study.

Research Method

The research data were collected face-to-face with a semi-structured interview form in an average of 30 minutes.

During the interview process, voice recordings of the nurses were taken, and their opinions were coded in such a way that their names were kept confidential.

Statistical Analysis

The researchers conducted the content analyses independently. In content analysis, the data were evaluated in four stages (1) coding the data, (2) finding codes, categories and themes, (3) organising the codes, categories and themes, and (4) describing and interpreting the findings.

Validity-reliability of the study: Kappa analysis was used to evaluate the appropriateness of the nurses' opinions and themes. A few opinions under the themes were randomly selected and sent to experts (academicians, expert nurses). The expert was asked to match the themes with the patient's statements. As a result of Kappa analysis, it was determined that there was an excellent level of agreement ($k=1$, $p<0.001$).

Internal validity (reliability): The average collection time of the research data was 30 minutes and reliable answers were obtained with long-term interviews. When the data reached the saturation point, the interviews were terminated. The researcher who conducted the interview received the confirmation of the nurses to verify the data. Two experts experienced in qualitative research examined the study in all aspects.

External validity (transferability): The opinions of the nurses were transferred without adding comments. Purposive sampling was used.

Internal reliability (consistency): The semi-structured interview form was prepared in line with the literature. The same interview form and voice recorder were used in the data collection process of the study.

External reliability (confirmability): The researchers analysed the data independently of each other. Then they came together and finalised the findings. This article was checked according to the COREQ checklist (22).

This study was conducted in accordance with the principles of the Declaration of Helsinki. Permission was obtained from the Ministry of Health Scientific Research Platform. Dokuz Eylül University Non-Interventional Research Ethics Committee approval was obtained for this study (decision no: 2020/19-26, date: 17.08.2020). Written institutional permission was obtained from the hospital where the research data were collected. Informed consent was obtained from the individuals participating in the study.

Results

The experiences of the nurses who participated in this study were summarized in six main themes.

In the study, 83% of the nurses participating in the study were female and 17% were male. 67% of them are in the 25-35 age range. 50% of this participants have been working for 1-9 years and 75% of them have been working in intensive care for 1-9 years. 67% of them had polymerase chain reaction (PCR) test, and 63% of them had PCR test 1-5 times (Table 1).

The nurses who participated in this study reported that they experienced fear, anxiety, and worry during the pandemic process and were generally afraid of infecting virus their families (Table 2).

"Nurses participating in the study reported that they had fear of being infected with the virus, infecting their relatives, stigma, and being away from their loved ones." (N3)

Table 1. Descriptive characteristics of nurses (n=12)			
Variable		**n**	**(%)**
Gender	Female Male	10 2	83% 17%
Age	25-35 35-45	8 4	67% 33%
Marital status	Married Single	6 6	50% 50%
Educational status	Pre-licence License Master's degree	1 10 1	8.3% 83.3% 8.3%
Work experience as a nurse	1-9 years 10-19 years 20-29 years	6 4 2	50% 33% 17%
Work experience as an intensive care nurse	1-9 years 10-19 years	9 3	75% 25%
Have you had a COVID-19 test?	Yes No	8 4	67% 33%
Why did he get COVID-19 test?	Contacted Symptom developed	3 5	63% 37%
How many times has the nurse been tested?	1-5 times 6-10 times	5 2	63% 37%
COVID-19: Coronavirus disease-2019			

Table 2. Emotions of intensive care nurses caring for the COVID-19 pandemic		
Theme	**Sub-themes**	**Nurses statements**
Emotions of intensive care nurses caring in the COVID-19 pandemic	Fear	N6: "When I first heard that I will start caring for a patient diagnosed with COVID-19, I was horrified, we were entering an unknown process, I felt like soldiers in the war." N4: "I was unafraid of being infected with the virus, I was afraid of infecting my children and relatives with the disease me." N9: "I was afraid of not being able to provide adequate care to patients and that I would be infected."
	Worry/anxiety	N11: "At first we were worried. Thanks to our experience and the support we give to each other with our teammates, our anxiety has decreased day by day." N1: "I was worried because we did not know the course of the disease at the beginning of the pandemic, and we did not know what awaited patients in the future." N7: "The sudden worsening of the patient's condition worried us."
COVID-19: Coronavirus disease-2019		

In this study, it has been reported that the intensive care nurses who care during the COVID-19 process have difficulty in applications such as aspiration, intubation, and oral care, which have a higher risk of virus transmission. It was stated that the most challenging equipment was glasses, masks, and overalls. Nurses reported that they were physically and psychologically worn out due to patient care and the use of difficult equipment (Table 3).

"The application that I think is the most challenging and with the highest risk of contamination during the pandemic process is an aspiration, oral care, intubation, feeding of the conscious patient, general body care, Ambu application, and CPAP application." (N5)

Table 3. Challenges of intensive care nurses during the COVID-19 pandemic		
Themes	**Sub-themes**	**Nurses statements**
Challenges of intensive care nurses during the COVID-19 pandemic	Coercive practices during a pandemic process	N12: "I am afraid to apply CPAP because it increases the risk of transmission." N8: "We were supporting the oral nutrition of conscious patients. Even though we had full protective equipment, we were in direct contact with the patient's secretions. We fed them with our hands. I think the risk of transmission is very high because we come into very close contact."
	Forceful equipment in the pandemic process	N2: "My most disturbing protective equipment in patient care was the N95 mask, overalls, and goggles." N6: "The glasses fog a lot and restrict the field of view when approaching the patient. It is very difficult to work with aprons all the time and I sweat all the time. The mask, on the other hand, makes it difficult for me to breathe easily and I always have pressure marks on my face." N7: "Sweat a lot in my overalls. I feel the need to constantly change uniforms. The glasses were making too much steam. I have asthma and have a hard time breathing with masks." N9: "We had to work more carefully because of the steam in the goggles. During this, we were both more careful and faster, and we intervened immediately. However, this process has worn us out physically and psychologically."
COVID-19: Coronavirus disease-2019		

Table 4. The precautions taken by intensive care nurses during the COVID-19 pandemic	
Themes	**Nurses statements**
Precautions taken by intensive care nurses during the COVID-19 pandemic	N6: "I didn't leave the house for 2-3 days and I applied room isolation when I stayed at home. I wore a mask at home. I separated forks and spoons. I was away from my children. During this time, I did not use public transportation." N3: "Clean the bathroom and toilet constantly. I had a shower before I came face to face with my children. We created an isolation room at home and ate our meals separately." N5: "At the beginning of the process, I stayed in dormitories arranged by the state. I was separated from my children for a month. Afterward, I realized that this process would not end immediately, I got used to the methods of protection, I knew better what to do now, I went back to my home." N4: "I haven't been in the same room with my 2 sons for about 3 months. I used a separate toilet. I used a mask during cooking. We made room isolation and ate our meals separately." N6: "Since I live with my family, I have stayed at my friends' house for 1.5 months. I was afraid of infecting my mother with the virus. When I saw these cases, which were transmitted from the children of hospitalized patients, I began to fear more. I didn't see my family."
COVID-19: Coronavirus disease-2019	

It was determined that the nurses who participated in this study stayed away from their homes and children during this process and those who stayed in the same house-applied room isolation (Table 4).

"I had a shower in the hospital, I was isolated at home, I used public transportation, I ate alone, I moved to a separate house, and I did not see my family members, children, and friends. In this process, I took these precautions." (N7)

Intensive care nurses reported the physical effects of the COVID-19 pandemic as back and leg pain, skin problems due to frequent hand washing, sweating due to protective equipment, and headaches due to masks. They started

the psychological and social effects of the pandemic as an increase in their longing for their relatives, a feeling of loneliness, and a sense of social stigma and exclusion due to being a healthcare worker (Table 5).

"I have back and leg pain. I have eczema and urticaria problems. I drink very little water as it is difficult to put on and take off the overalls. Therefore, urinary tract infections developed. It progressed in my leg varicose veins." (N1)

During this process, intensive care nurses reported that they received support from their families and teammates and that they wanted to receive financial support as well. Motivation sources are also to help patients and to be shown as a source of pride by society (Table 6).

"I did not receive support from psychiatry. Someone who has not experienced this process and this fear cannot know how I feel. Cannot support me in this matter." (N5)

Table 5. Effects of the COVID-19 pandemic on intensive care nurses (physical, psychological, social)

Themes	Sub-themes	Nurses statements
Effects of the COVID-19 pandemic on intensive care nurses	Physical problems occurring during the pandemic process	N6: "Because of the patient density, I stayed up longer. Since I could not meet my toilet needs overall, I drank almost less water. I had kidney pain. I've had many headaches attached to ffp2 masks. I felt exhausted after the seizure." N9: "Due to the workload, we couldn't rest enough, we stood for too long, and we were sweating a lot in our overalls. When we took off the overalls, we experienced back and leg stiffness. I had to change my jersey every time I got out of my overalls. I had an allergic runny nose, headache, and migraine attacks. Due to more frequent washing of our hands and the use of disinfectants, cracks and eczema occurred on our hands." N11: "When I took off my overalls, I was sweating down to my socks. I frequently uniform changed. I had foot and leg pains." N8: "I lose many fluids because I sweat excessively in the overalls. My uniform is soaked with sweat. I have constant headaches. I can't breathe easily in the mask. I am experiencing increased fatigue and pain."
	Psychological issues in pandemic process	N6: "I am experiencing problems such as sleep problems, longing, loneliness, anxiety, and tension during the pandemic process." N5: "We are so worn out psychologically. During this period, we supported each other with our colleagues. Being together with people who are in the same situation as us has increased my strength." N4: "My wife has hypertension, I was afraid of infecting her. This increased my stress even more." N1: "People around us were worried that we could infect them because we are healthcare professionals. When it was Boyle, I got nervous too. But as the process progressed, we started to gain acceptance." N9: "There were many negative people around me during this process. I was careful not to talk to people who weren't going through the same thing as me. I stayed away from them. They looked at me with pity." N3: "Because we do not have a social life and work is busy, I started to not be able to enjoy life, I went into burnout syndrome. I've come to the point of quitting my job. But we gave patient care in the best way possible. Seeing the patients recovering was raising our hopes."
	Social problems in a pandemic process	N11: "My partner was horrified at first. So, my partner and I stayed in different rooms. I didn't meet my parents for a while. I felt like my neighbors were looking at me with pity on my way to work. I never took off my mask in not to disturb my neighbors." N4: "Not being able to see our friends have affected us negatively. Even if we meet, I felt that they were uncomfortable with me because I was a hospital employee, I could not go to the meet." N5: "When my neighbors saw me, they were worried that you might infect us with a virus." N4: "I felt excluded, there were people who did not want to see me because I am a healthcare worker. My acquaintances conveyed their prayers to me through messages and telephone."

COVID-19: Coronavirus disease-2019

Table 6. Support and motivation resources of intensive care nurses in the COVID-19 pandemic		
Themes	**Sub-themes**	**Nurses statements**
Support and motivation resources of intensive care nurses in the COVID-19 pandemic	Support systems in the pandemic process financial support support from colleagues family, friend support moral support psychological support	N6: "In this process, I want to increase the number of nurses and let us rest more. We are exhausted physically and psychologically." N7: "Activities that will increase our motivation psychologically and socially can be planned. Concerts and events can only be organized for healthcare professionals." N2: "All occupational groups work with flexible hours, and health professionals work overtime. We, as health professionals, are exhausted."
	Motivation sources during the pandemic process	N6: "Since I had the COVID-19 disease, I could understand how the patients in the intensive care unit felt. I tried motivating the patients to get well. Caring for and supporting patients who needed me increased my motivation."
	We hope that the bad days will end one day	N11: "I didn't have any source of motivation. We continued to do our job in the hope that this disease will one day end."
	Being a source of pride	N8: "Patients were our biggest motivation." N7: "We were motivated by the thanks and applause support given to the healthcare professionals on social media and television."
COVID-19: Coronavirus disease-2019		

Table 7. Difference between the first pandemic shift and the shift at the end of two months		
Themes	**Sub-themes**	**Nurses statements**
The difference between the first pandemic seizure and the seizure at the end of 2 months	Experience and knowledge increase	N6: "As I gained experience in treatment and care planning, I started to do it better. I learned to motivate myself. I learned how to protect myself. I was more relaxed than the first shift."
	Learning to protect yourself	N9: "We learned to use protective equipment. We saw that it is not easy to infect. We have experienced that the equipment protects us. Our knowledge of the disease process has increased. We felt more comfortable while giving care."
	Relaxation when approaching the patient	N11: "I felt more comfortable. I could manage care better. Intensive care is an environment that requires teamwork. As we learned to manage the whole team, our risk of contagion decreased."
COVID-19: Coronavirus disease-2019		

During this period, they reported that they were more confident, experienced, and more comfortable while giving care to the patient during their seizures two months after the first patient care (Table 7).

"Started to do my job more confident. The stones have begun to fall into place. We are experienced in protection and care. Our stress and tension have decreased." (N12)

Most of the intensive care nurses reported that the process did not make a positive contribution. Some nurses reported that their professional development increased, their crisis management skills improved and their professional values increased in the society expressed (Table 8).

"I've seen too many complicated cases in a short time. I have developed myself more in terms of nursing. During this period, we became stronger as nurses. We saw the importance of teamwork more." (N9)

Discussion

In this study, COVID-19 pandemics of intensive care nurses involved throughout the process to determine both physical and psychological problems they experience in this process, how they cope with this problem, is conducted to determine what they feel. This study results have shown

Table 8. Positive contribution to the pandemic process		
Themes	**Sub-themes**	**Nurses statements**
Positive contribution to the pandemic process	Did not contribute positively	N12: "Don't think it has a positive effect. We are exhausted physically and psychologically."
	Professional development	N9: "Our professional development has increased in a short time. We learned fast patient care. We better understood the importance of seconds inpatient intervention."
	Increasing the value of the profession in society	N9: "It has been seen that the nursing profession has a very different and valuable dimension that distinguishes it from other professions. It has been seen how valuable and needed nurses who work for 24 h in patient care are during a pandemic. We have seen that we can overcome all difficulties."
	Crisis management	N1: "I feel more advanced. I learned more about nursing initiatives, nursing care, and crisis management in a short time. I used my coping skills."

once again the burden of nurses working in the pandemic. It is aimed to identify the aspects that need to be supported by nurses, who constitute the largest part of the healthcare system and to make their problems visible to increase their motivation. Nurses who experienced fear in the first periods of caring for COVID-19 patients reported that they provided care in a more comfortable and experienced manner in their shifts two months later. Nurses who provided care with negative emotions at the beginning of the process reported that negative emotions were replaced by positive emotions over time. In the Ebola and Middle East Respiratory syndrome coronavirus epidemics, the problems of nurses such as working hours, fatigue, and stress were similar to the problems in the COVID-19 pandemic. similar (5,23,24). In parallel with the study conducted by Sun et al. (25), in this study, nurses were afraid of transmitting the virus to family members. In the literature, many negative situations such as fear, anxiety, anxiety, and helplessness have been reported in healthcare professionals in epidemic disease situations (23,26). In this study, it was observed that nurses experienced fear and anxiety at the beginning of patient care.

In cases of an epidemic, nurses should be included in psychological support programs in the early period. As in the results of other studies, nurses in this study reported that they were afraid of the virus infecting themselves and their relatives (21,27). In addition to working in difficult conditions with fear, the fact that the nurses distanced themselves from their relatives reduced their social support, and the nurses who stayed home distanced themselves from their families in the form of room isolation. In many studies, epidemic diseases cause psychological trauma to caregivers (26,28). Because of this study, it was observed that nurses experienced negative emotions such as fear and anxiety during the patient care process. It has been reported that situations such as being appreciated, applauded, and thanked by society in addition to negative emotions make nurses proud. The nurses participating in the study reported that they were exhausted during this process, had difficulty staying with protective equipment during long working hours, and had many physical problems due to the equipment. They reported physical problems such as sweating a lot due to overalls, and low back and leg pain due to standing for a long time. because of the addition of fatigue and stress factors, the immune system of the nurses weakened, and the risk of getting sick increase. Liu et al. (29) In their study, reported that nurses had difficulties working with protective equipment, especially staying in overalls made them sweat and made movement difficult. Sun et al. (25) in their study "I have a headache, chest tightness, palpitations due to wearing protective clothing for a long time." nurses who care for patients infected with the COVID-19 virus have reported that working continuously with protective equipment increases their workload (1,30,31). It has been observed that the high workload of intensive care nurses affects both the risk of burnout and the quality of care (32).

Liu et al. (29) the sudden development of the epidemic dragged intensive care nurses onto an unknown path, but they reported that seeing a large number of cases in this short period of time contributed greatly to their professional development. Similar results were obtained in a study (30). Despite the various difficulties they face, the only aim of intensive care nurses is to serve their patients been to

providing quality care and ensuring their recovery. They have succeeded in overcoming situations such as fear, anxiety, and stress. They stated that the most important support systems in this process were their teammates, and they also stated that they had moral support from their families, albeit from a distance. During this difficult period, almost all of the intensive care nurses did not receive psychological support. However, it is recommended that nurses struggling with the epidemic receive expert support. Thanks that will help them deal with the problem (33). Some nurses who participated in this study had not seen their children for months. Some nurses stayed away from their children in the same house, and in this process, nurses needed psychological support. Nurses weren't afraid of getting infected They had a fear of infecting their families. Sun et al. (25) "My child and my mother cry every day, they are afraid that will infect me with a virus, but I am more worried about them..." Even if it is difficult to provide individual support programs, nurses' stress can be relieved by group interviews with the intensive care team. Studies on previous outbreaks have also reported that nurses experience burnout, fatigue, exhaustion, and a high workload (33). Nurses also had to contend with psychological and physical challenges. It is recommended that manager nurses and psychologists bring appropriate solutions to these negative situations experienced by intensive care nurses (34).

Conclusion

This study has shown that nurses play an important role in health care during the pandemic. Concrete measures should be taken, such as the need to develop support systems for nurses who are physically and psychologically under a heavy burden, increase the number of staff, reduce long working hours, and make plans to minimize the risk of contamination. In this study, it was observed that nurses experience positive and negative emotions at the same time. While thinking about their families, they also worried about their patients, and despite their physical exhaustion, they managed to provide the best patient care.

The fact that nurses who experienced fear and anxiety at the beginning of the pandemic gave care in a more comfortable, self-confident, and experienced manner in their shifts two months later shows that they came out of the negative process stronger. This study is important in terms of determining the needs and difficulties of intensive care nurses in the fight against a pandemic that will occur in the future and taking facilitating measures. It has shown that nurses, who are such a strong professional group, should be prioritized and supported more during this and similar crisis process.

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Ethics

Ethics Committee Approval: Ethics committee approval was obtained for this research. After the approval of the Dokuz Eylül University Non-Interventional Research Ethics Committee (decision no: 2020/19-26, date: 17.08.2020), written institutional permission was obtained from the state hospital in İzmir, where the research will be conducted.

Informed Consent: Informed consent was obtained from the individuals participating in the study.

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Authorship Contributions

Surgical and Medical Practices: D.B.B., Concept: D.B.B., M.G., Design: D.B.B., M.G., M.D, Data Collection and Process: M.G., Analysis or Interpretation: D.B.B., M.D., Literature Search: M.G., M.D., Writing: D.B.B., M.G., M.D.

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References

1. Bruyneel A, Lucchini A, Hoogendoorn M. Impact of COVID-19 on nursing workload as measured with the Nursing Activities Score in intensive care. Intensive Crit Care Nurs 2022;69:103170.
2. Republic of Turkey Ministry of Health General Directorate of Public Health. (2020). COVID-19 (SARS-CoV-2 Infection) Guide.
3. Marks S, Edwards S, Jerge EH. Rapid Deployment of Critical Care Nurse Education During the COVID-19 Pandemic. Nurse Lead 2021;19:165-9.
4. Huang L, Lin G, Tang L, Yu L, Zhou Z. Special attention to nurses' protection during the COVID-19 epidemic. Crit Care 2020;24:120.
5. Jackson D, Bradbury-Jones C, Baptiste D, Gelling L, Morin K, Neville S, Smith GD. Life in the pandemic: Some reflections on nursing in the context of COVID-19. J Clin Nurs 2020;29:2041-3.
6. Seale H, Leask J, Po K, MacIntyre CR. "Will they just pack up and leave?" - attitudes and intended behaviour of hospital health care workers during an influenza pandemic. BMC Health Serv Res 2009;9:30.
7. Hope K, Massey PD, Osbourn M, Durrheim DN, Kewley CD, Turner C, et al. Senior clinical nurses effectively contribute to the pandemic influenza public health response. Australian Journal of Advanced Nursing (Online) 2011;28:47.
8. Chiang HH, Chen MB, Sue IL. Self-state of nurses in caring for SARS survivors. Nurs Ethics 2007;14:18-26.
9. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med 2020;8:475-81.
10. Kıraner E, Terzi B, Türkmen E, Kebapçı A, Bozkurt G. Experiences of Turkish Intensive Care Nurses during the COVID-19 Outbreak. HEAD 2020;17:284-6.
11. Murthy S, Gomersall CD, Fowler RA. Care for Critically Ill Patients With COVID-19. JAMA. 2020;323:1499-500.

Halacli B, Kaya A, Topeli A. Critically-ill COVID-19 patient. Turk J Med Sci 2020;50:585-91.

12. Lam KK, Hung SY. Perceptions of emergency nurses during the human swine influenza outbreak: a qualitative study. Int Emerg Nurs 2013;21:240-6.
13. Holroyd E, McNaught C. The SARS crisis: reflections of Hong Kong nurses. Int Nurs Rev 2008;55:27-33.
14. Khalid I, Khalid TJ, Qabajah MR, Barnard AG, Qushmaq IA. Healthcare Workers Emotions, Perceived Stressors and Coping Strategies During a MERS-CoV Outbreak. Clin Med Res 2016;14:7-14.
15. Koh Y, Hegney D, Drury V. Nurses' perceptions of risk from emerging respiratory infectious diseases: a Singapore study. Int J Nurs Pract 2012;18:195-204.
16. Chung BP, Wong TK, Suen ES, Chung JW. SARS: caring for patients in Hong Kong. J Clin Nurs 2005;14:510-7.
17. Carmassi C, Foghi C, Dell'Oste V, Cordone A, Bertelloni CA, Bui E, et al. PTSD symptoms in healthcare workers facing the three coronavirus outbreaks: What can we expect after the COVID-19 pandemic. Psychiatry Res 2020;292:113312.
18. Ives J, Greenfield S, Parry JM, Draper H, Gratus C, Petts JI, et al. Healthcare workers' attitudes to working during pandemic influenza: a qualitative study. BMC Public Health 2009;9:56.
19. Corley A, Hammond NE, Fraser JF. The experiences of health care workers employed in an Australian intensive care unit during the H1N1 Influenza pandemic of 2009: a phenomenological study. Int J Nurs Stud 2010;47:577-85.
20. Fernandez R, Lord H, Halcomb E, Moxham L, Middleton R, Alananzeh I, et al. Implications for COVID-19: A systematic review of nurses' experiences of working in acute care hospital settings during a respiratory pandemic. Int J Nurs Stud 2020;111:103637.
21. Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. Int J Qual Health Care 2007;19:349-57.
22. Kim Y. Nurses' experiences of care for patients with Middle East respiratory syndrome-coronavirus in South Korea. Am J Infect Control 2018;46:781-7.
23. Kang HS, Son YD, Chae SM, Corte C. Working experiences of nurses during the Middle East respiratory syndrome outbreak. Int J Nurs Pract 2018;24:e12664.
24. Sun N, Wei L, Shi S, Jiao D, Song R, Ma L, et al. A qualitative study on the psychological experience of caregivers of COVID-19 patients. Am J Infect Control 2020;48:592-8.
25. O'Boyle C, Robertson C, Secor-Turner M. Nurses' beliefs about public health emergencies: fear of abandonment. Am J Infect Control 2006;34:351-7.
26. Arnetz JE, Goetz CM, Sudan S, Arble E, Janisse J, Arnetz BB. Personal Protective Equipment and Mental Health Symptoms Among Nurses During the COVID-19 Pandemic. J Occup Environ Med 2020;62:892-7.
27. Kang L, Li Y, Hu S, Chen M, Yang C, Yang BX, et al. The mental health of medical workers in Wuhan, China dealing with the 2019 novel coronavirus. Lancet Psychiatry 2020;7:e14.
28. Liu Q, Luo D, Haase JE, Guo Q, Wang XQ, Liu S, et al. The experiences of health-care providers during the COVID-19 crisis in China: a qualitative study. Lancet Glob Health 2020;8:e790-8.
29. Lucchini A, Giani M, Elli S, Villa S, Rona R, Foti G. Nursing Activities Score is increased in COVID-19 patients. Intensive Crit Care Nurs 2020;59:102876.
30. Hoogendoorn ME, Brinkman S, Bosman RJ, Haringman J, de Keizer NF, Spijkstra JJ. The impact of COVID-19 on nursing workload and planning of nursing staff on the Intensive Care: A prospective descriptive multicenter study. Int J Nurs Stud 2021;121:104005.
31. Rae PJL, Pearce S, Greaves PJ, Dall'Ora C, Griffiths P, Endacott R. Outcomes sensitive to critical care nurse staffing levels: A systematic review. Intensive Crit Care Nurs 2021;67:103110.
32. Joo JY, Liu MF. Nurses' barriers to caring for patients with COVID-19: a qualitative systematic review. Int Nurs Rev 2021;68:202-13.
33. Yin X, Zeng L. A study on the psychological needs of nurses caring for patients with coronavirus disease 2019 from the perspective of the existence, relatedness, and growth theory. Int J Nurs Sci 2020;7:157-60.

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ORIGINAL RESEARCH / *ÖZGÜN ARAŞTIRMA*

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The Efficacy of Continuous Renal Replacement Therapy and Hemoabsorption Treatments in COVID-19 Patients in the Intensive Care Unit: A Retrospective Evaluation

Yoğun Bakımda Yatan COVİD-19 Hastalarında Sürekli Renal Replasman Tedavisinin ve Hemoabsorbsiyon Tedavilerinin Etkinliğinin Retrospektif Değerlendirilmesi

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ABSTRACT *Objective:* The World Health Organization has emphasized that as there is no specific anti-coronavirus disease-2019 (COVID-19) treatment, supportive care according to disease severity is important. Previous studies have shown that acute kidney injury (AKI) develops in 30% of severe COVID-19 patients followed up in intensive care units and most these require renal replacement therapy. This study aimed to evaluate the COVID-19 prognosis, renal function, and organ systems of adult, severe COVID-19 patients treated with continuous renal replacement therapy (CRRT) and the effects on secondary hemophagocytic lymphohistiocytosis with the additional application of absorption filters.

Materials and Methods: A retrospective examination was made of the data of COVID-19 patients who applied for CRRT between 11.03.2020 and 15.06.2021. The demographic data of the patients were recorded together with the renal function test results before and after CRRT, and the biochemical parameters were included in the COVID-19 prognosis.

Results: Positive changes were determined in the kidney functions with CRRT applied to patients who developed AKI. No statistically significant difference was observed in the biochemical parameters included in the COVID-19 prognosis. In the 14 patients who applied with hemoabsorption, the need for short-term inotropic support was reduced. In our study, the mortality of the patients who were treated with CRRT was 95% (2 patients transferred to the ward), while the average intensive care unit stay was 18.2±11 days. While improvement was detected in renal function tests with CRRT applied to patients with AKI, no statistically significant difference was found in biochemical parameters in the prognosis of COVID-19. While mortality was 92.8% in 14 patients who underwent hemoabsorption, a short-term improvement was observed in the need for inotropes in these patients.

Conclusion: Although vaccinations are expected to definitively eliminate COVID-19, for critical COVID-19 patients for whom the treatment options are limited, it would seem rational to adopt immunomodulator strategies including extracorporeal blood purification and supportive treatment such as CRRT. The results of this study have shown that CRRT applied to severe COVID-19 patients who develop AKI is an effective treatment for kidney failure. However, the effect on the progression of COVID-19 could not be clearly shown.

Keywords: COVID-19, kidney failure, continuous renal replacement therapy, kidney functions, prognostic factors

ÖZ *Amaç:* Koronavirüs hastalığı-2019 (COVİD-19) enfeksiyonu için spesifik anti-COVİD-19 tedavisinin olmadığı ve hastalığın şiddetine göre destekleyici bakımın önemli olduğu, Dünya Sağlık Örgütü tarafından vurgulanmıştır. Çalışmalarda yoğun bakım ünitelerinde takip edilen, ciddi COVID-19 hastalarında %30 oranında akut böbrek hasarı (ABH) geliştiği ve çok büyük bir kısmında renal replasman tedavisi ihtiyacı olduğu görülmüştür. Çalışmamızda; yetişkin ağır COVİD-19 hastalarında sürekli renal replasman tedavisi (SRRT) ile organ sistemleri, böbrek fonksiyonları, COVİD-19 prognozu ve ek olarak uyguladığımız sitokin absorblama filtreleri ile sekonder hemofagositik lenfohistiyositoza etkilerini değerlendirmeyi amaçladık.

Gereç ve Yöntem: 11.03.2020-15.06.2021 tarihlerinde SRRT uygulanmış olan COVİD-19 hastalarının verileri retrospektif olarak incelendi. Hastaların demografik verileri, SRRT öncesi ve sonrası böbrek fonksiyon testleri ve COVİD-19 prognozunda yer alan biyokimyasal parametreler kaydedildi.
Bulgular: Çalışmamızda SRRT tedavisi uygulanan hastaların mortalitesi %95 (2 hasta servise devir) olarak tespit edilirken ortalama yoğun bakım yatış süresi 18,2±11 gün olarak değerlendirildi. ABH oluşan hastalara uygulanan SRRT ile böbrek fonksiyon testlerinde düzelme tespit edilirken COVİD-19 prognozunda yer alan biyokimyasal parametrelerde istatiksel olarak anlamlı fark bulunmadı. Hemoabsorbsiyon uygulanan 14 hastada mortalite %92,8 olarak tespit edilirken bu hastaların inotrop ihtiyacında kısa süreli bir iyileşme olduğu tespit edildi.
Sonuç: Aşıların COVİD-19'u kesin olarak ortadan kaldırmasını beklerken, sınırlı tedavi seçenekleri olan COVİD-19'lu kritik hastalara, SRRT gibi destek tedavisi ve ekstrakorporal kan pürifikasyonunun dahil olduğu immünomodülatör stratejileri benimsemek mantıklı görünmektedir. Çalışmamıza göre ABH gelişen ağır COVİD-19 hastalarına uygulanan SRRT, böbrek yetmezliğinde etkin bir tedavidir. Ancak COVİD-19 progresyonunda etkinliği net olarak ortaya konulamamıştır.
Anahtar Kelimeler: COVİD-19, böbrek yetmezliği, sürekli renal replasman tedavisi, böbrek fonksiyonları, prognostik faktörler

Introduction

Coronavirus disease-2019 (COVID-19) in adults and children is a disease with a broad clinical spectrum from asymptomatic or simple upper respiratory tract infection to severe respiratory or multiorgan failure with a need for intensive care. Previous studies have shown a significant association between multiorgan involvement and mortality (1). The clinical course in severe COVID-19 patients can be separated into three main phases; the early infection phase, the pulmonary phase, and the hyperinflammation phase. Phase 2 and phase 3 do not follow consecutively but overlap and this causes the development of multiorgan failure (2).

The first data coming from China at the beginning of the pandemic showed a relatively low incidence of acute kidney injury (AKI). It was reported to be seen at the rate of 0.5% in all cases and 2.9% of severe cases (3). In the subsequent period, this rate was seen to be as high as 28-37% in reports from the USA, and it was emphasized that the risk of AKI was even higher in hospitalised patients. In previous studies, the requirement for acute dialysis has been seen to vary between 20% and 50% in patients with COVID-19-related AKI (4).

The etiology of kidney damage associated with COVID-19 is multifactorial. These factors include hemodynamic instability, inflammation, cytokine expression, endothelial dysfunction, changes in the microcirculation, nephrotoxic exposure, and the effects of invasive mechanical ventilation (5).

In the intensive care unit (ICU) follow up of severe COVID-19 patients who develop AKI, continuous renal replacement therapy (CRRT) is generally selected rather than intermittent hemodialysis methods as patients are hemodynamically unstable (4,5). The advantage of CRRT methods is that in patients with septic shock, cytokine absorption systems can be integrated at the same time while applying this method, and the hyperininflammation phase of COVID-19 infection can also be treated at the same time (2).

Elevated levels of blood inflammatory mediators are predictive of the fatal outcome in COVID-19 patients. For this reason, immunomodulation therapies are considered as a part of standard practice in the management of severely ill COVID-19 patients. One way to make immunomodulation is specific or non-specific antagonism of the parts of the immune system. Examples for specific blockade are anakinra, tocilizumab, and baricitinib for IL-1, IL-6, and Janus kinase inhibition, respectively. Examples for non-specific immune system modulators are glucocorticoids, colchicine, mesenchymal stem cells, convalescent plasma. Another way for immunomodulation is the abovementioned extracorporeal blood purification (6).

The aim of this study was to evaluate the effect of CRRT on COVID-19 prognosis, renal functions and organ systems of COVID-19 patients who developed AKI during intensive care follow up and the effects on secondary hemophagocytic lymphohistiocytosis (sHLH) with the additional application of absorption filters.

Materials and Methods

Approval for the study was granted by the Non-Interventional Clinical Research Ethics Committee of Eskişehir Osmangazi University Faculty of Medicine (decision no: 32, dated: 06.04.2021). All procedures were in compliance with the principles of the Helsinki Declaration.

A retrospective evaluation was made of the data of severe COVID-19 patients applied with CRRT during follow up in the Anaesthesiology ICU of Eskişehir Osmangazi University Medical Faculty Hospital between 11.03.2020 and 15.06.2021.

Study Design

In the examination of the ICU patient records, it was seen that renal functions were evaluated according to the standard clinical guidelines criteria [Kidney Disease Improving Global Outcomes (KDIGO)]. According to these, patients with <0.3 mL/kg/hours (h) within 24 h were accepted as oliguria or within 12 h as anuric, evaluated as KDIGO grade 3 and above as indication for CRRT, and the records of these patients were examined.

Accordingly, the indication for starting CRRT evaluated according to the KDIGO recommendations (7) was determined as prescribed when effluent flow rate was 25-30 mL/kg/h (8), there was regional citrate anticoagulation of the anticoagulant selection and ionised calcium (iCa) after filtering for follow up was measured once in 6 h. The application was performed in our centre with two devices for continuous veno-venous hemodiafiltration. Multifiltrate (Fresenius, Bad Homburg vor der Höhe, Germany) and a 1.8 m^2 membrane (AV1000 set; Fresenius) and Prismaflex (Baxter Inc., Deerfield, IL, USA) and a 0.9 m^2 membrane (AN69 M100 and M150 filter set; Gambro) were used, and for hemoabsorption, CytoSorb (CytoSorbents Corporation, USA) and Oxirus (Baxter Inc., Deerfield, IL, USA).

Study Population

Patients were excluded from the study if they were aged <18 years, had a history of any renal disease, or did not have COVID-19 infection confirmed with a polymerase chain reaction (PCR) test during follow up. After exclusion of these patients, there were 280 patients remaining in the relevant time period. Of these 280 patients, 123 developed AKI, of which 41 met the KDIGO grade 3 criteria and were applied with CRRT. All other patients were excluded from the study and these 41 were included for analysis.

A retrospective record was made for each of these 41 patients applied with CRRT of demographic characteristics, comorbid diseases, medical treatments applied, the Sequential Organ Failure Assessment (SOFA) score, inotrope requirements, daily urine follow-up, CRRT modalities applied and the settings, the duration and number of applications, hemoabsorption column if applied, length of stay in ICU, requirement for mechanical ventilation, and mortality status.

To evaluate the efficacy of the CRRT treatment, kidney functions [urea, creatinine, glomerular filtration rate (GFR), Na, K, Cl, Ca, phosphorus], acute phase reactants, lactate dehydrogenase (LDH), ferritin, D-dimer, C-reactive protein (CRP), lymphocyte, procalcitonin, and lactate values were recorded pre and post-treatment.

Statistical Analysis

Data obtained in the study were analyzed statistically using IBM SPSS Statistics vn. 21.0 software (IBM Corpn. released 2012, SPSS Statistics for Windows, Armonk, NY, USA). Continuous data were stated as mean ± standard deviation values. In the comparisons of two groups of data with normal distribution, the independent samples t-test was used. For repeated measurements, two-way repeated measures ANOVA analysis (One Factor Repetition) was applied. A value of $p<0.05$ was accepted as statistically significant.

Results

Initial examination was made of the data of PCR (+) COVID-19 cases followed up in ICU between 11.03.2020 and 15.06.2021. Of 280 patients, 41 were applied with CRRT. The demographic data and laboratory parameters were recorded from the patient files. The patients comprised 51.21% males and 48.78% females with a mean age of 69.0±11.3 years. Comorbidities were determined as hypertension in 70.7% of the patients, diabetes mellitus in 48.8%, and malignancy in 21.9%. The demographic data are shown in Table 1.

When evaluated in terms of mortality, 95% (2 patients were transferred to the service, 39 patients died in the

Table 1. Demographics of 41 patients with COVID-19 infection

Age	69±11.3		
Gender	Male	21	51.21%
	Female	20	48.78%
Concomitant diseases	Hypertension	29	70.7%
	Diabetes mellitus	20	48.8%
	Malignancy	9	21.9%

COVID-19: Coronavirus disease-2019

ICU) mortality was detected in the patients we applied CRRT treatment. The time from symptom onset to the start of CRRT was determined as mean 12.1 days. The day of starting CRRT corresponded to phase 2 of the clinical stages of the disease. The access region selected for CRRT was determined to be the right jugular vein followed by the femoral vein. The severe COVID-19 patients with a need for CRRT were determined to have a high SOFA score (10.08±2.85). From the clinical observations of the patients who required CRRT, they were determined to be hemodynamically unstable, required inotropic support, and were oliguric or anuric in follow up. The anticoagulants were determined to be mostly regional citrate. iCa after filtration was monitored by measuring once in 6 h. The kidney functions routinely tested before and after CRRT and the acute phase reactants evaluated in the disease prognosis are summarised in Table 2. Following treatment, a significant improvement was determined in the urea, creatinine, GFR, potassium, chlorine and phosphorus values of the kidney functions.

The patients were observed to have elevated inflammation markers. Pre-treatment values were measured as ferritin: 1569.25 (13-150 ng/mL), D-dimer: 12.47 (0-0.5 mg/lt), CRP: 171.64 (0-5 mg/lt), neutrophil-lymphocyte ratio (NLR): 30.36 (1-3), lactate: 3.21 (0.56-1.39 mmol/lt), and procalcitonin: 8.74 (0-0.046 ng/mL). Following CRRT, the mean values were determined to be ferritin: 1243.07 (13-150 ng/mL), D-dimer: 7.72 (0-0.5 mg/lt), CRP: 147.32 (0-5 mg/lt), NLR: 26.0 (1-3), lactate: 3.00 (0.56-1.39 mmol/lt), and procalcitonin: 7.56 (0-0.046 ng/mL). The inflammation marker values were numerically better after CRRT, but the difference was not statistically significant. The values before and after CRRT of the biochemical parameters included in the disease prognosis are shown in Table 3.

Throughout the defined study period, CytoSorb (CytoSorbents Corporation, USA) or Oxirus (Baxter Inc., Deerfield, IL, USA) was used as cytokine filter in 14 patients in addition to CRRT. The inotrope requirement of the patients where cytokine filter was used in the clinical follow up was seen to be reduced in the short-term.

Table 2. Laboratory data before and after the start of CRRT

	Number of patients	Pre-CRRT values	Post-CRRT values	p-value
Ferritin	22	1569.25 (104-7403)	1243.07 (153-3248)	0.300
D-dimer	26	12.47 (0.480-80.0)	7.72 (0.310-34.1)	0.095
CRP	31	171.64 (11.5-383)	147.32 (24.4-420)	0.157
NLR	41	30.36 (2.30-97.0)	26.01 (4.40-96.0)	0.076
Lymphocyte	38	1.06 (0.200-7.10)	1.15 (0.140-5.40)	0.472
Lymphocyte %	37	5.13 (0.100-28.0)	5.49 (0.700-16.2)	0.595
Urea	40	62.07 (20.9-138)	32.13 (10.1-72.0)	<0.001
Creatinine	40	2.80 (0.980-6.89)	1.59 (0.570-5.20)	<0.001
GFR	40	27.90 (6.91-128)	51.63 (10.7-90.0)	<0.001
Na	41	141.24 (126-149)	140.24 (128-149)	0.444
K	41	5.05 (3.11-7.04)	3.70 (2.44-5.16)	<0.001
Cl	40	105.32 (91.6-120)	99.83 (92.8-106)	<0.001
Ca	40	7.68 (6.16-9.50)	8.56 (2.87-11.1)	0.001
P	40	5.63 (1.40-10.5)	3.82 (1.60-10.2)	<0.001
Lactate	41	3.21 (1.20-15.0)	3.00 (0.300-18.0)	0.570
Procalcitonin	31	8.74 (0.0200-68.0)	7.56 (0.270-58.0)	0.674
SOFA	41	10.80±2.848	10.83±3.016	0.931

CRRT: Continuous renal replacement therapy, CRP: C-reactive protein, NLR: neutrophil-lymphocyte ratio, GFR: glomerular filtration rate, SOFA: Sequential Organ Failure Assessment

Table 3. Biochemical parameters in the prognosis of COVID-19 before/after CRRT treatment				
	CRRT (before treatment)	CRRT (after treatment)	p-value	Normal values
Ferritin	1569.25 (104-7403)	1243.07 (153-3248)	0.300	13-150 ng/mL
D-dimer	12.47 (0.480-80.0)	7.72 (0.310-34.1)	0.095	0-0.5 mg/lt
CRP	171.64 (11.5-383)	147.32 (24.4-420)	0.157	0-5 mg/lt
NLR	30.36 (2.30-97.0)	26.01 (4.40-96.0)	0.076	1-3
Lactate	3.21 (1.20-15.0)	3.00 (0.300-18.0)	0.570	0.56-1.39 mmol/lt
Procalcitonin	8.74 (0.0200-68.0)	7.56 (0.270-58.0)	0.674	0-0.046 ng/mL

CRRT: Continuous renal replacement therapy, CRP: C-reactive protein, NLR: neutrophil-lymphocyte ratio, COVID-19: Coronavirus disease-2019. "Two way reapeated mesasures ANOVA (One Factor Repetition)" test was used ($p<0.05$).

Discussion

Several observational and retrospective studies have contributed to the understanding of the clinical status of COVID-19. However, in addition to providing supportive medical care, there continues to be uncertainty about the real efficacy of treatments which have been recommended by testing under dramatic clinical conditions (2).

Contradictions have emerged in therapeutic recommendations (antiviral drugs, steroids, anti-IL) and guidelines, and in the effects of rescue and supportive treatments applied to severe patients in emergency conditions. It must also be emphasized that guidelines and recommendations are being constantly developed as a result of new trials. The World Health Organization has stressed the importance of supportive treatments according to the severity of the disease, as there is no evidence on which to recommend any specific anti-COVID-19 treatment for severe cases with confirmed disease (9).

Although the respiratory system is the main target of COVID-19, other organs in the body can be infected by the virus through the circulation system (10). In literature, it can be observed that kidney involvement is frequent and can vary from mild proteinuria to advanced AKI (11).

The pathophysiology of AKI can be associated with COVID-19-specific mechanisms (direct viral entry, disproportional RAS activation, proinflammatory cytokines increased by viral infection, and thrombotic status) and non-specific mechanisms (right heart failure, hypovolemia, nosocomial sepsis, nephrotoxic drugs, mechanical ventilation, and hemodynamic changes). There is no specific treatment for AKI due to COVID-19 (10).

Current literature shows the frequency of AKI in COVID-19 patients varying between 0.5% and 45% and it has been reported to indicate a poorer prognosis. The reasons for the variability in incidence have been stated to be that different definitions are used to classify AKI, different populations have been studied, different criteria have been accepted and different countries have different resources (12).

In a study of 192 patients, Gameiro et al. (12) reported that AKI developed in 55.2%, of which 12.5% were determined to meet the KDIGO grade 3 criteria (12). Of the 280 COVID-19 patients in ICU screened in the current study, AKI was determined to have developed in 123 (43.9%). Of this patient group, 14% met the KDIGO grade 3 criteria, which was consistent with the literature.

The time to starting CRRT was mean 12.5 days in a study by Lowe et al. (13) and Ronco et el. (11) reported the start of CRRT on the 15th day after disease onset. From an examination of the records of the AKI patients in the current study, the time of starting CRRT was determined to be mean 12.5 days, consistent with the literature. It was also seen that the day on which CRRT was started corresponded to Phase 2 of the clinical stages of the disease.

In a study by Sabaghian et al. (14), the mean age of AKI patients was reported to be older (72±15 years) ($p<0.001$) and there was male gender predominance (69%) ($p<0.05$). A large-scale meta-analysis which included 21,060 COVID-19 patients, showed that in 39 of 41 studies there was a higher probability of severe disease in males than in females (15). In the current study, the mean age of the patients was 69.0±11.3 years, and unlike other studies, the numbers of male (51.21%) and female (48.78%) patients were close to each other.

There has been reported to be a significantly high frequency of hypertension and cardiovascular disease accompanying AKI (14). In a study by Gameiro et al. (12), comorbidities in AKI patients were determined to be

significantly high as hypertension (78.3% vs. 56.5%, p=0.001), chronic renal failure (28.3% vs. 9.4%, p=0.001), and COPD (19.8% vs. 7.1%, p=0.012) (11). In the current study patients, comorbidities were determined as hypertension in 70%, diabetes mellitus in 48.8, and malignancy in 21.9%.

Paek et al. (16) reported in-hospital mortality at the rate of 90% in AKI patients. Likewise in the current study, the frequency of mortality was 90%. In a study by Zarębska-Michaluk et al. (17), the mean time to mortality was determined as 8 days in 82 patients classified as kidney function GFR <30 mL/L/min. From the records of the current study patients, the time to mortality was mean 18 days. Although the mortality rate of the AKI grade 3 patients in the current study was high, with the rehabilitation including CRRT in ICU, the time to mortality was longer than reported in previous studies.

If organ dysfunction is to be measured objectively, the SOFA score can be used. Although this score was developed as a measure of the severity of organ dysfunction, it has prognostic value and has been used for that purpose in many studies (18). In a multicentre cohort study by Zhou et al. (19), a high SOFA score (7,15) in 191 patients was determined to be a potential risk factor for mortality (18). The severe COVID-19 patients who required CRRT in the current study were determined to have a high SOFA score (10.08±2.85).

There are various aims of extracorporeal blood purification for severe COVID-19 and AKI patients (2). These include the removal of solid loads such as creatinine and urea, convection of inflammatory mediators, cleaning wth absorption or therapeutic plasma exchange, reshaping immune homeostasis (20), correcting the body fluid compartment and decreasing excessive fluid burden (21), correcting the electrolyte and acid-base balance, and physically decreasing hyperthermia (21). In the patients examined in the current study, although the diuretic need arose associated with positive fluid balance, due to hemodynamic instability and the need for vasopressor asssociated wth endothelial damage, fluid loss to the third space, and renal hypoperfusion, there was progression to grade 3 AKI, and therefore CRRT was started. All the AKI patients who required CRRT were hemodynamically unstable and receiving inotropic support. Before CRRT, the urea (62.07) creatinine (2.80), potassium (5.05), phosphorus (5.63) and chlorine (105.32) values were determined to be high. Following CRRT, a significant improvement was determined in these kidney function values of urea (32.13) creatinine (1.59), GFR (51.63), potassium (3.70), phosphorus (3.82), and chlorine (99.83). Rhabdomyolysis, metabolic acidosis, and hyperkalemia can develop in COVID-19 patients and are almost always associated with hemodynamic instability (21). Urine analyses of AKI and biomarkers are usually abnormal in COVID-19 patients and can be used to characterise AKI in these patients (22). In the current study, the effects were evaluated of CRRT and hemoabsorption treatments applied to severe COVID-19 patients who developed AKI. In the light of these data, it can be considered that further prospective studies related to severe COVID-19 treatment and organ failure that may subsequently develop will reduce the uncertainty of treatment processes in the ongoing pandemic.

It has been reported that systemic inflammation markers, primarily ferritin, CRP, procalcitonin, and LDH, are higher in patients who develop AKI after COVID-19 infection compared to COVID-19 patients with normal kidney functions (22).

In a meta-analysis by Zarębska-Michaluk et al. (17), CRP was determined as 107 mg/L, procalcitonin as 2.83 ng/mL, and D-dimer as 5.113 mg/lt in patients with eGFR <30 mL/min/1.73 m^2, and CRP as 65.5 mg/L, procalcitonin as 0.28 ng/mL, and D-dimer as 1.638 mg/lt in patients with eGFR >60 mL/min/1.73 m^2. The inflammatory parameters were determined to be high in the eGFR <30 mL/min/1.73 m^2 patient group (17). Gameiro et al. (12) compared the NLR in patients with and without AKI, and determined higher values in the patient group with AKI (7.8±6.5 vs. 4.9±4.0). In addition, the ferritin value of 7600 ng/mL and lactate value of 0.89 mmol/lt were determined to be higher in the AKI group, but not at a significant level (12).

The inflammation markers of the patients in the current study were determined to be higher than data in literature. Pre-treatment values were measured as ferritin: 1569.25 (13-150 ng/mL), D-dimer: 12.47 (0-0.5 mg/lt), CRP: 171.64 (0-5 mg/lt), NLR: 30.36 (1-3), lactate: 3.21 (0.56-1.39 mmol/lt), and procalcitonin: 8.74 (0-0.046 ng/mL). Following CRRT, the mean values were determined to be ferritin:1243.07 (13-150 ng/mL), D-dimer: 7.72 (0-0.5 mg/lt), CRP: 147.32 (0-5 mg/lt), NLR: 26.0 (1-3), lactate: 3.00 (0.56-1.39 mmol/lt), and procalcitonin: 7.56 (0-0.046 ng/mL). Although the inflammation marker values included in the COVID-19 prognosis were numerically better after CRRT, the difference was not statistically significant.

In a study in which Chen et al. (23) evaluated inflammatory markers separately, COVID-19 patients with AKI were found to have higher serum CRP levels than the

patients without AKI. CRP is a marker for renal replacement therapy and for mechanical ventilation required by COVID-19 patients. Therefore, a high CRP value is associated with a poor clinical prognosis in COVID-19 patients. However, the role of CRP and the mechanisms in which it is included in AKI associated with COVID-19 are not fully known (23). When literature is examined, it can be seen that there may be a relationship between lymphopenia and the severity of infection. In a cohort of 450 COVID-19-positive patients, Qin et al. (24) analyzed the markers related to immune response irregularity, and reported that severe cases tended to have a lower lymphocyte count, higher leukocyte count, and a higher NLR than mild cases (25). The hematological (lymphocyte count, leukocyte count, NLR), inflammatory (CRP, sedimentation, IL-6), and especially biochemical (D-dimer, troponins, CK) parameters were found to be associated with a severe prognosis or mortality in COVID-19 patients, and therefore, it can be concluded that these can be used as estimation-based biomarkers (25). A laboratory score including hematological, inflammatory, biochemical, and immunological parameters would be useful in differentiating risk categories in the treatment methods and clinical follow-up of COVID-19 patients (25). The potential risk factors in the current study patients were determined to be high before starting CRRT. These risk factors explain the poor prognosis and high mortality of these patients. On the basis of these findings, laboratory scoring would be useful for clinicians to identify patients with a poor prognosis at the early stage and to organise treatments.

Since the reporting of the first cases, cytokine storm has been observed in the clinical course of severe COVID-19 patients (1,26). Similar to sepsis and septic shock, the nature of cytokine storm in COVID-19 patients has been observed to be organ dysfunction, increased vascular permeability, hypovolemia, hypoperfusion, hypotension, cardiomyopathy, tissue oedema, pleural effusion, increased intra-abdominal pressure and cross-reactions of organs with each other (18). Despite the initial low number of clinical studies therapeutic approaches have entered clinical practice to reduce severe acute pulmonary damage and multiorgan failure associated with COVID-19 (27). Of the treatments directed at suppressing the increased cytokine response with anti-inflammatory treatments, promising results have been obtained from reducing IL-6 (eg., tocilizumab, sarulimab, siltuximab), IL-1 receptor antagonist (eg., anakinra. canakinumab, rilonacept), and even TNF-α inhibitors (eg., adalimumab). The theoretical basis of only cytokine inhibition has been expanded with the hypothesis that potential benefits could be obtained from other immunomodulators which could be effective by targetting different cytokine types (26).

Consistent with findings in literature, it was seen in the current study that by using CRRT and cytokine absorption columns, both renal replacement and supportive treatment for sHLH developing in the course of the disease could be given. In a prospective, observational study, Villa et al. (27) determined a significant decrease in IL-6 concentrations, and a decrease in the SOFA score associated with an improvement in organ functions in patients treated with cytokine absorption (Oxiris membrane; Baxter, IL, USA).

The mean day of starting CRRT in the current study was the 12th day when hyperinflammation started. For the 14 patients where cytokine filter was used in addition to CRRT, CytoSorb (CytoSorbents Corporation, USA) or Oxirus (Baxter Inc., Deerfield, IL, USA) was used. From the daily monitoring records of the patients, there was determined to be a reduced need for short-term inotropes in patients applied with cytokine filtration.

Another point which is usually found in discussions related to treatment of sepsis-like syndromes is the timing and monitoring of treatment. Clinical conditions such as rhabdomyolysis (28), multiorgan failure related to thrombocytopenia (29), multiple myeloma (29), and acute rejection after organ transplantation (29) benefit from extracorporeal blood purification. The decision to start treatment is made when a series of mediators reach a peak (29). Together with the onset of symptoms, it is possible to determine biomarkers of the disease (eg., myoglobin, von Willebrand factor and ADAMTS-13, donor-specific antibodies). The same biomarkers can be examined repeatedly and the treatment efficacy is followed up objectively. Extracorporeal blood purification is directed at the target and the timing of starting and finishing the treatment is evident and clear (29). However, in the timing of extracorporeal blood purification treatment for COVID-19 cases, there are no specific biomarkers for starting and finishing the treatment.

Limitations of this study could be said to be the relatively limited number of patients, the variability in antibiotic levels because of CRRT, and that there was no information about whether or noot there was secondary infection in patients with a high SOFA score. There remains a need for further prospective studies on this subject.

Conclusion

Although vaccinations create immunity and are expected to definitively eliminate disease, for critical COVID-19 patients for whom the treatment options are limited, it would seem to be rational to adopt immunomodulator strategies including extracorporeal blood purification and supportive treatment such as CRRT. The results of this study have shown that CRRT applied to severe COVID-19 patients who develop AKI is an effective treatment for kidney failure. However, the effect on the progression of COVID-19 could not be clearly shown.

Ethics

Ethics Committee Approval: Approval for the study was granted by the Non-Interventional Clinical Research Ethics Committee of Eskişehir Osmangazi University Faculty of Medicine (decision no: 32, dated: 06.04.2021).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: E.P.Ş., Concept: E.P.Ş., O.Ö.A., B.Y., Design: E.P.Ş., O.Ö.A., B.Y., Data Collection and Process: E.P.Ş., Z.G., B.Y., Analysis or Interpretation: E.P.Ş., E.K., Z.G., B.Y., Literature Search: E.P.Ş., E.K., O.Ö.A., B.Y., Writing: E.P.Ş., E.K., Z.G., B.Y.

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References

1. Sherren PB, Ostermann M, Agarwal S, Meadows CIS, Ioannou N, Camporota L. COVID-19-related organ dysfunction and management strategies on the intensive care unit: a narrative review. Br J Anaesth 2020;125:912-25.
2. Romagnoli S, Peris A, De Gaudio AR, Geppetti P. SARS-CoV-2 and COVID-19: From the Bench to the Bedside. Physiol Rev 2020;100:1455-66.
3. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med 2020;382:1708-20.
4. Sohaney R, Shaikhouni S, Ludwig JT, Tilea A, Bitzer M, Yessayan L, et al. Continuous Renal Replacement Therapy among Patients with COVID-19 and Acute Kidney Injury. Blood Purif 2022;51:660-7.
5. Durvasula R, Wellington T, McNamara E, Watnick S. COVID-19 and Kidney Failure in the Acute Care Setting: Our Experience From Seattle. Am J Kidney Dis 2020;76:4-6.
6. Abdullayev R, Gul F, Bilgili B, Seven S, Cinel I. Cytokine Adsorption in Critically Ill COVID-19 Patients, a Case-Control Study. J Intensive Care Med 2022;37:1223-8.
7. Acosta-Ochoa I, Bustamante-Munguira J, Mendiluce-Herrero A, Bustamante-Bustamante J, Coca-Rojo A. Impact on Outcomes across KDIGO-2012 AKI Criteria According to Baseline Renal Function. J Clin Med 2019;8:1323.
8. Alvarez G, Chrusch C, Hulme T, Posadas-Calleja JG. Renal replacement therapy: a practical update. Can J Anaesth 2019;66:593-604.
9. Alhazzani W, Møller MH, Arabi YM, Loeb M, Gong MN, Fan E, et al. Surviving Sepsis Campaign: guidelines on the management of critically ill adults with Coronavirus Disease 2019 (COVID-19). Intensive Care Med 2020;46:854-87.
10. Ahmadian E, Hosseiniyan Khatibi SM, Razi Soofiyani S, Abediazar S, Shoja MM, Ardalan M, et al. Covid-19 and kidney injury: Pathophysiology and molecular mechanisms. Rev Med Virol 2021;31:e2176.
11. Ronco C, Reis T, Husain-Syed F. Management of acute kidney injury in patients with COVID-19. Lancet Respir Med 2020;8:738-42.
12. Gameiro J, Fonseca JA, Oliveira J, Marques F, Bernardo J, Costa C, Carreiro C, Braz S, Lopes JA. Acute kidney injury in hospitalized patients with COVID-19: A Portuguese cohort. Nefrologia (Engl Ed) 2021:S0211-6995(21)00097-7.
13. Lowe R, Ferrari M, Nasim-Mohi M, Jackson A, Beecham R, Veighey K, et al. Clinical characteristics and outcome of critically ill COVID-19 patients with acute kidney injury: a single centre cohort study. BMC Nephrol 2021;22:92.
14. Sabaghian T, Ahmadi Koomleh A, Nassiri AA, Kharazmi AB, Khalili S. Acute Kidney Injury Outcome in COVID-19 Patients. Iran J Kidney Dis 2022;1:44-51.
15. Li X, Zhong X, Wang Y, Zeng X, Luo T, Liu Q. Clinical determinants of the severity of COVID-19: A systematic review and meta-analysis. PLoS One 2021;16:e0250602.
16. Paek JH, Kim Y, Park WY, Jin K, Hyun M, Lee JY, et al. Severe acute kidney injury in COVID-19 patients is associated with in-hospital mortality. PLoS One 2020;15:e0243528.
17. Zarębska-Michaluk D, Jaroszewicz J, Rogalska M, Lorenc B, Rorat M, Szymanek-Pasternak A, et al. Impact of Kidney Failure on the Severity of COVID-19. J Clin Med 2021;10:2042.
18. Lelubre C, Vincent JL. Mechanisms and treatment of organ failure in sepsis. Nat Rev Nephrol 2018;14:417-27.
19. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020;395:1054-62.
20. Carter MJ, Shankar-Hari M, Tibby SM. Paediatric Inflammatory Multisystem Syndrome Temporally-Associated with SARS-CoV-2 Infection: An Overview. Intensive Care Med 2021;47:90-3.
21. Ronco C, Reis T. Kidney involvement in COVID-19 and rationale for extracorporeal therapies. Nat Rev Nephrol 2020;16:308-10.
22. Nadim MK, Forni LG, Mehta RL, Connor MJ Jr, Liu KD, Ostermann M, et al. COVID-19-associated acute kidney injury: consensus report of the 25th Acute Disease Quality Initiative (ADQI) Workgroup. Nat Rev Nephrol 2020;16:747-64.
23. Chen J, Wang W, Tang Y, Huang XR, Yu X, Lan HY. Inflammatory stress in SARS-COV-2 associated Acute Kidney Injury. Int J Biol Sci 2021;17:1497-506.
24. Qin C, Zhou L, Hu Z, Zhang S, Yang S, Tao Y, et al. Dysregulation of Immune Response in Patients With Coronavirus 2019 (COVID-19) in Wuhan, China. Clin Infect Dis 2020;71:762-8.
25. Ponti G, Maccaferri M, Ruini C, Tomasi A, Ozben T. Biomarkers associated with COVID-19 disease progression. Crit Rev Clin Lab Sci 2020;57:389-99.
26. Remy KE, Brakenridge SC, Francois B, Daix T, Deutschman CS, Monneret G, et al. Immunotherapies for COVID-19: lessons learned from sepsis. Lancet Respir Med 2020;8:946-49.
27. Villa G, Romagnoli S, De Rosa S, Greco M, Resta M, Pomarè Montin D, et al. Blood purification therapy with a hemodiafilter featuring enhanced adsorptive properties for cytokine removal in patients presenting COVID-19: a pilot study. Crit Care 2020;24:605.
28. Scharf C, Liebchen U, Paal M, Irlbeck M, Zoller M, Schroeder I. Blood purification with a cytokine adsorber for the elimination of myoglobin in critically ill patients with severe rhabdomyolysis. Crit Care 2021;25:41.
29. Romagnoli S, Ricci Z, Ronco C. Controversies on Non-renal Extracorporeal Therapies in Critically Ill COVID-19 Patients. In: Vincent JL, editor. Annual Update in Intensive Care and Emergency Medicine. Springer; 2021. p. 35-42.

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ÖZGÜN ARAŞTIRMA / *ORIGINAL RESEARCH*

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Yoğun Bakım Ünitesinde Takip Edilen Ağır COVİD-19 Hastalarında Farklı Solunum Desteği Yöntemlerinde Alveolo-arteriyel Oksijen Gradyanı ve Mortalitenin Değerlendirilmesi

Evaluation of Alveolo-arterial Oxygen Gradient and Mortality in Different Respiratory Support Methods in Severe COVID-19 Patients Followed in the Intensive Care Unit

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ÖZ *Amaç:* Ağır pnömoni, koronavirüs hastalığı-2019 (COVİD-19) enfeksiyonunda önemli bir mortalite nedenidir. Bu çalışma, yoğun bakım ünitesinde takip edilen ağır COVİD-19 hastalarında hipoksemik solunum yetmezliği tedavisinde kullanılan nazal kanül, yüksek akışlı nazal kanül, non-invaziv pozitif basınçlı ventilasyon ve invaziv mekanik ventilasyon ile solunum desteğine göre pulmoner gaz değişimini ve mortaliteyi değerlendirmeyi hedeflemektedir.
Gereç ve Yöntem: Pamukkale Üniversitesi Hastanesi Anesteziyoloji Yoğun Bakım Ünitesi'nde tedavi gören 140 ağır COVİD-19 hastasının kayıtları retrospektif olarak incelendi. Hastaların 3, 7, 14 ve 21. günlerdeki arteriyel kan gazı sonuçları kaydedildi.
Bulgular: Hastaların alveolo-arteriyel oksijen gradyanı karşılaştırıldığında nazal kanül ile oksijen alan hastaların alveolo-arteriyel oksijen gradyanı, yüksek akışlı nazal kanül, non-invaziv ve invaziv mekanik ventilasyon desteği alan hastalara göre anlamlı olarak daha düşüktü. Diğer gruplar kendi arasında karşılaştırıldığında yüksek akışlı nazal kanül, non-invaziv ve invaziv mekanik ventilasyon desteği alan hastaların alveolo-arteriyel oksijen gradyanları arasında anlamlı fark izlenmedi. Entübe olarak kabul edilen hastaların mortalitesinin diğer gruplara göre anlamlı olarak daha yüksek olduğu izlendi.
Sonuç: Ağır COVİD-19 hastalarının kabul sırasında ve 3 haftalık takipte invaziv ve non-invaziv oksijen desteğinin benzer alveolo-arteriyel oksijen gradyanları ile sonuçlandığını ancak entübe olan hastaların mortalitelerinin daha yüksek olduğu izlendi.
Anahtar Kelimeler: COVİD-19, nazal kanül, oksijen tedavisi, alveolo-arteriyel oksijen gradyanı, mekanik ventilasyon

ABSTRACT *Objective:* Severe pneumonia is an important cause of mortality in coronavirus disease-2019 (COVID-19) infection. This study evaluated pulmonary gas exchange and mortality according to nasal cannula, high flow nasal cannula, non-invasive positive pressure ventilation and invasive mechanical ventilation used for treating hypoxemic respiratory failure in severe COVID-19 patients.
Materials and Methods: Hundred and forty severe COVID-19 patients who were treated in Department of Anesthesiology Intensive Care Unit of Pamukkale University Hospital were reviewed retrospectively. Arterial blood gas results on the 1st, 3rd, 7th, 14th, and 21st days of admission were recorded.
Results: The alveolo-arterial oxygen gradient of the patients receiving oxygen via nasal cannula was significantly lower than the patients receiving high-flow nasal cannula, non-invasive and invasive mechanical ventilation. When the other groups were compared, no significant difference was observed between the alveolo-arterial oxygen gradients of the patients who received high-flow nasal cannula, non-invasive and invasive mechanical ventilation support. We observed that the mortality of the patients who were admitted as intubated was significantly higher than the other groups.
Conclusion: Invasive and non-invasive oxygen support resulted in similar alveolo-arterial oxygen gradients in severe COVID-19 patients at admission and at 3-week follow-up, but mortality was higher in intubated patients.
Keywords: COVID-19, nasal cannula, oxygen treatment, alveolo-arterial oxygen gradient, mechanical ventilation

Giriş

Şiddetli akut solunum sendromu koronavirüs-2 (SARS-CoV-2) ilk olarak Aralık 2019'un sonlarında tanımlanan ve özellikle solunum sistemini etkileyen küresel bir pandeminin nedenidir (1). Tüm enfekte bireylerin yaklaşık %20'sinde, akut solunum sıkıntısı sendromu (ARDS) tanımıyla uyumlu birçok klinik özelliğe sahip koronavirüs hastalığı-2019 (COVİD-19) pnömonisi gelişir. Spesifik olarak, radyolojisinde bilateral akciğer infiltratları, PaO_2/FiO_2 oranı <300 mmHg ile karakterize oksijenasyon defekti ve ölü boşluk ventilasyonunda artış izlenir (2). Düşük alveolo-arteriyel O_2 (A-a O_2) gradyanı düzeyleri ARDS hastalarında bozulmuş gaz değişimi ve hipokseminin bir başka göstergesi olup özellikle ağır COVİD-19 pnömonisi ile ilişkilidir (3).

Düşük PaO_2/FiO_2 oranına rağmen, çoğu hastanın başvuru anında akciğer hacimleri korunmuştur ve akciğer radyolojisinde esas olarak periferik dağılım ve minimal parankimal konsolidasyon ile bilateral multifokal buzlu cam görünümü görülmektedir (4). Diğer nedenlere bağlı ARDS'ye göre hipokseminin şiddeti çok daha fazladır (5).

Her ne kadar tüm hastalar ortak bir etiyoloji ile aynı hastalığa maruz kalmış olsa da hastane başvurusundaki klinik prezentasyon ve oksijen desteğine yanıtı oldukça değişkendir (6). Yüksek akışlı nazal kanül (YANK) ve non-invaziv pozitif basınçlı ventilasyon (NİPBV) dahil olmak üzere non-invaziv solunum desteğinin kullanımı oksijenasyonu destekleyebilir ve invaziv mekanik ventilasyonu (İMV) geciktirerek iyileşme için zaman tanıyabilir (7). Optimal modalitenin seçimi, tedavi başarısızlığını tanımak ve gecikmiş entübasyonu önlemek için belirsizliğini korumaktadır. Mekanik olarak ventile edilen hastalarda hastalık seyri ve solunum dinamikleri ve gaz değişimi üzerindeki etkileri iyi tanımlanmıştır (8). Ancak COVİD-19'a bağlı solunum yetmezliği olan hastalarda mekanik ventilasyona bağlı ölüm oranı %50-60 civarında olup, çoğu zaman birçok komplikasyonla ilişkilidir (9).

NİPBV'nin, hipoksemik solunum yetmezliğinde, İMV endikasyonu olan bir grup COVİD-19 hastasında başarıyla kullanılabildiği gösterilse de (10) literatürde bu modalitelerin karşılaştırmalı çalışması oldukça azdır.

Bu çalışmada, yoğun bakım ünitemizde (YBÜ) takip edilen ağır COVİD-19 hastalarında aldıkları O_2 desteğine göre pulmoner gaz değişimininin bir göstergesi olan A-a O_2 gradyanı düzeylerini ve mortalite ilişkisini değerlendirmeyi hedefledik.

Gereç ve Yöntem

Pamukkale Üniversitesi Hastanesi Anesteziyoloji YBÜ'de Eylül 2020-Şubat 2021 tarihleri arasında tedavi gören 140 ağır COVİD-19 hastasının kayıtları retrospektif olarak incelendi. Hastaların demografik verileri kaydedildi. Nazal kanül ile O_2 desteği alan, invaziv ventilasyon veya non-invaziv ventilasyon desteği alan hastalar çalışmaya dahil edildi. Bazı hastaların sonuçları hem entübe olmadıkları dönemde ve hem de akabinde entübe oldukları dönemlerde farklı zamanlarda incelendi.

Bilgisayarlı tomografide bilateral pulmoner infiltrasyon ve SARS-CoV-2 için pozitif orofaringeal sürüntüler ile COVİD-19 pnömonisi doğrulandı. Tedavi stratejisi; Glasgow koma skoru, arteriyel oksijen basıncı/inspiratuvar oksijen fraksiyonu (PaO_2/FiO_2), dakika solunum sayısı ve dispne varlığına göre düzenlendi.

İstatistiksel Analiz

Veri analizi için SPSS 22.0 (IBM, Armonk, NY, ABD) kullanıldı. Verilerin değerlendirilmesinde, tanımlayıcı istatistiksel yöntemler olarak sayı, yüzde, ortalama, standart sapma, medyan ve minimum-maksimum değerler kullanıldı. Verilerin normal dağılım özellikleri Kolmogorov-Smirnov ve Shapiro-Wilk testleri ile sınandı. İki bağımsız grup arasında niceliksel sürekli verilerin karşılaştırılmasında Mann-Whitney U testi, ikiden fazla bağımsız grup arasında niceliksel sürekli verilerin karşılaştırılmasında Kruskal-Wallis testi kullanıldı. Kategorik verilerin karşılaştırılmasında ki-kare testi kullanıldı. Tüm istatistiksel analizlerde anlamlılık düzeyi $p<0,05$ alındı.

Hastaların demografik verileri, kabul sırasında, takiplerinin 3, 7, 14 ve 21. günlerde alınan arteriyel kan gazı sonuçları, oksijen desteği kayıtları, Akut Fizyoloji ve Kronik Sağlık Değerlendirmesi II (APACHE-II) skorları, radyolojik bulguları ve COVİD-19 Raporlama ve Veri Sistemi skorları incelenerek kaydedildi.

Hastaların A-a O_2 gradyanı, $[(FiO_2 x(Patm-PH_2O))-(PaCO_2 \div 0.8)]-PaO_2$ formülü ile hesaplandı. Denizli ilinde atmosferik basınç (Patm) 730 mmHg, vücut sıcaklığında su buharı basıncı (PH_2O) 47 mmHg olarak kabul edildi.

Çalışma için, Pamukkale Üniversitesi Tıp Fakültesi Girişimsel Olmayan Klinik Araştırmalar Etik Kurulu'ndan onay alınmıştır (no: E-60116787-020-14366, tarih: 02.02.2021). Çalışma protokolü, 1964 Helsinki Deklarasyonu'nun etik kurallarına uygundur.

Bulgular

Hastaların ortalama yaşı 67,54±12,83 idi, %57,1'i (80) erkek, %42,9'u (60) kadınlardan oluşmaktaydı. Kadın hastaların 26'sı (%43,3), erkek hastaların 42'si (%52,5) takipte eksitus olduğu izlendi. Hastaların cinsiyete göre mortaliteleri istatistiki olarak benzerdi (p=0,448). Yoğun bakım kabulü sırasında A-a O_2 gradient seviyeleri istatistiksel anlamlılık sınırında olmasa da erkeklerde daha yüksek saptandı (kadınlarda 214,3+95,3; erkeklerde 267,8+125,1; p=0,054) (Tablo 1).

Hastalar 65 yaş sınır kabul edilerek iki gruba ayrıldığında, 94 hastanın 65 yaş ve üstünde olduğu, 46 hastanın 65 yaş altında olduğu izlendi. Bu iki grubun mortaliteleri istatistiki olarak benzerdi (p=0,551). Altmış beş yaş üstündeki ve altındaki hasta gruplarında YBÜ'ye kabul sırasında bu iki grup arasında A-a O_2 gradyanı istatistiki olarak benzerdi (<65 yaş hasta grubunda 259,6±127,2 >65 yaş hasta grubunda 237,6±110,3) (p=0,187) (Tablo 1).

Hastaların YBÜ'ye kabulünde, 3. gün, 7. gün, ve 14. günlerde aldıkları O_2 desteğine göre A-a O_2 karşılaştırıldığında nazal kanül ile O_2 alan hastaların A-a O_2 gradyanı, YANK, non-invaziv ve İMV desteği alan hastalara göre sırasıyla anlamlı olarak daha düşüktü (p<0,001, p<0,001, p<0,001, p<0,001) (Tablo 2). 21. günde NİPBV alan hasta olmasa da diğer üç grup solunum paternleri arasında A-a O_2 gradyanı açısından fark izlenmedi (p=0,170). Ancak 21. günde takibi devam eden hasta sayısının 24 gibi az bir sayı olması bu değerlendirmenin güvenilirliğini etkilemektedir.

Hastaların invaziv veya non-invaziv olarak oksijen desteği alması ile ilk ve ikinci A-a O_2 gradyan arasında değişim farkı anlamlı değildi (p=0,168).

Hastaların YBÜ'ye kabulü sırasında 62'sinin (%44,3) nazal kanül ile 6'sının (%4,3) YANK ile 30'unun (%21,4) NİPBV ile 42'sinin (%30) İMV ile solunum desteği aldığı görüldü. Bu hastalardan nazal kanül ile solunum desteği alanların 16'sının (%25,8), YANK ile solunum desteği alanların 4'ünün (%66,7), NİPBV ile solunum desteği alanların 14'ünün (%46,7), İMV ile solunum desteği alanların 36'sının (%85,7) takipte eksitus olduğu görüldü. YBÜ kabulü sırasında entübe olan hastaların mortalitesinin diğer gruplara göre anlamlı olarak daha yüksek olduğu izlendi (p<0,001).

YBÜ'ye kabul sırasında entübe olarak alınan 42 hasta dışında, takipte 20 hastanın daha entübasyon ihtiyacı oldu. Entübe olarak kabul edilenlerle, takipte entübe edilenlerin mortaliteleri karşılaştırıldığında istatistiki olarak fark izlenmedi (p=0,209).

APACHE-II skoru ile YBÜ'ye kabul sırasındaki A-a O_2 gradyanı arasında pozitif yönde korelasyon saptandı (p=0,013, r=0,295). Hastaların kabul sırasında hesaplanan medyan APACHE-II skoru 15'ti, APACHE-II skoru 15 ve altında olan 82 hastanın ortalama A-a O_2 gradyanı 215,0±83,0; APACHE-II skoru 15'in üzerinde olan 58 hastanın ortalama A-a O_2 gradyanı 287,1±141,3 olarak saptandı (p=0,006). Bu iki grubun mortalite oranlarında ise istatistiksel anlamlı fark saptanmadı (p=0,057) (Tablo 1).

Tartışma

COVİD-19 ile YBÜ'ye kabul edilen hastalarda görülen baskın özellik, genellikle standart O_2 tedavisinin üzerinde ek solunum desteği gerektiren hipoksemik solunum yetmezliğidir. Çalışmamızda, YBÜ'ye alınan ağır COVİD-19 hastalarının, YBÜ'ye kabulünde ve 3, 7 ve 14. günlerde kan gazı sonuçlarına göre nazal kanül ile O_2 desteği alan hastaların A-a O_2 gradyanını diğer O_2 desteği yöntemlerine göre anlamlı olarak daha düşük bulduk. Bu sonuç bu hasta grubunda ventilasyon/perfüzyon dengesinin henüz bozulmaya başlamamış olmasıyla açıklanabilir. YANK, NİPBV ve İMV ile O_2 desteği alan hastaların YBÜ'ye kabul sırasında ve 3 haftalık takipte A-a O_2 gradyanı ile oksijenizasyonu

Tablo 1. Hastaların klinik ve demografik özelliklerine göre alveolo-arteriyel oksijen gradyanları ve mortalite oranları

		n	YB kabulü sırasında A-a O_2 gradyan	p-değeri	Mortalite n (%)	p-değeri
Cinsiyet	Kadın	60	214,3±95,3	0,054	26 (%43,3)	0,448
	Erkek	80	267,8±125,1		42 (%52,5)	
Yaş	<65	46	259,6±127,2	0,187	20 (%43,5)	0,551
	≥65	94	237,6±110,3		48 (%51,1)	
APACHE-II	≤15	82	215,0±83,0	0,006	32 (%39)	0,057
	>15	58	287,1±141,3		36 (%62,1)	

APACHE-II: Akut Fizyoloji ve Kronik Sağlık Değerlendirmesi II, YB: Yoğun bakım, A-a O_2 gradyan: alveolo-arteriyel oksijen Gradyan

Tablo 2. Hastaların YBÜ'ye kabulünde, 3. gün, 7. gün, 14. ve 21. günlerde aldıkları O_2 desteğine göre A-a O_2 karşılaştırması				
Kan gazı günü	**Solunum desteği**	**Hasta sayısı (n)**	**A-a O_2 gradyanı (mmHg)**	**p-değeri**
1. gün	Nazal kanül	62	167,51 (±22,55)	p=0,00
	YANK	6	288,20 (±27,28)	
	NİPBV	30	251,72 (±94,01)	
	İMV	42	348,03 (±135,63)	
3. gün	Nazal kanül	32	154,27 (±43,40)	p=0,00
	YANK	24	294,27 (±59,40)	
	NİPBV	26	258,20 (±45,49)	
	İMV	48	345,61 (±109,91)	
7. gün	Nazal kanül	30	158,55 (±10,90)	p=0,00
	YANK	18	319,68 (±71,92)	
	NİPBV	20	251,42 (±50,76)	
	İMV	26	284,50 (±107,65)	
14. gün	Nazal kanül	24	151,30 (±13,60)	p=0,00
	YANK	6	251,10 (±35,07)	
	NİPBV	10	268,48 (±29,84)	
	İMV	16	305,93 (±121,00)	
21. gün	Nazal kanül	10	144,45 (±12,01)	p=0,170
	YANK	4	272,02 (±38,92)	
	NİPBV	-	-	
	İMV	10	268,13 (±151,72)	
YANK: Yüksek akışlı nazal kanül, NİPBV: non-invaziv pozitif basınçlı, İMV: invaziv mekanik ventilasyon, A-a O_2 gradyan: alveolo-arteriyel oksijen gradienti				

değerlendirildiğinde istatistiki fark saptayamadık. Bu sonuç, hastaların invaziv ventilasyon desteği ve non-invaziv destek almasının doku oksijenizasyonu açısından benzer sonuçlara yol açtığını düşündürmektedir.

Mekanik ventilasyona bağlanan hastaların diğer O_2 desteği alan hasta gruplarına göre anlamlı olarak mortalitesinin daha yüksek olduğunu izledik. Bu durum İMV'ye özgü komplikasyonlarla (barotravma, ventilatör ilişkili pnömoni vb.) ilişkili olabilir (9,11). Mellado-Artigas ve ark.'nın (12), başlangıçta YANK ile tedavi edilen hastalara karşı, hastaneye yatışlarının 1. gününde invaziv ventilasyon uygulanan hastaları karşılaştırdığı çalışmada, YANK kullanımının mortalitede fark olmaksızın YBÜ'de kalış süresinde azalma ile ilişkilendirilmiştir. Ancak Vaschetto ve ark. (13) CPAP sonrası entübasyondaki gecikmenin artmış mortalite riski ile ilişkili olduğunu bildirmiştir.

Çalışmamızda YBÜ'ye kabul sırasında entübe olarak alınanlarla takipte entübe edilen hastaların mortalitesini benzer olarak saptadık. Bu konuda literatürde farklı görüşlere rastlanmıştır. Dupuis ve ark. (14) erken entübasyonun mortaliteyi artırdığını saptamasına karşın, Daniel ve ark. (15), non-invaziv ventilasyon periyodundan sonra entübe edilenlerle entübe olarak kabul edilen grup arasında mortalite açısından hiçbir fark bulamadılar; bununla birlikte, non-invaziv ventilasyona devam edebilenlerde mortalite önemli ölçüde daha düşüktü.

Çalışmamızda, standart nazal kanül ile O_2 tedavisi alan hastaların mortalitesinin diğer solunum destek tedavilerine göre en düşük olduğunu izledik. Literatürde ise standart O_2 tedavisine kıyasla non-invaziv oksijenasyon stratejileri ile tedavi, daha düşük ölüm riski ile ilişkilendirilmiştir (16,17). Recovery-RS randomize kontrollü çalışmasında, 30 günlük entübasyon ihtiyacı veya mortalite sonucu açısından NİPBV'nin üstün olduğu ancak YANK'nin konvansiyonel O_2 tedavisine göre hiçbir fayda sağlamadığı gösterilmiştir (18). Bizim çalışmamızda hastaların YBÜ'ye kabulü sırasındaki APACHE-II skoru ile A-a O_2 gradyanı arasındaki pozitif yönde korelasyon nazal kanül ile O_2 desteği alan hastaların mortalitesinin daha düşük olmasının nedeninin doku oksijenizasyonunun ötesinde mortaliteyi etkileyen diğer faktörlerin olduğunu düşündürmektedir.

Biz çalışmamızda COVİD-19 hastalarının aldığı O_2 desteğine göre A-a O_2 gradyanlarını karşılaştırdık ancak COVİD-19 pnömonisinde NİPBV kullanımının etkinliğini araştıran prospektif multisentrik bir çalışmada HACOR (kalp hızı, asidoz, bilinç, oksijenasyon ve solunum hızı) skorunun, A-a O_2 gradyana göre daha duyarlı bir prediktör olduğu gösterilmiştir (19).

Literatürde erkek hastalarda ve ileri yaştaki COVİD-19 hastalarında mortalite daha yüksek bulunmuştur (20). Çalışmamızda ise mortalite üzerinde yaş ve cinsiyet etkisini gösteremedik. Yaş gruplarında A-a O_2 gradyanında farklılık gösterilemedi, cinsiyetler arasında değerlendirildiğinde ise istatistiksel olarak anlamlılık sınırına yakın düzeyde erkeklerde daha yüksek saptandı. Bu sonuçlar hasta sayımızın az olmasıyla açıklanabilir.

Prone pozisyon uygulaması ARDS hastalarında pulmoner gaz değişimini etkilediği gösterilmiş (21) bir yöntem olmakla birlikte çalışmamızda değerlendirilen kan gazı analizleri sırasında prone pozisyon uygulaması yapılan hasta yoktu. Bu, gruplar arasındaki gaz değişimi sonuçlarını etkileyecek ek bir dış faktörden kaçınmayı sağlamıştır.

Çalışmanın kısıtlılıkları: Çalışmanın retrospektif olması, hasta sayısının azlığı ve özellikle ilerleyen günlerde hasta sayısının daha azalması, yoğun bakım öncesi sürecin değerlendirilememesidir. Çalışmamızın diğer kısıtlılıkları hastaların komorbiditeleri ve aldıkları medikal tedavilerin göz önünde bulundurulmamış olmasıdır.

Sonuç

Çalışmamızda ağır COVİD-19 hastalarında 21. gün ölçümleri dışında solunum destek yöntemleri arasında A-a O_2 gradyan farkı saptansa da YBÜ'ye kabul ve 3. gün kan gazı ölçümlerinde invaziv ventilasyon desteği veya non-invaziv destek almasının benzer A-a O_2 gradyanı değişimi ile sonuçlandığını (p=0,168) ve entübe olan hastaların mortalitesinin diğer gruplara göre anlamlı olarak daha yüksek olduğunu izledik (p<0,001). İnvaziv ventilasyon desteği öncesi diğer destek tedavilerinin kullanılmasının mortaliteyi azaltılabileceği sonucu çıkarılabilir.

Etik

Etik Kurul Onayı: Çalışma için, Pamukkale Üniversitesi Tıp Fakültesi Girişimsel Olmayan Klinik Araştırmalar Etik Kurulu'ndan onay alınmıştır (no: E-60116787-020-14366, tarih: 02.02.2021). Çalışma protokolü, 1964 Helsinki Deklarasyonu'nun etik kurallarına uygundur.

Hasta Onamı: Retrospektif çalışma.

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Kaynaklar

1. Lai CC, Shih TP, Ko WC, Tang HJ, Hsueh PR. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease-2019 (COVID-19): The epidemic and the challenges. Int J Antimicrob Agents 2020;55:105924.
2. Camporota L, Cronin JN, Busana M, Gattinoni L, Formenti F. Pathophysiology of coronavirus-19 disease acute lung injury. Curr Opin Crit Care 2022;28:9-16.
3. Singh A, Soni KD, Singh Y, Aggarwal R, Venkateswaran V, Ashar MS, et al. Alveolar Arterial Gradient and Respiratory Index in Predicting the Outcome of COVID-19 Patients; a Retrospective Cross-Sectional Study. Arch Acad Emerg Med 2022;10:e28.
4. Shi H, Han X, Jiang N, Cao Y, Alwalid O, Gu J, et al. Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: a descriptive study. Lancet Infect Dis 2020;20:425-34.
5. Chiumello D, Busana M, Coppola S, Romitti F, Formenti P, Bonifazi M, et al. Physiological and quantitative CT-scan characterization of COVID-19 and typical ARDS: a matched cohort study. Intensive Care Med 2020;46:2187-96.
6. Churpek MM, Gupta S, Spicer AB, Parker WF, Fahrenbach J, Brenner SK, et al. Hospital-Level Variation in Death for Critically Ill Patients with COVID-19. Am J Respir Crit Care Med 2021;204:403–11.
7. Oranger M, Gonzalez-Bermejo J, Dacosta-Noble P, Llontop C, Guerder A, Trosini-Desert V, et al. Continuous positive airway pressure to avoid intubation in SARS-CoV-2 pneumonia: a two-period retrospective case-control study. Eur Respir J 2020;56:2001692.
8. Gattinoni L, Chiumello D, Caironi P, Busana M, Romitti F, Brazzi L, et al. COVID-19 pneumonia: different respiratory treatments for different phenotypes? Intensive Care Med 2020;46:1099-102.
9. Castaneda C, Ah Rhee CJ, Magh A, Eng C, Mann J, Sanso L, et al. Impact of ventılator model on mortalıty: a retrospectıve cross-sectıonal study ın 147 mechanıcally ventılated patıents wıth COVID-19 ARDS. Chest 2020;158:A617
10. Brusasco C, Corradi F, Di Domenico A, Raggi F, Timossi G, Santori G, et al. Continuous positive airway pressure in COVID-19 patients with moderate-to-severe respiratory failure. Eur Respir J 2021;57:2002524.
11. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med 2020;8:475-81.
12. Mellado-Artigas R, Ferreyro BL, Angriman F, Hernández-Sanz M, Arruti E, Torres A, et al. High-flow nasal oxygen in patients with COVID-19-associated acute respiratory failure. Crit Care 2021;25:58.
13. Vaschetto R, Barone-Adesi F, Racca F, Pissaia C, Maestrone C, Colombo D, et al. Outcomes of COVID-19 patients treated with continuous positive airway pressure outside the intensive care unit. ERJ Open Res 2021;7:00541-2020.
14. Dupuis C, Bouadma L, de Montmollin E, Goldgran-Toledano D, Schwebel C, Reignier J, et al. Association Between Early Invasive Mechanical Ventilation and Day-60 Mortality in Acute Hypoxemic Respiratory Failure Related to Coronavirus Disease-2019 Pneumonia. Crit Care Explor 2021;3:e0329.
15. Daniel P, Mecklenburg M, Massiah C, Joseph MA, Wilson C, Parmar P, et al. Non-invasive positive pressure ventilation versus endotracheal intubation in treatment of COVID-19 patients requiring ventilatory support. Am J Emerg Med 2021;43:103-8.
16. Ferreyro BL, Angriman F, Munshi L, Del Sorbo L, Ferguson ND, Rochwerg B, et al. Association of Noninvasive Oxygenation Strategies With All-Cause Mortality in Adults With Acute Hypoxemic Respiratory Failure: A Systematic Review and Meta-analysis. JAMA 2020;324:57-67.
17. Ángel Mejía VE, Arango Isaza D, Fernández Turizo MJ, Vasquez Trespalacios EM, Rincón JA. High flow nasal cannula useful for severe SARSs-CoV-2 pneumonia. Med Intensiva (Engl Ed) 2022;46:107-9.
18. Perkins GD, Ji C, Connolly B, Couper K, Lall R, Baillie K, et al. An adaptive randomized controlled trial of non-invasive respiratory strategies in acute respiratory failure patients with COVID-19. medRxiv 2021:1-25.
19. Santus P, Pini S, Amati F, Saad M, Gatti M, Mondoni M, et al. Predictors of Helmet CPAP Failure in COVID-19 Pneumonia: A Prospective, Multicenter, and Observational Cohort Study. Can Respir J 2022;2022:1499690.
20. Weerakkody S, Arina P, Glenister J, Cottrell S, Boscaini-Gilroy G, Singer M, et al. Non-invasive respiratory support in the management of acute COVID-19 pneumonia: considerations for clinical practice and priorities for research. Lancet Respir Med 2022;10:199-213.
21. Guérin C, Albert RK, Beitler J, Gattinoni L, Jaber S, Marini JJ, et al. Prone position in ARDS patients: why, when, how and for whom. Intensive Care Med 2020;46:2385-96.

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ÖZGÜN ARAŞTIRMA / *ORIGINAL RESEARCH*

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Yoğun Bakım Ünitesi Dışında Yüksek Akımlı Oksijen ve Non-invaziv Ventilasyon Uygulanan COVİD-19 Pnömonili Hastaların Özellikleri

Characteristics of Patients with COVID-19 Pneumonia Treated with High-flow Oxygen and Non-invasive Ventilation Outside the Intensive Care Unit

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ÖZ *Amaç:* Yoğun bakım ünitesi dışı koronavirüs hastalığı-2019 (COVİD-19) servisinde yatan hastalara uygulanan yüksek akımlı oksijen (HFO) ve non-invaziv ventilasyon (NİV) tedavi yöntemlerini karşılaştırmaktır.
Gereç ve Yöntem: Kasım 2020 ve Haziran 2021 tarihleri arasında devlet hastanesi yoğun bakım ünitesi dışı COVİD servisinde yatarak tedavi olan yüksek akımlı oksijen (n=26), ve NİV (n=23) uygulanan hastaların demografik özellikleri, hastanede yatış ve uygulanma süreleri, akut faz reaktanları, ROX indeksleri, komorbid durumları, radyolojik skorları ve sonuçları retrospektif olarak değerlendirildi.
Bulgular: Çalışmaya 27'si erkek, 22'si kadın 49 hasta alındı. Yaş ortalaması 55,6±14,6 idi. Komorbidite olarak en sık hipertansiyon (n=27), diyabet (n=15) saptandı. HFO grubundaki hastalar 16,6±9,4 gün hastanede yatarken, 6±4,6 gün HFO uygulandı. NİV grubundaki hastalar 9,4±6,4 gün yatarken, 5,8±4,2 gün NİV uygulandı. HFO uygulanan hastaların satürasyonları (84,1±4,6), NİV uygulananlara (88,7±2) göre daha düşük saptandı. Kırk dokuz hastadan %18,37'sinin eks olduğu bunlardan 5'inin HFO tedavisi alan, 4'ünün NİV tedavisi alanlardan olduğu saptandı. ROX indeksi eks olan grupta (n=9) yaşayanlara (n=40) göre anlamlı olarak düşük saptandı. Radyolojik görüntülemede HFO ve NİV tedavisi uygulanan hastaların pnömoni şiddetleri açısından anlamlı fark yoktu. Hastaneye yatış anındaki akut faz reaktanlarından eks grupta laktat dehidrogenaz ve C-reaktif protein belirgin olarak yüksekti.
Sonuç: Yoğun bakım dışı COVİD servisinde HFO ya da NİV'nin mortalite açısından farklı olmadığı saptandı.
Anahtar Kelimeler: COVİD-19, yüksek akımlı oksijen, non-invaziv ventilasyon

ABSTRACT *Objective:* Comparing high-flow oxygen (HFO) and non-invasive ventilation (NIV) treatment methods applied to patients hospitalized in the coronavirus disease-2019 (COVID-19) service outside the intensive care unit.
Materials and Methods: Demographic characteristics, duration of hospitalization and application times, acute phase reactants, ROX index, comorbid conditions, radiological scores and results were evaluated retrospectively in patients treated with HFO (n=26) and NIV (n=23) who were hospitalized in the COVID service outside the intensive care unit of the state hospital between November 2020 and June 2021.
Results: A total of 49 patients, 27 males and 22 females, were included in the study. The mean age was 55.6±14.6 years. The most common comorbidities were hypertension (n=27), diabetes (n=15). Patients in the HFO group were hospitalized for 16.6±9.4 days, HFO was applied for 6±4.6 days. Patients in the NIV group were hospitalized for 9.4±6.4 days, NIV was applied for 5.8±4.2 days. The saturation of the patients who were administered HFO (84.1±4.6) were found to be lower than those who received NIV (88.7±2). It was determined that 18.37% of 49 patients e.g. 5 of whom were treated with HFO and 4 of them were those who received NIV treatment. The ROX index was found to be significantly lower in the death group (n=9) compared to the survivors (n=40). In radiological imaging, there was no significant difference in the severity of pneumonia in patients treated with HFO and NIV. Lactate dehydrogenase and C-reactive protein from acute phase reactants at the time of hospitalization were significantly higher in the group who ex.
Conclusion: It was determined that HFO or NIV was not different in terms of mortality in thr non-intensive care COVID service.
Keywords: COVID-19, high-flow oxygen, non-invasive ventilation

Giriş

Dünyada ilk olarak Aralık 2019'da gözlenen ve pandemiye neden olan koronavirüs hastalığı-2019 (COVİD-19) hastalığı en sık solunum sistemini etkilemektedir. Solunum yetmezliği semptomları hafif, orta ve ağır olmak üzere değişken düzeylerde gözlenen en önemli klinik belirtilerdir ve mortalitenin ana nedenini oluşturur. Solunum yetmezliği gözlenen hastalarda, solunum desteğinin sürdürülmesi ana yönetim hedefi olarak yer alır. Solunum desteği oksijen tedavisi, yüksek akımlı oksijen (HFO) tedavisi, non-invaziv ventilasyon (NİV) ve invaziv mekanik ventilasyon (İMV) olarak uygulanabilir (1).

Pandeminin başında, hastalığın yayılma hızı, onunla ilişkili morbidite ve mortalite, kanıta dayalı yönetim kılavuzlarının yetersizliği nedeni ile hastanelerin en büyük endişelerinden birisi de enfeksiyonun sağlık çalışanları arasında yayılması idi. Virüs esas olarak solunum damlacıkları ve aerosol haline getirilmiş partiküller tarafından yayıldığından, birçok sağlık kuruluşunda artan oksijen gereksinimleri olan hastalar aerosol oluşturan prosedürlere maruz kalmamak için acilen entübe edildi ve mekanik olarak ventile edildi. Deneyimle, doktorlar invaziv olarak ventile edilen hastaların mortalitesinin yüksek olduğunu ve bu hastaların çoğunu ekstübe etmenin kolay olmadığını fark ettiler. Pandeminin başında aerosol üreten prosedürlerden (NİV ve HFO) mümkün olduğunca kaçınılması veya negatif basınçlı odalarda uygulanması gerektiği vurgulanmış olmasına rağmen, tüm dünyada olduğu gibi ülkemizde de pandeminin çok yoğun olduğu dönemlerde bu yöntemler hasta servislerinde uygulanmak zorunda kalmıştır (2).

Akut hipoksemik solunum yetmezliğinde HFO ve NİV tedavisinin yoğun bakım ünitesinde entübasyon gereksinimini ve mortalite oranlarını azalttığı gösterilmiştir (3,4). HFO tedavisi yüksek akım ve konsantrasyonlarda ısıtma ve nemlendirme ile oksijen uygulayarak anatomik ölü boşlukta azalmanın yanı sıra, sürekli bir ekspiratuvar pozitif havayolu basıncı sağlayarak hasta konforunda artış, solunum iş yükünde azalma ve oksijenizasyonda artış sağlar (3,5).

NİV uygulaması kronik hiperkapnik havayolu hastalıkları ve uyku apne sendromu yönetiminde yer alan yöntemler arasındadır. Günümüzde, COVİD-19'da akut solunum yetmezliğini azaltmadaki başarısı nedeniyle akut hipoksemik solunum yetmezliği tedavisinde yaygın olarak kullanılmaktadır (6,7).

Pandeminin başlangıç dönemindeki yaklaşımların aksine son dönemlerde Dünya Sağlık Örgütü (DSÖ), acil entübasyon gerektirmeyen akut hipoksemik solunum yetmezliği olan ciddi veya kritik COVİD-19'lu hastaların standart oksijen tedavisi yerine HFO, CPAP veya NİV (BiPAP) ile tedavi edilmesini önermektedir (8).

Çalışmamızda pandeminin yoğun olduğu dönemde COVİD-19 pnömonisi nedeni ile akut solunum yetmezliği gelişen ve yoğun bakımda yer olmadığından yoğun bakım ünitesi dışındaki COVİD servisinde HFO ve NİV tedavisi uygulanan hastaların özelliklerinin karşılaştırılması amaçlanmıştır.

Gereç ve Yöntem

Çalışma tek merkezli olarak, Kasım 2020-Haziran 2021 tarihleri arasında Dörtyol Devlet Hastanesi yoğun bakım ünitesi dışı COVİD servisinde yatarak tedavi olan 485 hastadan, HFO (n=26), ve NİV (n=23) uygulanan hastalarda yapıldı.

Hastaların demografik özellikleri, yandaş hastalıkları, hastanedeki yatış süreleri ile non-invaziv ve HFO tedavi uygulanma süreleri, ROX indeksleri, radyolojik skorları ve yatış anındaki akut faz reaktanları [hemogram, C-reaktif protein (CRP), ferritin, D-dimer] retrospektif olarak değerlendirildi.

Hastaların radyolojik skorlaması, yüksek rezolüsyonlu toraks tomografisinde (General Electric HiSpeed Dual Scanner, Rosslyn, US) görüntülerin aksiyal, koronal ve sagittal düzlemde incelenmesinden sonra yapıldı. Akciğer buzlu cam opasite alanlarının lober (sağ akciğer 3, sol akciğer 2 lob) yerleşiminin radyolojik değerlendirilmesi 0 ile 5 (toplam 25) arasında görsel olarak skorlandı (Lober tutulum: 0; yok, 1; ≤%5, 2; %5-25, 3; %26-49, 4; %50-75; 5; >%75). Tomografideki tutulumun ciddiyeti hafif (<8), orta (9-15) ve ağır (>15) olarak belirtildi (9).

Tüm hastalara medikal tedavi olarak Sağlık Bakanlığı'nın 2020 COVİD-19 tedavi rehberinde (10) yer alan favipiravir 2x1600 mgr yükleme, 2x600 mg idame 5 günlük tedavisi ile birlikte, 1-2 mg/kg/gün metilprednizolon, düşük molekül ağırlıklı heparin (enoksaparin), non-spesifik (levofloksasin grubu) antibiyotik ve destek tedavisi (hidrasyon, parasetamol, C vitamini, D vitamini) başlandı.

Geleneksel düşük akımlı oksijen (10 L dk^{-1}) tedavisine rağmen, hemodinamik olarak stabil, bilinci açık, oryante, koopere ve dakika solunum sayısı >30, parmak ucu satürasyon (SpO_2) <%93 olan hastalara cihazların uygunluk durumuna göre serviste kardiyak (elektrokardiyografi, tansiyon) ve solunum (dakika solunum sayısı ve SpO_2) monitörizasyonu yapılarak HFO veya NİV uygulandı.

NİV tam yüz maskesi ile başlangıç basınçları inspiratuvar pozitif havayolu basıncı (IPAP) 12, ekspiratuvar pozitif

havayolu basıncı (EPAP) 5 cm-H_2O olarak ayarlandı. Hastaların SpO_2 ≥93 olacak şekilde IPAP ve/veya EPAP basınçlarında 2 cm-H_2O artışlar yapılarak basınçlar titre edildi.

HFO tedavisi için başlangıç, 31 °C sıcaklıkta, 40 L dk^{-1} akım ile SpO_2 ≥93 olacak şekilde FiO_2 ayarlanarak başlandı. %100 FiO_2'ye rağmen SpO_2 ≥93 olmayan hastalarda akım kademeli olarak 60 L dk^{-1}'ye kadar çıkıldı.

Medikal ve HFO veya NİV tedavisine rağmen hemodinamisi bozulan, bilici kapanan, solunum/kardiyak arrest gelişen hastalarda HFO ve NİV tedavisi sonlandırıldı ve İMV ile solunum desteği sağlandı.

HFO ve NİV uygulanan hastaların 12 saat sonraki ROX indeksleri yatak başı (SpO_2/FiO_2)/solunum sayısı formülü ile hesaplandı (11).

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İstatistiksel Analiz

İstatiksel değerlendirme için SPSS 23.0 (SPSS Inc., Chicago, IL, ABD) programı kullanıldı. Elde edilen veriler değerlendirilmesinde, normal dağılımlı değişkenler için ortalama ± standart sapma, kategorik değişkenler için ki-kare testi ve parametrik veriler için bağımsız örneklem t-testi uygulandı. P<0,05 değerleri istatistiksel olarak anlamlı kabul edildi.

Bulgular

Çalışmaya 49 hasta alındı (HFO: 26, NİV: 23). Hastaların 27'si erkek, 22'si kadındı. Yaş ortalaması 55,6±14,6 (kadın: 52,2±13,3, erkek: 59,7±15,3), (HFO: 48,4±11,5, NİV: 63,7±13,6) idi. Otuz dört hastada komorbidite saptandı. En sık hipertansiyon (n=27, %55,1), diyabet (n=15, %30,6), astım (n=9, %18,4) ve kalp yetmezliği (n=8, %16,3) saptandı. HFO grubundaki hastalar 16,6±9,4 gün hastanede yatarken, 6±4,6 gün HFO uygulandı. NİV grubundaki hastalar 9,4±6,4 gün yatarken, 5,8±4,2 gün NİV uygulandı (p<0,05). HFO uygulanan hastaların başlangıç satürasyonları (SpO_2: 84,1±4,6), NİV uygulananlara (SpO_2: 88,7±2) göre daha düşük saptandı (p<0,05). NİV ve HFO uygulanan hastaların 12 saat sonraki değerlerinden ROX indeksleri hesaplandığında NİV uygulanan grupta 3,77±0,2 iken, HFO uygulanan grupta 3,67±0,3 idi. Kırk dokuz hastadan HFO tedavisi alan 5 hastanın, NİV tedavisi alanlardan da 4 hastanın entübe olduğu ve ölümle sonuçlandığı saptandı. On iki saat sonraki ROX indeksi ölen grupta (n=9) (ölüm: 3,1±0,24, yaşayan: 3,86±0,08) yaşayanlara (n=40) göre anlamlı olarak düşük saptandı (p<0,05). HFO tedavisi uygulanan hastaların radyolojik olarak 4'ü ağır, 15'i orta, 7'si hafif pnömoniye sahipken, NİV tedavisi uygulanan hastalarda 4'ü ağır, 9'u orta, 10'u hafif pnömoniye sahipti (Tablo 1).

HFO ve NİV tedavisi uygulanan hastaların akut faz reaktanları (hemogram, CRP, ferritin, D-dimer) tabloda gösterilmiştir (Tablo 2). Hastaneye yatış anındaki akut faz reaktanlarından eks olan grupta laktat dehidrogenaz (LDH) (eks: 541±251,3, yaşayan: 391,3±147,5) ve CRP (eks: 132,1±129,6, yaşayan: 106,2±67) belirgin olarak yüksekti (p<0,05).

Tartışma

Mart 2020'de DSÖ tarafından pandemi olarak ilan edilen COVİD-19 hastalığı tüm dünyada akut solunum yetmezliği nedeniyle çok fazla kayıpların yaşanmasına neden olmuştur. Antiviral tedavinin yetersiz kaldığı bu hastalıkta akut solunum yetmezliğine yönelik tedavi yöntemlerinin hastalığın erken döneminde etkin ve doğru kullanılması halen hayati önem arz etmektedir.

Bizim çalışmamızda, yoğun bakım ünitesi dışında COVİD-19 servisinde takip edilen radyolojik olarak hastalık şiddeti açısından farkları olmayan ancak hastaneye kabulünde oksijen satürasyon düzeyi daha düşük olan HFO tedavisi uygulanan hastalarla, oksijen satürasyon düzeyi diğer gruba göre daha yüksek olan NİV uygulanan hastalar arasında yaşam oranları açısından anlamlı fark olmadığını, ancak HFO tedavisinde hastanedeki yatış süresinin uzadığını saptadık.

COVİD-19'un şiddeti ve prognozu ile ilgili epidemiyolojik komorbidite faktörlerinin araştırıldığı 258 çalışmanın (n=369.036) meta-analizinde komorbidite olarak en sık hipertansiyon, diyabet, kronik kalp hastalıkları, kronik akciğer hastalıkları, maligniteler, kronik karaciğer ve böbrek hastalıkları saptanmıştır. Mortalite ile ilişkili olarak da en sık ileri yaş, erkek cinsiyet, hipertansiyon ve diyabet bulunmuştur (12). Biz de 34 hastada komorbidite saptadık. Çalışmamızda literatürle uyumlu olarak, hipertansiyon (n=27, %55,1), diyabet (n=15, %30,6), astım (n=9, %18,4), kalp yetmezliği (n=8, %16,3), obezite (n=4, %8,1), kronik obstrüktif akciğer hastalığı (n=3, %6), romatoid artrit (RA) (n=2, %4) gibi hastalıklar yüksek olarak saptandı. Eks olan hastalarda da (n=9) komorbidite olarak hipertansiyon (n=5), diyabet (n=5), astım (n=3), obezite (n=2), RA (n=2) mevcuttu.

HFO ve NİV tedavisi alan hastaların değerlendirildiği 19 çalışmanın meta-analizinde, 8 çalışmada hastanede yatış sürelerinin de değerlendirildiği ve yatış süresi açısından iki

Tablo 1. Hastaların demografik özellikleri			
	HFO	**NİV**	**p-değeri**
Yaş (Ortalama ± SS)	48,4±11,5	63,7±13,6	0,001
Cinsiyet (n, %)			
Erkek	17	10	0,15
Kadın	9	13	
Komorbidite (n, %)			
Hipertansiyon	10 (37)	17 (63)	
Diyabet	7 (46,7)	8 (53,3)	
Astım	3 (33,3)	6 (66,7)	
Kalp yetmezliği	1 (12,5)	7 (87,5)	
Obezite	3 (75)	1 (25)	
KOAH	1 (33,3)	2 (66,7)	
RA	1 (50)	1 (50)	
Hastane yatış (gün)	16,6±9,4	9,4±6,4	0,03
Uygulama süresi (gün)	6±4,6	5,8±4,2	>0,05
Satürasyon, %	84,1±4,6	88,7±2	0,001
Radyolojik şiddeti (n, %)			
Hafif	7 (26,9)	10 (43,5)	
Orta	15 (57,7)	9 (39,1)	
Ağır	4 (15,4)	4 (17,4)	
Yaşayan (n, %)	21 (80,8)	19 (82,6)	
Eks (n, %)	5 (19,2)	4 (17,4)	
ROX indeks			
Yaşayan, 3,86±0,08	3,67±0,3	3,77±0,2	<0,05
Eks, 3,1±0,24			
HFO: Yüksek akımlı nazal oksijen tedavisi, NİV: non-invaziv mekanik ventilasyon, KOAH: kronik obstrüktif akciğer hastalığı, RA: romatoid artrit, SS: standart sapma			

Tablo 2. HFO/NİV tedavisi alan ve yaşayan/ölen hastaların başlangıç laboratuvar bulgularının karşılaştırması						
	HFO (n=26)	**NİV (n=23)**	**p-değeri**	**Yaşam (n=40)**	**Ölüm (n=9)**	**p-değeri**
Beyaz küre	9,9±4,3	10,4±4,3	>0,05	12,5±5,6	9,6±3,8	>0,05
Nötrofil	8,8±3,6	8,8±4		11,1±4,9	8,3±3,5	
Nötrofil %	87,9±5	84±8,2		85,5±7,1	88,7±5,6	
Lenfosit	0,65±0,36	0,91±0,61		0,78±0,52	0,73±0,51	
Lenfosit %	7,2±4	11,7±10,6		10±8,6	6,3±3,8	
Ferritin	744,1±477,8	561,9±365,6		648,5±450,6	703,2±372,9	
D-dimer	1,16±1,96	1,53±1,72		1,4±2	0,98±0,55	
CRP	104,6±73,6	118,2±89,6		106,2±67	132,1±129,6	<0,05
LDH	477,4±179,8	352,5±153,6		391,3±147,5	541±251,3	<0,05
HFO: Yüksek akımlı nazal oksijen tedavisi, NİV: non-invaziv mekanik ventilasyon, CRP: C-reaktif protein, LDH: laktat dehidrogenaz						

grup arasında anlamlı fark saptanmadığı gözlendi (13). Biz bu çalışmalardan farklı olarak HFO grubundaki hastaların NİV grubundakilere göre daha uzun süre hastanede yattığını saptadık (HFO: 16,6±9,4 gün, NİV: 9,4±6,4 gün). Radyolojik olarak hastalık şiddeti açısından gruplar arasında fark olmasa da HFO uygulanan gruptaki hastaların başlangıç oksijen satürasyonlarının düşük olması bunu açıklamaktadır.

Akut hipoksemik solunum yetmezliği nedeni ile yoğun bakım ve yoğun bakım dışında uygulanan HFO ve NİV'nin değerlendirildiği 23 çalışmanın meta-analizinde 4 çalışmada uygulama sürelerinin değerlendirildiğini gözledik (14). Duan ve ark.'nın (15) 36 hastada (HFO/NİV 23/12) yoğun bakımda yaptığı çalışmada HFO 5,3 gün, NİV 4,6 gün, Alharthy ve ark.'nın (16) 30 hastada (HFO/NİV 15/16) yaptığı çalışmada HFO 3,3 gün, NİV 4,1 gün saptanırken, yoğun bakım dışında Perkins ve ark.'nın (17) 797 hastada yaptığı (HFO/NİV 417/380) çalışmada HFO 4,1 gün, NİV 4,6 gün, Sykes ve ark.'nın (18) yaptığı 140 hastanın değerlendirildiği çalışmada da (HFO/NİV 48/92) HFO 9,8 gün, NİV 17,4 gün olarak saptandı. Çalışmamızda HFO tedavisi alanlarda tedavi süresi 6,00±4,66 gün, NİV uygulananlarda ise 5,87±-4,28 gün idi. Uygulama süresi açısından diğer çalışmalarda olduğu gibi bizim çalışmamızda da iki grup arasında fark yoktu.

ROX indeksi Roca ve ark. (11) tarafından HFO ile tedavi edilen akut solunum yetmezliği olan pnömoni hastalarında entübasyon riski düşük ve yüksek olan hastaları belirlemeye yardımcı olabilecek bir indeks olarak tanımlanmıştır. COVİD-19 pnömonisinde birçok çalışmada (yoğun bakım/yoğun bakım dışı) HFO uygulanan hastalarda da ROX indeksi HFO'nun başarısı ile ilişkilendirilmiştir. Bin dokuz yüz otuz üç hastayla yapılan dokuz çalışmanın meta-analizinde ROX indeksinin HFO uygulanan hastalarda yüksek entübasyon riskini zamanında tespit ettiği saptanmıştır (19). Yapılan çalışmalarda ROX indeksinin daha çok HFO uygulanan COVİD-19 pnömonili hastalarda bakıldığını gözlemledik. Biz farklı olarak HFO ile birlikte NİV uygulanan hastaların da ROX değerlerine baktık. NİV veya HFO'nun 12. saatindeki ROX indeksleri iki grup arasında benzer iken, entübe olan hastalarda diğer çalışmalarda olduğu gibi belirgin olarak düşüktü.

HFO ve NİV uygulanan hastaların mortalite açısından karşılaştırıldığı 23 çalışmanın değerlendirildiği bir meta-analizde 20 çalışmada (n=5.196) mortalite oranı bildirilmiştir. Çalışmalarda HFO tedavisi alan hastalarda NİV'ye göre mortalitenin düşük olduğu gösterilmiştir. Yapılan alt grup analizlerinde mortalitenin NİV'nin helmet maskesi ile uygulanan hasta grubunda HFO ile aynı olduğu, yüz maskesi ile uygulanan grupta ise anlamlı olarak yüksek olduğu saptanmıştır. Ancak, NİV helmet maskesi uygulanan hasta grubuna göre HFO grubunda mortalitede anlamlı bir farklılık gözlenmemiştir (14). Biz çalışmamızda 49 hastamızın 9'unun invaziv mekanik ventilatöre bağlandığını ve eks olduğunu (%18,3), bunlardan 5'inin HFO tedavisi, 4'ünün NİV tedavisi alanlardan olduğunu saptadık. Meta-analizden farklı olarak ölüm oranları açısından anlamlı farklılık saptamadık. Bu ölen hasta sayımızın az olması ya da her iki tedavinin de serviste uygulanma başarılarının aynı olabileceğini düşündürebilir.

Hasta sayımızın az olması ve verilerin retrospektif olarak değerlendirilmesi çalışmamızın kısıtlılıkları arasındadır. Literatürde akut faz reaktanlarının COVİD-19 şiddeti ve mortalitesi ile ilgili pek çok çalışma olmasına rağmen, HFO ve NİV ile ilgili çalışmalarda akut faz reaktanları değerlendirilmemiştir. Yapılan çalışmalarda başvuru anında alınmış kan tetkiklerinde kan lenfosit sayısı <800/μL veya CRP >40 mg/L veya ferritin >500 ng/mL veya D-dimer >1000 ng/mL olması kötü prognostik ölçüt olarak değerlendirilmiştir (10). Biz de başvuru anında alınan akut faz reaktanlarından eks olan grupta yaşayanlara göre LDH ve CRP düzeylerini yüksek saptadık.

Sonuç

COVİD-19 pnömonili servis hastalarında her iki yöntemin başarısını kıyaslayan çok az çalışma mevcuttu. Çalışmamızda yoğun bakım dışı COVİD servisinde uyguladığımız HFO ya da NİV'nin mortalite açısından farklı olmadığını saptadık. Çalışmamızın her iki yöntem arasındaki başarıyı kıyaslayan daha büyük örneklemlerle desteklenmesi gerekmektedir.

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Kaynaklar

1. Winck JC, Scala R. Non-invasive respiratory support paths in hospitalized patients with COVID-19: proposal of an algorithm. Pulmonology 2021;27:305-12.
2. Raoof S, Nava S, Carpati C, Hill NS. High-Flow, Noninvasive Ventilation and Awake (Nonintubation) Proning in Patients With Coronavirus Disease 2019 With Respiratory Failure. Chest 2020;158:1992-2002.
3. Rochwerg B, Granton D, Wang DX, Helviz Y, Einav S, Frat JP, et al. High flow nasal cannula compared with conventional oxygen therapy for acute hypoxemic respiratory failure: a systematic review and meta-analysis. Intensive Care Med 2019;45:563-72.
4. Caparlar ÖC, Uyar BS. High Flow Nasal Oxygenation and Indications. JARSS 2021;29:211-8
5. Frat JP, Thille AW, Mercat A, Girault C, Ragot S, Perbet S, et al. High-flow oxygen through nasal cannula in acute hypoxemic respiratory failure. N Engl J Med 2015;372:2185-96.
6. Winck JC, Ambrosino N. COVID-19 pandemic and non invasive respiratory management: Every Goliath needs a David. An evidence based evaluation of problems. Pulmonology 2020;26:213-20.
7. Grieco DL, Menga LS, Cesarano M, Rosà T, Spadaro S, Bitondo MM, et al. Effect of Helmet Noninvasive Ventilation vs High-Flow Nasal Oxygen on Days Free of Respiratory Support in Patients With COVID-19 and Moderate to Severe Hypoxemic Respiratory Failure: The HENIVOT Randomized Clinical Trial. JAMA 2021;325:1731-43.
8. World Health Organization. Management of critical COVID-19 Advanced non-invasive respiratory support: high-flow nasal oxygen and non-invasive ventilation-Characteristics of NIV. 2022. Available from: URL: https://www.who.int/publications/m/item/management-of-critical–covid-19-advanced-non-invasive-respiratory-support---high-flow-nasal-oxygen-and-non-invasive-ventilation
9. Pan F, Ye T, Sun P, Gui S, Liang B, Li L, et al. Time Course of Lung Changes at Chest CT during Recovery from Coronavirus Disease 2019 (COVID-19). Radiology 2020;295:715-21.
10. T.C. Sağlık Bakanlığı. (2020). COVID-19 (SARS-CoV-2 Enfeksiyonu) Rehberi. https://covid19bilgi.saglik.gov.tr/depo/rehberler/COVID-19_Rehberi.pdf
11. Roca O, Caralt B, Messika J, Samper M, Sztrymf B, Hernández G, et al. An Index Combining Respiratory Rate and Oxygenation to Predict Outcome of Nasal High-Flow Therapy. Am J Respir Crit Care Med 2019;199:1368-76.
12. Li J, Huang DQ, Zou B, Yang H, Hui WZ, Rui F, et al. Epidemiology of COVID-19: A systematic review and meta-analysis of clinical characteristics, risk factors, and outcomes. J Med Virol 2021;93:1449-58.
13. Beran A, Srour O, Malhas SE, Mhanna M, Ayesh H, Sajdeya O, et al. High-Flow Nasal Cannula Versus Noninvasive Ventilation in Patients With COVID-19. Respir Care 2022;67:1177-89.
14. Peng Y, Dai B, Zhao HW, Wang W, Kang J, Hou HJ, et al. Comparison between high-flow nasal cannula and noninvasive ventilation in COVID-19 patients: a systematic review and meta-analysis. Ther Adv Respir Dis 2022;16:17534666221113663.
15. Duan J, Chen B, Liu X, Shu W, Zhao W, Li J, et al. Use of high-flow nasal cannula and noninvasive ventilation in patients with COVID-19: A multicenter observational study. Am J Emerg Med 2021;46:276-81.
16. Alharthy A, Faqihi F, Noor A, Soliman I, Brindley PG, Karakitsos D, Memish ZA. Helmet Continuous Positive Airway Pressure in the Treatment of COVID-19 Patients with Acute Respiratory Failure could be an Effective Strategy: A Feasibility Study. J Epidemiol Glob Health 2020;10:201-3.
17. Perkins GD, Ji C, Connolly BA, Couper K, Lall R, Baillie JK, et al. Effect of Noninvasive Respiratory Strategies on Intubation or Mortality Among Patients With Acute Hypoxemic Respiratory Failure and COVID-19: The RECOVERY-RS Randomized Clinical Trial. JAMA 2022;327:546-58.
18. Sykes DL, Crooks MG, Thu Thu K, Brown OI, Tyrer TJP, Rennardson J, et al. Outcomes and characteristics of COVID-19 patients treated with continuous positive airway pressure/high-flow nasal oxygen outside the intensive care setting. ERJ Open Res 2021;7:00318-2021.
19. Zhou X, Liu J, Pan J, Xu Z, Xu J. The ROX index as a predictor of high-flow nasal cannula outcome in pneumonia patients with acute hypoxemic respiratory failure: a systematic review and meta-analysis. BMC Pulm Med 2022;22:121.

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ORIGINAL RESEARCH / *ÖZGÜN ARAŞTIRMA*

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The Incidence and Risk Factors of Acute Kidney Injury After Left Ventricular Assist Device Implantation

Sol Ventrikül Destek Cihazı Sonrası Akut Böbrek Hasarının İnsidansı ve Risk Faktörleri

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ABSTRACT *Objective:* Left ventricular assist device surgery (LVAD) associated acute kidney injury (AKI) is a severe complication of cardiac surgery with 15-45% incidence. The study evaluated AKI in the early postoperative period after LVAD surgery using the Kidney Disease: Improving Global Outcomes (KDIGO) criteria and compare patients with and without AKI to determine the incidence, risk factors, and clinical outcomes.

Materials and Methods: In this retrospective cohort study, the medical records of all patients aged between 18 and 75 years who underwent LVAD implantation from January 2011 to December 2016 were reviewed. Patients were divided into two groups based on the development of AKI to analyze demographic features and perioperative variables. AKI was defined according to the KDIGO criteria.

Results: Out of 57 patients, 10 (18%) were female, and the cohort's mean age was 44.6±16.1 years. Thirty-six patients (63%) developed AKI following LVAD implantation. Logistic regression analysis revealed the duration of cardiopulmonary bypass (CPB), mean arterial pressure, and cumulative fluid balance on the first postoperative day as independent risk factors for AKI [odds ratio (OR): 1.013, confidence interval (CI) 95% 1.000-1.025, p=0.05; OR: 0.929, CI 95% 0.873-0.989, p=0.02; OR: 1.001, CI 95% 1.000-1.001, p=0.04 respectively]. Hospital mortality (58% vs. 24%, p=0.01) and 30-day mortality (39% vs. 5%, p=0.01) were significantly higher in patients who had AKI.

Conclusion: Risk factors for the occurrence of AKI include a longer duration of CPB, lower mean arterial pressures, and higher cumulative fluid balance on the first postoperative day. Therefore, AKI is one of the most important causes of morbidity and mortality after LVAD.

Keywords: Acute kidney injury, intensive care, left ventricle assist device

ÖZ *Amaç:* Sol ventrikül destek cihazı cerrahisi (LVAD) ile ilişkili akut böbrek hasarı (ABH), %15-45 insidans ile kalp cerrahisinin ciddi bir komplikasyonudur. Çalışma, LVAD cerrahisi sonrası erken dönemde ABH'yi Böbrek Hastalığı: Küresel Sonuçların İyileştirilmesi (KDIGO) kriterlerini kullanarak değerlendirmeyi ve ABH olan ve olmayan hastaları insidans, risk faktörleri ve klinik sonuçları belirlemek için karşılaştırmayı amaçladı.

Gereç ve Yöntem: Bu retrospektif kohort çalışmada, Ocak 2011 ile Aralık 2016 arasında LVAD implantasyonu uygulanan 18-75 yaş arasındaki tüm hastaların tıbbi kayıtları gözden geçirildi. Hastalar, demografik özellikleri ve perioperatif değişkenleri analiz etmek için ABH gelişimine göre iki gruba ayrıldı. ABH, KDIGO kriterlerine göre tanımlandı.

Bulgular: Elli yedi hastanın 10'u (%18) kadındı ve ortalama yaş 44,6±16,1 yıldı. Otuz altı hastada (%63) LVAD implantasyonunu takiben ABH gelişti. Lojistik regresyon analizi, ABH için bağımsız risk faktörleri olarak postoperatif birinci günde kardiyopulmoner bypass süresi, ortalama kan basıncı ve kümülatif sıvı dengesini ortaya koydu [olasılık oranı (OR): 1.013, güven aralığı (GA) %95 1,000-1,025, p=0,05; OR: 0,929, GA %95 %0,873-0,989, p=0,02; OR: 1,001, GA %95 1,000-1,001, p=0,04]. ABH'li hastalarda hastane mortalitesi (%58'e karşı %24, p=0,01) ve 30 günlük mortalite (%39'a karşı %5, p=0,01) anlamlı olarak daha yüksekti.

Sonuç: Sonuçlarımız, LVAD cerrahisi sonrası hastaların %63'ünde ABH geliştiğini göstermektedir. ABH oluşumu için risk faktörleri, uzun kardiyopulmoner bypass süresini, daha düşük ortalama kan basınçlarını ve postoperatif ilk gün daha yüksek kümülatif sıvı dengesini içerir. Bu nedenle ABH, LVAD'den sonra en önemli morbidite ve mortalite nedenlerindendir.

Anahtar Kelimeler: Akut böbrek hasarı, yoğun bakım, sol ventrikül destek cihazı

Introduction

Left ventricular assist devices (LVAD) is used as a safe treatment for end-stage heart failure patients. Acute kidney injury (AKI) that can occur following LVAD surgeries is one of the life-threatening complications. A wide range of AKI incidence among patients undergoing LVAD has been reported in previous studies (15-45%) (1). This study aimed to determine the incidence and perioperative risk factors for AKI and postoperative outcomes associated with AKI following LVAD implantation in our cohort.

Materials and Methods

This study was approved by the Institutional Review Board of the Başkent University (no: KA 17/75, date: 02.06.2017). We retrospectively analyzed the records of patients who underwent LVAD implantation between January 2011 to December 2016. Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) classification is a classification system that assists physicians in deciding on mechanical assist devices or heart transplant treatment for patients with advanced heart failure. This registry system, which aims to support the choice of mechanical assist devices in which patients, the regulations for the devices developed, and the treatments for heart failure, has determined 7 patient profiles that can classify advanced heart failure patients more appropriately (2). LVAD is planned with the INTERMACS system in our hospital.

Patients between 18-75 years of age were included in the study. Patients with chronic renal failure, preoperative acute renal failure and those requiring renal replacement therapy (RRT) before surgery were excluded from the study. Preexisting renal failure is defined as abnormalities of kidney structure or function, present for >3 months, with implications for health, and requires one of two criteria documented or inferred for >3 months: either glomerular filtration rate (GFR) <60 mL/min/1.73 m^2 or markers of kidney damage, including albuminuria (3). AKI was determined according to Kidney Disease: Improving Global Outcomes (KDIGO) 2012 criteria. According to KDIGO criteria, AKI is defined as an increase in serum creatinine by 0.3 mg/dL in 48 hours or an increase of serum creatinine of 1.5 times or more versus baseline or urine output within 0.5 mL/kg/h in the first 6 hours (4). Incidence and stages of early postoperative AKI among the included patients were evaluated. Patients were then divided into two groups according to the presence of AKI to define risk factors and clinical outcomes.

Anesthesia was induced with intravenous midazolam 0.02-0.05 mg/kg, fentanyl 500 µg, and rocuronium bromide 0.6-1 mg/kg. Desflurane was used for maintenance anesthesia at a 4-6% concentration and 10 µg/kg/h fentanyl. Routine monitoring included electrocardiography, pulse oximetry, capnography, nasopharyngeal temperature, invasive arterial blood pressure (radial pressure), and central venous pressure via the subclavian or internal jugular vein. Transesophageal echocardiography (TEE) was performed in all cases. And a pulmonary artery catheter was placed in all patients intraoperatively.

LVAD (HeartWare®, Medtronic, MN, USA) type was continuous flow and implantations were performed through a standard median sternotomy on the beating heart, utilizing cardiopulmonary bypass (CPB) through aortic and right atrial cannulation. The driveline was tunneled subcutaneously before systemic heparinization and existed in the patients' abdominal wall in the subcostal region. The velocity of circulation (in rate/min) was optimized to ensure proper cardiac output to the patients and to decompress the left ventricle. We changed the device's velocity to left atrial pressure at 15 to 20 mmHg and maintained central venous pressure at 10 to 15 mmHg, with interventricular septum in the midline position for TEE. Deairing was done under TEE guidance. Weaning from CPB was accomplished by gradual increases in assist device pump speed under TEE guidance.

After surgery, all patients were admitted to intensive care unit (ICU) with vasoactive drug support and mechanical ventilatory support [S1 (Hamilton Medical, Switzerland)]. Transthoracic echocardiographic studies were done for hemodynamic management and flow settings of LVADs on the following postoperative days. Blood pressure in the postoperative period was measured continuously with invasive artery cannulation and the mean arterial pressure (MAP) was followed. Weaning from vasoactive drug support and mechanical ventilatory support was performed according to hemodynamic and blood gas parameters. The same surgical, anesthesia, and intensivist teams were assigned during the perioperative period for all patients.

Statistical Analysis

SPPS 25 (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0, Armonk, NY: IBM Corp.) statistical package program is used for the analysis. Variables' mean,

standard deviation, percentage, and frequency values are used. Variables are considered after accounting for normality and homogeneity of variances (Shapiro-Wilk and Levene test). For data analysis, the independent 2-group t-test (Student's t-test) is used to compare the two groups, and Mann-Whitney U test is used when the prerequisites are not met. Categorical data are analyzed by Fisher's Exact test and chi-square test. In cases where the expected frequencies are less than 20%, Monte Carlo Simulation Method is used to include these frequencies in the analysis. For the significance level of the tests, $p<0.05$ and $p<0.01$ are considered.

Results

Out of 57 patients, 10 (17.5%) were female, and the mean age was 44.6±16.1 years. Dilated cardiomyopathy was the main diagnosis for most cases [n=55 (96.5%)], and destination therapy was the leading indication for LVAD implantation. The demographic characteristics and main diagnosis of the patients included in the study are shown in Table 1.

The patients were divided into two groups based on the development of postoperative AKI. Thirty-six patients (63.2%) developed AKI following LVAD implantation. Out of 36 patients 13 (36.1%) had stage 1, 5 (13.9%) had stage 2, 18 (50%) had stage 3 AKI. The two groups were similar in demographic characteristics, preoperative circulatory support devices, intraoperative anesthetic and surgical management, and postoperative LVAD flow rates. Redo cases included in the study. There was no significant difference in terms of redo cases in the 2 group comparisons. Preoperative laboratory values, INTERMACS score and vital signs were similar between the two groups ($p>0.05$) (Table 2, 3). Intraoperative duration of CPB was longer in the patients who developed AKI ($p=0.04$), (Table 4). Intraoperative and postoperative lactate levels were higher in patients who developed AKI during this period when compared to those without AKI ($p=0.03$, and $p=0.04$, respectively), (Table 4, 5). Postoperative mechanical ventilation times were longer in the group with AKI when compared to those without AKI ($p=0.02$), (Table 5).

Fluid balance (FB) was higher in the first two days in patients who developed AKI in the postoperative period compared to patients who did not develop AKI ($p=0.04$, and $p=0.03$, respectively). Creatine levels were found to be significantly higher only on the 2nd day in patients who developed AKI ($p=0.01$). Patients who developed AKI had lower MAP ($p=0.01$), (Table 5). Patients who developed AKI required more frequent RRT ($p=0.01$). Prolonged mechanical ventilation (PMV) was defined as the inability to wean from the ventilator for more than 24 hours after surgery and/or a total duration on mechanical ventilation more than 24 hours following admission to ICU. The frequency of PMV among patients with AKI was higher when compared to those without AKI ($p=0.01$). Patients who developed AKI had higher incidences of postoperative infection, and higher frequency of norepinephrine (NE) usage on the postoperative first day ($p<0.01$, $p=0.02$, respectively). Hospital mortality ($p=0.01$) and 30-day mortality ($p=0.01$) were significantly higher in patients who developed AKI (Table 6). Logistic regression analysis revealed the duration of CPB, MAP, and cumulative FB on the postoperative first day as independent risk factors for AKI [Odds ratio (OR): 1.013, confidence interval (CI) 95% 1.000-1.025, $p=0.05$; OR: 0.929, CI 95% 0.873-0.989, $p=0.02$; OR: 1.001, CI 95% 1.000-1.001, $p=0.04$, respectively) (Table 7).

Table 1. Demographic characteristics and main diagnosis of the study population [median (minimum-maximum), mean ± SD or n (%)]

	n=57 (%)
Age (years)	44.6±16.1
Female	10 (17.5)
Diagnosis	
Dilated cardiomyopathy	55 (96.5)
Restrictive cardiomyopathy	2 (3.5)
Indications for LVAD	
Destination	28 (49.1)
Bridge to transplantation	22 (38.6)
Bridge to recovery	7 (12.3)

LVAD: Left ventricular assist device, SD: standard deviation

Table 2. Comparison of two groups in terms of demographics and preoperative features [median (minimum-maximum), mean ± SD or n (%)]			
	AKI (-) (n=21)	**AKI (+) (n=36)**	**p-value**
Age (years)	44.7±16.5	44.5±16.0	0.97
Female (n, %)	1 (5)	9 (25)	0.05
Body weight index (kg)	67.7±16.9	72.4±17.8	0.33
Height (cm)	169±12.9	167.3±10.5	0.71
Redo patients	8 (38.1%)	19 (52.8%)	0.41
Ejection fraction (%)	17.7±4	22.4±13.2	0.06
TAPSE (mm)	14.8±4.3	13.8±3.4	0.34
Systolic pulmonary artery pressure (mmHg)	52.5±14.2	54.7±14.2	0.63
Urine output* (mL)	2056.4±1454.2	1519.3±1115.4	0.36
Requriment for renal replacement therapy	3 (14.3%)	7 (19.4%)	
Continuous renal replacement therapy	0	6	0.70
Intermittent hemodialysis	2	0	
Slow continuous ultrafiltration	1	1	
Use of bronchodilators (n, %)	0 (0)	1 (2.8)	0.46
INTERMACS score			
1	3 (14.3%)	7 (19.4%)	0.95
2	6 (28.6%)	9 (25%)	
3	4 (19%)	6 (16.7%)	
4	8 (38.1%)	14 (38.9%)	
Comorbidities (n, %)	14 (66.7)	23 (63.9)	0.83
Diabetes	8 (38.1)	8 (22.2)	0.20
Hypertension	6 (28.6)	13 (36.1)	0.56
COPD	1 (4.8)	4 (11.1)	0.41
Coronary artery disease	3 (14.3)	3 (8.3)	0.48
History of cardiac arrest	1 (4.8)	4 (11.1)	0.44
Use of inotropic agent			
Use of dobutamine (µg/kg/min)	11 (52.4)	15 (41.6)	0.43
Use of dopamine (µg/kg/min)	4 (19)	7 (19.4)	0.97
Intraaortic balloon pump (n, %)	0 (0)	1 (2.8)	0.44
Extracorporeal membrane oxygenation (n, %)	3 (14.3)	4 (11.1)	0.73

INTERMACS: Interagency Registry for Mechanically Assisted Circulatory Support, AKI: acute kidney injury, COPD: chronic obstructive pulmonary disease, TAPSE: tricuspid annular plane systolic excursion, SD: standard deviation
*The day before surgery

Table 3. Comparison of two groups in terms of preoperative laboratory values and vital signs [median (minimum-maximum) mean ± SD or n (%)]			
Preoperative laboratory values	**AKI (-) (n=21)**	**AKI (+) (n=36)**	**p-value**
Hemoglobin (g/dL)	12.2±2.5	11.9±2.1	0.64
White blood cells (1000/mm^3)	9.8±4.6	9±2.7	0.44
AST (U/L)	25.8±15.4	29.7±16.9	0.45
ALT (U/L)	61.9±81.2	36.9±69.5	0.22
Total bilirubin (g/dL)	1.5±0.9	2.2±1.4	0.20
Direct bilirubin (g/dL)	0.7±0.6	0.6±0.3	0.90
BUN (mg/dL)	26±14.3	26.7±13.7	0.85
Creatinine (mg/dL)	1.1±0.8	1.1±0.4	0.70
Albumin (g/dL)	3.7±0.4	3.4±0.6	0.06
Sodium (mmol/L)	192.4±251.1	134.5±4.5	0.33
Potassium (mmol/L)	4.1±0.4	7.9±23	0.46
Magnesium (mg/dL)	2.2±0.3	2±0.4	0.45
INR	1.3±0.3	1.4±0.3	0.61
AKI: Acute kidney injury, ALT: alanine aminotransferase, AST: aspartate aminotransferase, BUN: blood urea nitrogen, INR: international normalized ratio, SD: standard deviation			

Table 4. Comparison of two groups in terms of intraoperative features [median (minimum-maximum) mean ± SD or n (%)]			
	AKI (-) (n=21)	**AKI (+) (n=36)**	**p-value**
Duration of surgery (hrs)	5.8±1.4	6±2	0.72
Duration of CPB (min)	128.7±48.6	162.5±58.2	0.04
Blood products			
Packed red blood cells	21 (100%)	30 (90.9%)	0.38
Fresh frozen plasma	18 (85.7%)	32 (88.9%)	0.10
Platelets	0	3 (8.3%)	0.29
Urine output (mL)	669.5±433.7	699.7±634.6	0.85
Highest lactate level (mmol/L)	3.7±1.7	5.2±3.5	0.03
Lowest systolic blood pressure (mmHg)	77.9±13	74.6±14.1	0.39
Use of inotropic agents			
Highest dose of dobutamine (µg/kg/min)	8.6±1.6	9.4±3.4	0.34
Highest dose of dopamine (µg/kg/min)	7.6±2	9±4.5	0.19
Highest dose of adrenaline (µg/kg/min)	0.3±0.2	0.6±1.1	0.13
Highest dose of norepinephrine (µg/kg/min)	0.1±0.1	0.1±0.3	0.77
Highest dose of milrinone (µg/kg/min)	0.7±0	1.1±1.5	0.51
AKI: Acute kidney injury, CPB: cardiopulmonary bypass, SD: standard deviation			

Table 5. Comparison of two groups in terms of postoperative features [median (minimum-maximum) mean ± SD or n (%)]			
	AKI (-) (n=21)	AKI (+) (n=36)	p-value
LVAD flow rate (L/min)	4.1±1	3.9±1.4	0.50
Ejection fraction (%)	22±7.5	23.1±11.6	0.81
TAPSE (mm)	11±2.9	11.3±3.1	0.82
Systolic pulmonary artery pressure (mmHg)	40±7.1	45±8.3	0.45
Postoperative first day mean arterial pressure (mmHg)	62.8±6.9	54.9±13.1	0.01
Hemoglobin (g/dL)	10.2±1.2	10±1.4	0.51
Hematocrit (%)	32±6.7	30±4.3	0.17
White blood cells (1000/mm^3)	13±3	15±7	0.14
Platelets (1000/mm^3)	7993.3±35974.8	133.8±51.8	0.33
AST (U/L)	53.4±16.7	121.1±123.6	0.05
ALT (U/L)	29.2±21.8	53.4±87.7	0.12
BUN (mg/dL)	24.2±11.3	30.7±12.6	0.06
Creatine (mg/dL)	1.1±1	1.7±0.6	0.01
Total bilirubin (g/dL)	2.3±2	2.3±1.7	0.91
Direct bilirubin (g/dL)	0.5±0.3	1.7±1.6	0.03
Albumin (g/dL)	3.3±0.4	3.1±0.4	0.06
INR	1.4±0.3	1.5±0.5	0.18
Sodium (mmol/L)	138.8±3.7	138.4±4.4	0.73
Potassium (mmol/L)	4±0.6	4.1±0.6	0.76
Magnesium (mg/dL)	7.9±23.5	2.5±0.5	0.35
Highest lactate level (mmol/L)	4.5±2.1	6.3±4.3	0.04
Duration of mechanical ventilation (hrs)	32.3±28.3	87.4±134.9	0.02
Fluid balance			
POD1 (mL)	1240.8±1160.4	2316.7±2109.9	0.04
POD2 (mL)	541.9±897	1457.8±1934.2	0.03
POD3 (mL)	-162.7±1393	-121.3±1627.9	0.93

AKI: Acute kidney injury, LVAD: left ventricular assist device, ALT: alanine aminotransferase, AST: aspartate aminotransferase, BUN: blood urea nitrogen, INR: international normalized ratio, POD: postoperative day, TAPSE: tricuspid annular plane systolic excursion, SD: standard deviation

Discussion

In this retrospective review of 57 LVAD implanted patients, the incidence of AKI was 63%. Out of 36 patients with AKI, 22.8% had mild, 8.7% had moderate, 31.5% had severe AKI. Almost 1/4 of patients (26%) with severe AKI required RRT. Postoperative hypotension and NE usage was significantly higher in patients with AKI when compared to patients without AKI. Longer CPB time, lower MAP and higher cumulative FB on the first postoperative day were determined as risk factors for AKI development among LVAD implanted patients. Besides, AKI after LVAD implantation was associated with an increased incidence of PMV, hospital mortality and 30-day mortality.

It has been reported that AKI incidence is as high as 70% after LVAD surgery, there are also publications reporting lower incidences like 28% (5). The incidence of AKI after LVAD surgery was 63% in our cohort, similar to the study by Muslem et al. (5), who reported AKI incidence as 70% after LVAD surgery. In our study, we defined AKI according to the KDIGO criteria. We calculated the incidence by evaluating stages 1 to 3 and including them in the results. In their study where Harmon et al. (6) reported AKI incidence as 28% after LVAD surgery, they obtained this incidence by

Table 6. Comparison of groups in terms of postoperative follow-up and outcomes [median (minimum-maximum) mean ± SD or n (%)]			
	AKI (-) (n=21)	AKI (+) (n=36)	p-value
Requriment for renal replacement therapy	2 (10%)	15 (41.7%)	
Continuous renal replacement therapy	0	14	0.01
Intermittant hemodialysis	2	1	
Prolonged mechanical ventilation (day)	5 (23.8%)	21 (58.3%)	0.01
Need for ECMO	2 (9.5%)	8 (22.2%)	0.22
Revision surgery	3 (14.3%)	12 (33.3%)	0.16
Infections	6 (28.6%)	21 (58.3%)	0.03
Catheter-related blood circulation Infection	2 (9.5%)	9 (25%)	0.50
Wound occupied infection	2 (9.5%)	4 (11.1%)	0.70
Pnomonia	1 (4.8%)	4 (11.1%)	0.67
Urinary tract infection	1 (4.8%)	4 (11.1%)	0.64
Cardiac arrest	1 (4.8%)	13 (36.1%)	0.01
Use of inotropic agent			
Norepinephrine	3 (14.3%)	16 (44.4%)	0.02
Dobutamine	20 (95.2%)	33 (91.7%)	0.61
Adrenaline	17 (81%)	31 (86.1%)	0.61
Dopamine	17 (81%)	22 (61.1%)	0.12
Length of ICU stay (days)	16.6±12.7	24.1±23.6	0.12
Length of hospital stay (days)	34.1±17.4	44.4±36.9	0.16
30 day mortality	1 (4.8%)	14 (38.9%)	0.01
Hospital mortality	5 (23.8%)	21 (58.3%)	0.01

AKI: Acute kidney injury, ECMO: extracorporeal membrane oxygenation, ICU: intensive care unit, RRT: renal replacement therapy, SD: standard deviation

Table 7. Results of logistic regression analysis to find risk factors associated with postoperative acute kidney injury			
	Odds ratio	95% CI	p-value
Duration of CPB (min)	1.013	1.000-1.025	0.05
Postoperative first day mean arterial pressure (mmHg)	0.929	0.873-0.989	0.02
Cumulative fluid balance (L)	1.001	1.000-1.001	0.04

CI: Confidence interval, CPB: cardiopulmonary bypass

including moderate and severe AKI. However, they did not include mild/stage 1 AKI (6). Consistent with the publications reporting that the incidence of RRT after LVAD surgery is between 10-35%, we also found the incidence of RRT to be 26% in our study (5).

Our study found that the duration of CPB is a risk factor for AKI development. It has been reported in many studies that the prolongation of the CPB time during cardiac surgery is a risk factor for the development of renal failure (7). For similar reasons, prolonged CPB after LVAD surgery is a risk factor for AKI development (5).

We observed in our study that lactate concentrations increased significantly during and after LVAD surgery and were substantially higher in patients with LVAD-AKI. Significant elevations in serum lactate may originate from renal tissues under circumstances of hypoperfusion during cardiac revascularization procedures (8). Previous studies have examined postoperative serum lactate levels and have

shown a correlation between these levels and patients with cardiac surgery-associated AKI (8). Pölönen et al. (9) showed that normalizing lactate concentrations as a therapeutic goal reduce morbidity and hospital stay among patients with cardiac surgery. Our results indicate that hyperlactatemia and long-term lactate clearance were consistent with AKI, similar to other reports (8).

The effect of optimum blood pressure in preventing AKI development, especially in vasopressor-dependent patients, cannot be ignored. Although our data show the relationship between hypotension and AKI, the optimal treatment of hypotension remains controversial. In a randomized study of 292 high-risk, elderly patients, most of whom had undergone abdominal surgery, Futier et al. (10) developed an individualized management strategy systolic blood pressure (SBP) was targeted to remain within ±10% of the reference value (i.e., patient's resting SBP) using a continuous infusion of NE. Ultimately, they showed that the risk of postoperative organ dysfunction, including AKI, was reduced from 63% to 46% with individualized management aimed at SBP compared to standard therapy. We think that in addition to vasopressor therapy, anesthesiologists can treat the hypotensive patient with fluid resuscitation, inotropic support, or reducing dosage of cardiovascular depressant sedative, analgesic, or anesthetic agents. Previous studies have shown that changes in renal blood flow are associated with AKI (11). Lehman et al. (12) reported that the severity and duration of hypotension were risk factors for AKI development. Large observational studies have suggested that even brief exposure to a 10 mmHg reduction in SBP below 80 mmHg or a 5 mmHg reduction in MAP below 70 mmHg is associated with adverse outcomes (13). Our results show that hypotension, especially on the postoperatıve fırst day, is a risk factor for the development of AKI, similar to other studies. Accordingly, a requirement for NE was higher among those who developed AKI.

Several studies have found that positive FB is associated with adverse outcomes after cardiac surgery (14). In adult patients who have undergone cardiovascular surgery, a positive FB of >849 mL on the first postoperative day has been shown to be at high risk for AKI (15). Patients with hemodynamic instability may take in excess fluid. This paves the way for the development of AKI. In addition, patients who develop AKI may remain in a positive FB because they have low urine output. Whatever the cause, fluid overload can cause impaired tissue oxygenation in the kidneys (16). Similar to studies published, we determined that after LVAD surgery, postoperative first day high cumulative FB (2317 mL) is a risk factor for AKI development (17).

Previous studies have examined right ventricular (RV) function as associated with the development of AKI and described that preoperative RV function was associated with an increased risk and severity of AKI in heart transplant patients (18,19). This may be explained by that long-standing venous congestion makes the kidneys more vulnerable to the development of AKI after heart transplantation or LVAD (20). Wiersema et al. (21) found that lower tricuspid annular plane systolic excursion (TAPSE) was independently significantly associated with the development of AKI in critically ill patients. However, in our study, TAPSE was low in all groups, and our results showed no difference in AKI development. In addition, it has been reported that the evaluation of isolated TAPSE can be potentially misleading (22). Other indices of RV function, such as inferior vena cava measurements, may also reflect venous congestion and be associated with AKI (23). FB may influence RV function and thus interact with the association with AKI (24). In conclusion, we think that the combination of RV failure variables may indicate a higher predictive value for venous congestion and AKI in critically ill patients compared to TAPSE alone.

Many publications suggest that acute renal failure developing after LVAD surgery increases 30-day, 180-day, and 1-year mortality and total hospital mortality (5). However, these studies defined AKI according to the creatinine-based RIFLE "Risk" criteria. Studies defining AKI as an RRT requirement reported 40-70% high mortality rates in AKI patients and emphasized that patients requiring RRT were at the highest risk of mortality after LVAD implantation (25). Consistent with this, we also found that postoperative AKI increased 30-day mortality and hospital mortality. However, we classified the mortality risk of the patients according to the KDIGO criteria and found the hospital mortality to be 58% and the 30-day mortality to 39% in patients who developed AKI. Multiple preoperative risk stratification systems have been developed to predict the development of AKI and mortality in conventional cardiac surgery (26). However, such a classification system has not been developed after LVAD implantation yet. With further prospective studies on this, a risk classification can be established. In addition, our analysis determined that postoperative AKI is associated with postoperative PMV development. We think that this may be due to fluid overload and deterioration of lung mechanics as

a result. We found that the need for RRT and the incidence of postoperative infection was statistically higher in patients who developed PMV.

Limitations of this study include those related to any retrospective analyses. Renal function was assessed using calculated estimates of GFR; other renal variables such as renal histology or ultrasonography were not routinely available. In addition, conditions such as sarcopenia and cachexia cause lower creatinine levels. The diagnosis of AKI was made according to the increase in serum creatinine. Therefore, the use of muscle-independent biomarkers (NGAL, cystatin C) may be appropriate for prospective studies. It may be useful to support this study with the results of prospective studies.

Conclusion

AKI is a common and severe complication after LVAD implantation, usually seen in advanced stages and associated with high morbidity and mortality. Risk factors for the occurrence of AKI included longer CPB time, hypotension and higher cumulative FB on the postoperative first day after LVAD surgery. A peroperative AKI risk classification system for patients undergoing LVAD surgery may help to indentify patients at risk and hereby reduce AKI occurrence after LVAD surgery.

Ethics

Ethics Committee Approval: This study was approved by the Institutional Review Board of the Başkent University (no: KA 17/75, date: 02.06.2017).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Ö.E., Concept: H.Ş., Design: A.Ö., Data Collection and Process: F.A., Analysis or Interpretation: P.Z., Literature Search: F.A., Writing: F.A.

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References

1. Yalcin YC, Bunge JJH, Guven G, Muslem R, Szymanski M, den Uil CA, et al. Acute kidney injury following left ventricular assist device implantation: Contemporary insights and future perspectives. J Heart Lung Transplant 2019;38:797–805.
2. Stewart GC, Kittleson MM, Patel PC, Cowger JA, Patel CB, Mountis MM, et al. INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support) Profiling Identifies Ambulatory Patients at High Risk on Medical Therapy After Hospitalizations for Heart Failure. Circ Heart Fail 2016;9:e003032.
3. Moe S, Drüeke T, Cunningham J, Goodman W, Martin K, Olgaard K, et al. Kidney Disease: Improving Global Outcomes (KDIGO). Definition, evaluation, and classification of renal osteodystrophy: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). Kidney Int 2006;69:1945-53.
4. Summary of Recommendation Statements. Kidney Int Suppl 2012;2:8-12.
5. Muslem R, Caliskan K, Akin S, Sharma K, Gilotra NA, Constantinescu AA, et al. Acute kidney injury and 1-year mortality after left ventricular assist device implantation. J Heart Lung Transplant 2018;37:116-23.
6. Harmon DM, Tecson KM, Lima B, Collier JDG, Shaikh AF, Still S, et al. Outcomes of Moderate-to-Severe Acute Kidney Injury following Left Ventricular Assist Device Implantation. Cardiorenal Med 2019;9:100-7.
7. Liu K, Li M, Li L, Wu B, Xu X, Ge Y, et al. The Effect of Coronary Angiography Timing on Cardiac Surgery Associated Acute Kidney Injury Incidence and Prognosis. Front Med (Lausanne) 2021;8:619210.
8. Zhang Z, Ni H. Normalized lactate load is associated with development of acute kidney injury in patients who underwent cardiopulmonary bypass surgery. PLoS One 2015;10:e0120466.
9. Pölönen P, Ruokonen E, Hippeläinen M, Pöyhönen M, Takala J. A prospective, randomized study of goal-oriented hemodynamic therapy in cardiac surgical patients. Anesth Analg 2000;90:1052-9.
10. Futier E, Lefrant JY, Guinot PG, Godet T, Lorne E, Cuvillon P, et al. Effect of Individualized vs Standard Blood Pressure Management Strategies on Postoperative Organ Dysfunction Among High-Risk Patients Undergoing Major Surgery: A Randomized Clinical Trial. JAMA 2017;318:1346-57.
11. Garcia-Martinez R, Noiret L, Sen S, Mookerjee R, Jalan R. Albumin infusion improves renal blood flow autoregulation in patients with acute decompensation of cirrhosis and acute kidney injury. Liver Int 2015;35:335-43.
12. Lehman LW, Saeed M, Moody G, Mark R. Hypotension as a Risk Factor for Acute Kidney Injury in ICU Patients. Comput Cardiol (2010) 2010;37:1095-8.
13. Monk TG, Bronsert MR, Henderson WG, Mangione MP, Sum-Ping ST, Bentt DR, et al. Association between Intraoperative Hypotension and Hypertension and 30-day Postoperative Mortality in Noncardiac Surgery. Anesthesiology 2015;123:307-19.
14. Stein A, de Souza LV, Belettini CR, Menegaz- zo WR, Viégas JR, Costa Pereira EM, et al. Fluid overload and changes in serum creatinine after cardiac surgery: predictors of mortality and longer intensive care stay. A prospective cohort study. Crit Care 2012;16:R99.
15. Dass B, Shimada M, Kambhampati G, Ejaz NI, Arif AA, Ejaz AA. Fluid balance as an early indicator of acute kidney injury in CV surgery. Clin Nephrol 2012;77:438-44.
16. Kitani T, Kidokoro K, Nakata T, Kirita Y, Nakamura I, Nakai K, et al. Kidney vascular congestion exacerbates acute kidney injury in mice. Kidney Int 2022;101:551-62.
17. Chen X, Xu J, Li Y, Shen B, Jiang W, Luo Z, et al. The Effect of Postoperative Fluid Balance on the Occurrence and Progression of Acute Kidney Injury After Cardiac Surgery. J Cardiothorac Vasc Anesth 2021;35:2700-6.
18. Mullens W, Abrahams Z, Francis GS, Sokos G, Taylor DO, Starling RC, et al. Importance of venous congestion for worsening of renal function in advanced decompensated heart failure. J Am Coll Cardiol 2009;53:589-96.
19. Guven G, Brankovic M, Constantinescu AA, Brugts JJ, Hesselink DA, Akin S, et al. Preoperative right heart hemodynamics predict postoperative acute kidney injury after heart transplantation. Intensive Care Med 2018;44:588-97.
20. Zhu S, Zhang Y, Qiao W, Wang Y, Xie Y, Zhang X, et al. Incremental value of preoperative right ventricular function in predicting moderate to severe acute kidney injury after heart transplantation. Front Cardiovasc Med 2022;9:931517.
21. Wiersema R, Koeze J, Hiemstra B, Pettilä V, Perner A, Keus F, et al. Associations between tricuspid annular plane systolic excursion to reflect right ventricular function and acute kidney injury in critically ill patients: a SICS-I sub-study. Ann Intensive Care 2019;9:38.
22. Huang SJ, Nalos M, Smith L, Rajamani A, McLean AS. The use of echocardiographic indices in defining and assessing right ventricular systolic function in critical care research. Intensive Care Med 2018;44:868-83.
23. Singh J, Muhammad Iqbal A, Soujeri B. 7 venous congestion as measured by echocardiography predicts severity of renal dysfunction and survival in patients with heart failure. Heart 2016;102:A6.
24. Perner A, Hjortrup PB, Pettilä V. Focus on fluid therapy. Intensive Care Med 2017;43:1907-9.
25. Gürcü ME, Altaş Yerlikhan Ö, Özer T, Erkılınç A, Altınay E, Erdem E, et al. The mid-term effect of left ventricular assist devices on renal functions. Turk Gogus Kalp Damar Cerrahisi Derg 2019;27:320-8.
26. Thakar CV, Arrigain S, Worley S, Yared JP, Paganini EP. A clinical score to predict acute renal failure after cardiac surgery. J Am Soc Nephrol 2005;16:162-8.

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ORIGINAL RESEARCH / *ÖZGÜN ARAŞTIRMA*

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Comparison of Calculated and Measured Energy Expenditure Determination Methods

Hesaplanan ve Ölçülen Enerji Tüketimi Belirleme Yöntemlerinin Karşılaştırılması

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ABSTRACT *Objective:* Indirect calorimetry (IC) is considered the gold standard in the accurate determination of energy consumption in intensive care patients. This study compared measured energy expenditure (MEE) with estimated energy expenditure (EEE), calculated from predictive equations, in mechanically ventilated patients.

Materials and Methods: This study was conducted on 40 patients hospitalized in our medical/surgical intensive care unit. Twenty four-hour energy consumption measured by IC and energy consumption calculated by adding correction factors for actual and corrected weights using Harris-Benedict, Schofield, Ireton-Jones and Swinamer equations were compared.

Results: MEE was 2697.9±606.0 kcal/day. All of the EEE values, calculated using equations were moderately correlated with MEE and correlations were stronger with adjusted body weights, however, Bland-Altman statistics represent wide limits of agreement. From another perspective, EEE corresponding to between 80% and 110% of MEE was considered an adequate feeding range and provided the best levels of proficiency using adjusted body weight and Long factors; however, at least, 20% of patients remained at under-or overfeeding risk.

Conclusion: It was concluded that the estimation equations are unreliable in determining energy consumption in mechanically ventilated intensive care patients due to wide limits of agreement. Estimates falling in the range of 80-110% of MEE also indicate the possibility of malnutrition. Our study supports previous studies, which indicated that nutrition management requires an individual approach.

Keywords: Indirect calorimetry, estimating energy expenditure, mechanical ventilation, nutrition, intensive care unit

ÖZ *Amaç:* Yoğun bakım hastalarında enerji tüketiminin doğru belirlenmesinde indirekt kalorimetri (İK) altın standart olarak kabul edilir. Bu çalışmanın amacı mekanik ventilasyon uygulanan hastalarda ölçülen enerji tüketimini (ÖET), tahmin ettirici eşitliklerle hesaplanan enerji tüketimi (HET) ile karşılaştırmaktır.

Gereç ve Yöntem: Bu çalışma tıbbi/cerrahi yoğun bakım ünitemize yatırılan kırk hasta üzerinde yapıldı. İK ile ölçülen 24 saatlik enerji tüketimi ile Harris-Benedict, Schofield, Ireton-Jones ve Swinamer denklemleri kullanılarak aktüel ve düzeltilmiş kilolara göre, düzeltme faktörleri de eklenerek karşılaştırıldı.

Bulgular: ÖET'nin ortalaması 2697,9±606,0 kcal/gün olarak bulundu. Eşitlikler kullanılarak hesaplanan tüm HET değerleri ÖET ile koreleydi ve düzeltilmiş kilolar ile korelasyon güçlenmekteydi, bununla birlikte Bland-Altman analizi uyum limitlerinin geniş olduğunu gösterdi. HET'nin ÖET'nin %80 ve %110 arasına tekabül etmesi yeterli beslenme aralığı olarak kabul edildi ve düzeltilmiş vücut ağırlığı ve Long faktörlerinin kullanılması ile en iyi yeterlilik düzeylerini sağladı; ancak en iyi ihtimalde bile hastaların %20'sinin düşük veya yüksek beslenme riski altındaydı.

Sonuç: Geniş uyum limitleri nedeniyle mekanik ventilasyon uygulanan yoğun bakım hastalarında enerji tüketimini belirlemede tahmin denklemlerinin güvenilir olmadığı sonucuna varılmıştır. ÖET'nin %80-110'u aralığına giren tahminler de yetersiz beslenme ihtimalini işaret etmektedir. Çalışmamız, beslenme yönetiminin bireysel yaklaşım gerektirdiğini işaret eden çalışmaları desteklemektedir.

Anahtar Kelimeler: İndirekt kalorimetri, enerji tüketiminin tahmini, mekanik ventilasyon, beslenme, yoğun bakım ünitesi

Introduction

Nutrition is one of the most important parts of critical care. Underfeeding leads to increase infections, organ failure, risk of mortality and prolonged mechanical ventilation, and length of hospital stay. Hyperglycemia, hyperlipidemia, hepatic steatosis, azotemia, hypercapnia, and increased mortality are considered complications related with overfeeding. Therefore determining adequite energy needs prevent critically ill patients from the harmful effects of overfeeding and underfeeding (1,2).

Indirect calorimetry (IC) devices measure energy expenditure (MEE). The working principle of indirect calorimeter is described by Weir Equation obtained from the values of inspired oxygen (VO_2) and expired carbon dioxide (VCO_2) (3). IC is the gold standard for assessing EE and for managing nutrition in critically ill patients (1,4). European Society for Clinical Nutrition and Metabolism (ESPEN) and American Society for Parenteral and Enteral Nutrition guidelines recommended IC, in critical care settings (1,4-6). IC devices are expensive and measuremets are time-consuming and needs trained staff. Therefore, predictive equations have been more commonly used to predict EE in critically ill patients (2,4,5,7).

This study aims to compare widely used four predictive equations [Harris-Benedict (HB), Schofield (SCH), Ireton-Jones (IJ), and Swinamer (SW)] with IC measurements in mechanically ventilated patients within the first 48 hours of admission.

The association between MEE and Acute Physiology and Chronic Health Evaluation II (APACHE-II) and Simplified Acute Physiology score II (SAPS II) scores, was also investigated.

Materials and Methods

After Selçuk University Meram Faculty of Medicine Ethics Committee approval (decision no: 2007/167, date: 23.07.2007), written informed consent was obtained from the legal guardians of the patients. Mechanically ventilated patients, within the first 48 hours of admission were included in this study.

Patients younger than 18 years old, needed FiO_2 >0.6 or positive end-expiratory pressure >12 cm H_2O, had a chest tube leak, were ventilated via tracheostomy, underwent lobectomy or pneumonectomy operation, with an amputated limb, and required continuous renal replasman therapy were excluded.

Patients whose measurements were not completed due to extubation or exitus and whose respiratory quotient (RQ) values were measured outside of physiological values (<0.7 or >1.3) were not included in the study.

Patients' primary diagnosis, height, weight, age, and gender were recorded. Patients were grouped according to their body mass index (BMI): BMI <19 kg/m^2, BMI between 19-29.9 kg/m^2, and BMI ≥30 kg/m^2 in order to calculate adjusted body weights (ABW) for underweight and obese patients using predictive equations (8).

HB, SCH, IJ, and SW equations were used to calculate estimated energy expenditure (EEE). Previous studies have reported better results with a correction coefficient between 1.1 and 1.6 (8-10). Long factors are coefficient factors related to the patient's mobility and disease severity and are used as adjustment factors for calculating EEE with HB equation (11). For this reason, the results calculated by HB and SCH equations were multiplied by 1.3 and 1.6 and the results calculated by HB equation were also calculated by adding Long factors (Table 1).

Pressure or volume-targeted assist/- controlled ventilation modes were used in accordance with the cause of respiratory failure and patients' requirements. Patients were given sedatives and analgesics either to avoid ventilator asynchrony or to reduce pain and anxiety for achieving Ramsey sedation score 2-3 if needed. IC measurement was performed via the Datex-Ohmeda M-CAiOVX module (GE Healthcare/Datex-Ohmeda, Helsinki, Finland) for 24 hours, and mean MEE values were recorded for each patient.

Routine nursing care including suctioning, daily body care, and repositioning was performed in accordance with the general principles of intensive care.

All patients were receiving nutritional support based on ESPEN guidelines on clinical nutrition in the intensive care unit (5). Standard isocaloric enteral formulas were used for enteral nutrition. The parenteral route was used when enteral nutrition was insufficient or not possible.

APACHE-II and SAPS II were recorded within 24 hours of the study period.

Table 1. Long factors

Activity factor	Use	Injury factor	Use
Confined to bed	1.2	Minor operation	1.2
Out of bed	1.3	Skeletal trauma	1.35
		Sepsis	1.6
		Severe thermal burn	2.1

Agreement was defined as EEE within 80% and 110% of MEE, in accordance with the literature (12,13). The frequency of EEE, using study equations within 80-110%, below 80%, and above 110% was calculated.

Data are presented as mean ± standard deviation (SD). P values <0.05 were accepted statistically significant for the Pearson correlation test and p<0.0001 for Bland-Altman analysis with 95% confidence intervals.

Statistical Analysis

Statistical software program (SPSS 12.0 2003, SPSS Inc., Chicago, IL, USA) and MedCalc software (Mariakerke, Belgium) were used for statistical analysis. Descriptive statistical methods (mean, SD, frequency) were used for data analysis. Pearson correlation was used to determine the relationship between MEE, and EEE values of the equations, APACHE-II, and SAPS II scores. Bland-Altman limits of agreement analysis were undertaken to determine the extent of error with MEE and EEE.

Results

Fifty-seven patients were enrolled in the study. After excluding seven patients due to the RQ values outside of the physiological quotient, five patients due to extubation, three patients because of death, and 2 patients as their oxygen requirements rose above 0.6; the study was conducted with forty patients (Table 2).

Patients whose BMI were between 19.9-29.9 accounted for 72.5% (n=29). Three (7.5%) of the remaining were underweight, while eight (20%) of them were overweight/obese. Since the study was conducted in a mixed intensive care unit both medical and surgical patients have been included in the study. Sepsis (n=12, 30%), multiple trauma (n=8, 20%), intracranial hemorrhage (n=7, 17.5%), Guillain-Barré syndrome (n=5, 12.5%), HELLP syndrome (n=4, 10%) were predominant causes of admission, the rest of them were admitted for other medical conditions. Four of the sepsis patients (33.3%), two of the multi-trauma patients (20%) and two of the intracranial hemorrhage patients (28.6%), and all of the HELLP patients (n=4) were admitted after surgery.

All of the EEE, calculated by equations were moderately correlated with MEE and correlations were stronger with ABW: HB =0.62 and HBadj =0.87; SCH =0.55 and SCHadj =0.82; IJ =0.52 and IJadj =0.85; SW =0.57 (p<0.05).

Bland Altman's analysis showed wide limits of agreement for all equations and in all adjustment groups (Table 3) (Figure 1). Therefore, these wide limits of agreements emphasize the potential under-or overfeeding with a nutrition protocol based on predictive equations.

From the point of view of 80-110% of MEE, HB with ABW and Long factors represents the best fit with 80% adequacy. This context of definition showed the benefits of Long factors and ABW, in general (Table 4).

Mean ± SD in MEE was 2697,9±606.0 kcal/day. Mean ± SD values of APACHE-II and SAPS II were 20.6±8.8 and 47.9±19.9, respectively. There was no correlation between MEE and severity scores (p<0.05).

Table 2. Patient characteristics

Variables		Number of patients	Mean ± SD
Sex	F	16	
	M	24	
Age (years)		40	45.8±18.9
Height (cm)		40	166.5±10.2
Body weight (kg)		40	73.9±15.6
BMI (kg/m^2)		40	26.7±5.7
BSA (m^2)		40	1.8±0.2
APACHE-II		40	20.6±8.8
SAPS II		40	47.9±19.9
MEE (kcal/day)		40	2697,9±606.0

F: Female, M: male, SD: standard deviation, BMI: body mass index, BSA: body surface area, APACHE-II: Acute Physiology and Chronic Health Evaluation II, SAPS II: Simplified Acute Physiology score, MEE: measured energy expenditure

Table 3. Bland-Altman analysis: Differences between MEE and EEE calculated using different prediction equations, adjusted body weights, and correction factors

Bland-Altman tests	Bias	r (p)
HB	-1145±77.7	0.80 (<0.0001)
HBx1.3	-678±75.5	0.71 (<0.0001)
HBx1.6	-272±78.3	0.10 (=0.0013)
HBxL	-91±62.5	-0.07 (>0.0001)
HBadj	-1071±88.3	0.58 (<0.0001)
HBadjx1.3	-768±80.1	0.54 (<0.0001)
HBadjx1.6	-319±76.8	0.22 (=0.0002)
HBadjxL	-141±59.9	0.08 (=0.0235)
SCH	-999±88.5	0.62 (<0.0001)
SCHx1.3	-670±85.7	0.53 (<0.0001)
SCHx1.6	-192±86.0	0.08 (=0.0310)
SCHadj	-1019±92.8	0.58 (<0.0001)
SCHadjx1.3	-705±85.1	0.52 (<0.0001)
SCHadjx1.6	-234±84.9	0.16 (=0.0080)
I-J	-590±83.8	0.60 (<0.0001)
I-Jadj	-657±82.4	0.64 (<0.0001)
SW	-1115±83.7	0.62 (<0.0001)

HB: Harris-Benedict, SCH: Schofield, I-J: Ireton-Jones, SW: Swinamer, MEE: measured energy expenditure, EEE: estimated energy expenditure

Discussion

The results of the study showed that none of the equations is sufficient to determine the actual caloric needs of the patients, and even when using estimated values corresponding to 80-110%, at least 20% of the patients are under- or overfed.

Optimal nutrition constitutes one of the important treatment components in reducing mortality and morbidity in intensive care patients. IC is accepted as the gold standard for determining resting EE (1,2). There are different types of IC devices in the market. In this study, M-CAiOVX modules, integrated into the hemodynamic monitors (GE Healthcare/ Datex-Ohmeda, Helsinki, Finland) were used. This module has the advantages of continuous gas sampling and measurement of EE and is user-friendly.

It is known intermittent measurements of REE have shown wide variations. Activities within routine nursing care have been shown associated with increased EE and the more clinically stable patients demonstrated less variability in measurements. Continuous measurement was preferred because; especially in the first few days of admission to the intensive care unit, only a few patients could reach to required stability for short-term or intermittent IC measurements (14).

Mean MEE was 2697,9±606 kcal/day and was higher than in previous studies (12-15). However, Reid (12) studied 27 patients for five days and use the mean value of the days. In our study, measurements were commenced within 48 hours of admission, and only for 24 hours, Sungurtekin et al. (15) conducted a study on 100 patients, according to a 30-minute duration protocol. Short-duration measurements, at a steady-state condition, may not reflect 24 hours. Because, energy costs associated with interventions during daily nursing care such as aspiration, repositioning, and pulmonary physiotherapy are not reflected in the measurements (7). In addition, the study population (mean age 45.8 years) was younger than previous studies that found lower MEE (12,15,16), but on the other hand, the mean MEE value of the study was similar to a study in which mean age of the patients were comparable (14). Furthermore, the high prevalence of surgery and trauma patients might have contributed to the high MEE values.

Predictive equations are found moderately correlated with IC and the correlation was even stronger when correction coefficients were added. These findings are consistent with the previous studies (7,8,12,15). However, Bland Altman's analysis showed that the agreement between MEE and the EEE values of the four equations was poor. This poor agreement did not change when different correction factors or Long coefficient factors and/or ABW of MEE were used. The lowest bias was found with SCH equation, added Long factor (0.1±65.8 kcal/day), but even here, the limits of agreements were wide (-815/816 kcal/day).

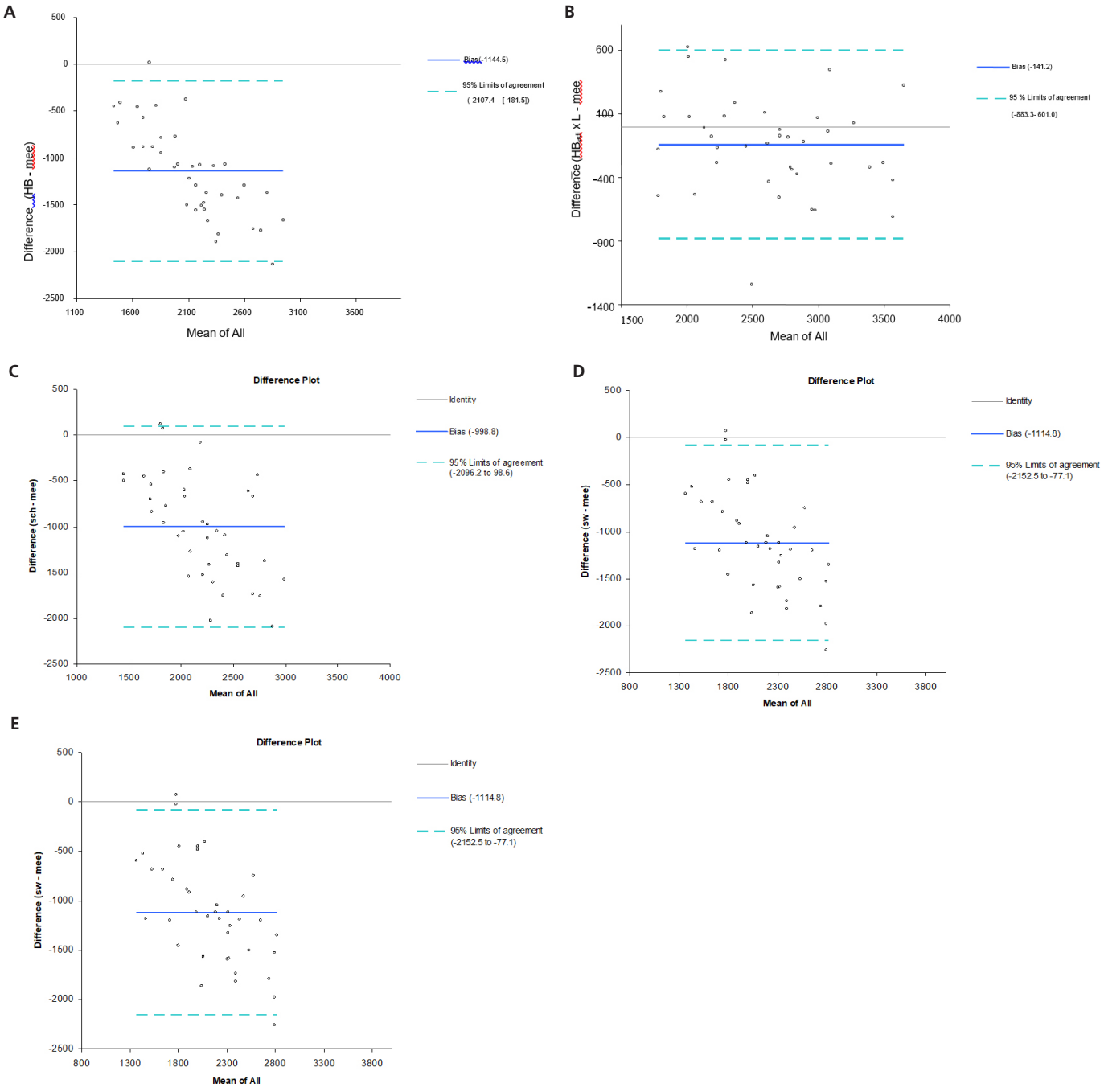

Figure 1. Bland-Altman plots. Differences between measured energy expenditure (MEE) and estimated energy expenditure calculated using different prediction equations: **(A)** MEE versus Harris-Benedict (HB) equation; **(B)** MEE versus HB equation with adjusted body weight, and Long factor; **(C)** MEE versus Schofield (SCH) equation **(D)** MEE versus Ireton-Jones (IJ) equation; **(E)** MEE versus Swinamer (SW) equation

Table 4. Number (%) of energy expenditure estimates (calculated using the different equations and adjustments) within 80% and 110% of MEE values and the number (%) of estimates that would result in under (<80% MEE) and overfeeding (>110% MEE)

Equation	Mean ± SD	Percentage of EEE <80% of MEE	Percentage of EEE within 80-110% of MEE	Percentage of EEE >110% of MEE
MEE	2698±606			
HB	1553±250	95.0	5.0	0.0
HBx1.3	2020±326	70.0	27.5	25.0
HBx1.6	2478±397	20.0	62.5	17.5
HBxL	2067±547	10.0	72.5	17.5
HBadj	1524±242	95.0	5.0	0.0
HBadjx1.3	1982±315	72.5	25.0	2.5
HBadjx1.6	2431±383	25.0	60.0	15.0
HBadjxL	2556±523	7.5	80	12.5
SCH	1599±244	92.5	7.5	0.0
SCHx1.3	2083±318	57.5	40.0	2.5
SCHx1.6	2559±391	20.0	55.0	25.0
SCHadj	1573±237	20.0	55.0	25.0
SCHadjx1.3	2049±309	60.0	37.5	2.5
SCHadjx1.6	2517±380	22.5	55.0	22.5
I-J	2055±306	65.0	27.5	7.5
I-Jadj	2041±311	65.0	27.5	7.5
SW	1515±316	95.0	5.0	0.0

HB: Harris-Benedict, SCH: Schofield, I-J: Ireton-Jones, SW: Swinamer, MEE: measured energy expenditure, SD: standard deviation

When the frequency of EEE values corresponding to <80% below, 80-110%, and 110% above the MEE were calculated, HB with ABW and Long factors addition found the most reliable equation. 80% of patients were found within the adequate range; 5% were in underfeeding, and 12.5% were in overfeeding categories. Although the use of ABW in the calculation of energy consumption is still controversial (17), in our study, using ABW for both HB and SCH equations provided lower overestimation and higher adequate estimations. However, these results may still be unreliable, at least 20% of patients likely to receive inaccurate feeding.

These findings were correlated with those published in the literature (12,13,15,18). Reid (12) compared IC with HB, SCH, and American College of Chest Physicians equation in 27 critically ill patients with 192 days of measurements, and found wide limits of agreement with Bland Altman analysis in their study.

According to the aforementioned percentage approach, the number of patients in the adequate feeding range was highest when the ABW and Long factors were used; however, it is important to realize that a high proportion of patients are at risk of under- or overfeeding.

Faisy et al. (18) compared HB equation with IC in their study, which was conducted on 70 mechanically ventilated patients. They found a mean bias of 73±502 kcal/day between MEE and calculated EE and the limits of agreements between the two methods were -932/-1078. In another study conducted with 100 mechanically ventilated patients, predictive values of HB, SCH, SW, IJ, and Penn State equations were investigated (15). High confidence intervals indicated the equations unreliability of the equations. De Waele et al. (16) found an unacceptable correlation between elderly and obese critically ill patients, in a study, they examined three hundred and twenty-five IC measurements of 161 patients' recordings to determine the agreement between eleven predictive equations and IC. Recently, Zusman et al. (13) concluded a retrospective validation study with different predictive equations and Long correction factor addition. They analyzed a total of 3573 REE measurements of 1440 patients and found that HB with a correction factor of 1.3 showed the highest correlation, while

none of the equations provided acceptable percentages of adequate feeding (85-115%).

Although previous studies have been conducted on different patient groups and with different methods, all have pointed out that the predictive equations are unreliable in EEE (12,13,15,18). Studies suggested an individualized nutritional approach due to the individual and iatrogenic factors, which might cause highly variable EEs among patients (1,19). It is also reported that adding Long factors provided more accurate estimates for each patient than adding a standard coefficient factor for all. These findings supported the individual management of nutrition (11,15,18).

The correlation between illness severity scores and MEE is still debated. Swinamer et al. (7) reported a good correlation between APACHE-II scores and MEE, but on the other hand, Brandi et al. (20) and Sungurtekin et al. (15) documented that there was no correlation between disease severity and EE. Our results also indicated that there was no correlation between APACHE-II and SAPS II scores, and MEE.

The study has limitations. First of all, it is a single-center study and conducted on a heterogenic patient population. Therefore, although heterogeneous, its small sample size was not enough for detailed subgroup analysis. The second limitation is the evaluation of only four equations despite a huge amount of equations being defined in the literature.

Conclusion

This study confirms the variability of EE among critically ill patients and pointed out the importance of IC. Although its small sample size, this study, like many before it, showed that, the level of accuracy of predictive equations was insufficient in mechanically ventilated patients. Wide limits of agreement and high overestimation and underestimation ratios indicate that, with equation-based nutrition, critically ill patients are at notable risk of under-or overfeeding.

Ethics

Ethics Committee Approval: Ethics committee approval was obtained from the Selçuk University Meram Faculty of Medicine (decision no: 2007/167, date: 23.07.2007).

Informed Consent: Written informed consent was obtained from the legal guardians of the patients.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: M.D., A.Y., Design: M.D., A.Y., Data Collection and Process: M.D., Analysis or Interpretation: M.D., A.Y., Literature Search: M.D., Writing: M.D.

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

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References

1. Delsoglio M, Achamrah N, Berger MM, Pichard C. Indirect Calorimetry in Clinical Practice. J Clin Med 2019;8:1387.
2. Ndahimana D, Kim EK. Energy Requirements in Critically Ill Patients. Clin Nutr Res 2018;7:81-90.
3. WEIR JB. New methods for calculating metabolic rate with special reference to protein metabolism. J Physiol 1949;109:1-9.
4. Oshima T, Berger MM, De Waele E, Guttormsen AB, Heidegger CP, Hiesmayr M, et al. Indirect calorimetry in nutritional therapy. A position paper by the ICALIC study group. Clin Nutr 2017;36:651-62.
5. Singer P, Blaser AR, Berger MM, Alhazzani W, Calder PC, Casaer MP, et al. ESPEN guideline on clinical nutrition in the intensive care unit. Clin Nutr 2019;38:48-79.
6. McClave SA, Taylor BE, Martindale RG, Warren MM, Johnson DR, Braunschweig C, et al. Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). JPEN J Parenter Enteral Nutr 2016;40:159-211.
7. Swinamer DL, Phang PT, Jones RL, Grace M, King EG. Twenty-four hour energy expenditure in critically ill patients. Crit Care Med 1987;15:637-43.
8. Barak N, Wall-Alonso E, Sitrin MD. Evaluation of stress factors and body weight adjustments currently used to estimate energy expenditure in hospitalized patients. JPEN J Parenter Enteral Nutr 2002;26:231-8.
9. Boullata J, Williams J, Cottrell F, Hudson L, Compher C. Accurate determination of energy needs in hospitalized patients. J Am Diet Assoc 2007;107:393-401.
10. MacDonald A, Hildebrandt L. Comparison of formulaic equations to determine energy expenditure in the critically ill patient. Nutrition 2003;19:233-9.
11. Long CL, Schaffel N, Geiger JW, Schiller WR, Blakemore WS. Metabolic response to injury and illness: estimation of energy and protein needs from indirect calorimetry and nitrogen balance. JPEN J Parenter Enteral Nutr 1979;3:452-6.
12. Reid CL. Poor agreement between continuous measurements of energy expenditure and routinely used prediction equations in intensive care unit patients. Clin Nutr 2007;26:649-57.
13. Zusman O, Kagan I, Bendavid I, Theilla M, Cohen J, Singer P. Predictive equations versus measured energy expenditure by indirect calorimetry: A retrospective validation. Clin Nutr 2019;38:1206-10.
14. Frankenfield DC, Coleman A, Alam S, Cooney RN. Analysis of estimation methods for resting metabolic rate in critically ill adults. JPEN J Parenter Enteral Nutr 2009;33:27-36.
15. Sungurtekin H, Karakuzu S, Serin S. Energy Expenditure in Mechanically Ventilated Patients: Indirect Calorimetry vs Predictive Equations.Turkish Journal of Medical & Surgical Intensive Care Medicine/ Dahili ve Cerrahi Bilimler Yoğun Bakım Dergisi 2019;10.
16. De Waele E, Opsomer T, Honoré PM, Diltoer M, Mattens S, Huyghens L, et al. Measured versus calculated resting energy expenditure in critically ill adult patients. Do mathematics match the gold standard? Minerva Anestesiol 2015;81:272-82.
17. Ireton-Jones C. Adjusted body weight, con: why adjust body weight in energy-expenditure calculations? Nutr Clin Pract 2005;20:474-9.
18. Faisy C, Guerot E, Diehl JL, Labrousse J, Fagon JY. Assessment of resting energy expenditure in mechanically ventilated patients. Am J Clin Nutr 2003;78:241-9.
19. Vasileiou G, Qian S, Iyengar R, Mulder MB, Gass LM, Parks J, et al. Use of Predictive Equations for Energy Prescription Results in Inaccurate Estimation in Trauma Patients. Nutr Clin Pract 2020;35:927-32.
20. Brandi LS, Santini L, Bertolini R, Malacarne P, Casagli S, Baraglia AM. Energy expenditure and severity of injury and illness indices in multiple trauma patients. Crit Care Med. 1999;27:2684-9.

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ORIGINAL RESEARCH / *ÖZGÜN ARAŞTIRMA*

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Sequential Application of Oxygen Therapy via High-flow Nasal Cannula and Non-invasive Ventilation in COVID-19 Patients with Acute Respiratory Failure in the Intensive Care Unit: A Prospective, Observational Study

Yoğun Bakım Ünitesinde Akut Solunum Yetmezliği Olan COVİD-19 Hastalarında Yüksek Akışlı Nazal Kanül ve İnvaziv Olmayan Ventilasyon Yoluyla Oksijen Tedavisinin Sıralı Uygulanması: Prospektif, Gözlemsel Bir Çalışma

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ABSTRACT *Objective:* Non-invasive mechanical ventilation (NIV) and high-flow nasal oxygen therapy (HFNO) are the most frequently used methods for treating hypoxemia in those diagnosed with coronavirus disease-2019 (COVID-19) in the intensive care unit (ICU). In this prospective study, we compared the effects of these two treatment modalities applied alternately in the same patient.
Materials and Methods: Standard oxygen therapy (SOT) was administered for 1 hour to patients hospitalized in the ICU with a diagnosis of acute hypoxemic respiratory failure (AHRF) and acute respiratory distress syndrome (ARDS) due to COVID-19. HFNO and NIV were applied alternately to patients who met the inclusion criteria, and we evaluated the effects of HFNO and NIV applied to the same patient.
Results: Thirty of forty-five patients admitted to the ICU for COVID-19 ARDS met the inclusion criteria for the study. According to the first and second arterial blood gas (ABG) values, the PaO_2/FiO_2 (P/F) ratio was significantly higher during NIV compared to both baseline and HFNO. In addition, the ROX index was significantly higher during NIV than HFNO, and SpO_2 in NIV increased significantly compared with the baseline value. In both methods, patient satisfaction according to the visual analog scale was better than that of SOT. Eighty percent (24/30) of the patients were orotracheally intubated; 13 patients were transferred to the ward (43.3%), 2 patients were discharged home (6.7%), and 15 patients died (50%).
Conclusion: Starting respiratory support with HFNO and/or NIV rather than SOT is more effective in improving oxygenation in patients with AHRF and ARDS due to COVID-19 and other causes. NIV is more effective than HFNO in increasing the SpO_2 and P/F ratio.
Keywords: COVID-19, intensive care units, non-invasive ventilation, respiratory distress syndrome, visual analog scales

ÖZ *Amaç:* Yoğun bakım ünitesinde (YBÜ) koronavirüs hastalığı-2019 (COVİD-19) tanısı alan hastalarda hipokseminin tedavisinde en sık kullanılan stratejiler yüksek akışlı nazal oksijenizasyon (HFNO) ve non-invaziv ventilasyon (NİV) stratejileridir. Bu prospektif çalışmada, aynı hastada dönüşümlü olarak uygulanan bu iki tedavi yönteminin etkilerini karşılaştırmayı amaçladık.
Gereç ve Yöntem: Akut hipoksemik solunum yetmezliği (AHSY) ve COVİD-19'a bağlı akut respiratuvar distress sendromu (ARDS) tanısı ile YBÜ'de yatan hastalara 1 saat standart oksijen tedavisi uygulandı. Dahil edilme kriterlerini karşılayan hastalara dönüşümlü olarak HFNO ve NİV uygulandı ve aynı hasta üzerinde HFNO ile NİV etkileri araştırıldı.
Bulgular: COVİD-19 ARDS nedeniyle YBÜ'ye kabul edilen kırk beş hastadan otuzu çalışmanın dahil edilme kriterlerini karşıladı. Birinci ve ikinci arter kan gazı değerlerine göre NİV sırasında PaO_2/FiO_2

(P/F) oranı hem başlangıca hem de HFNO'ya göre anlamlı olarak yüksekti. Ek olarak, ROX indeksi, NİV sırasında HFNO'dan önemli ölçüde daha yüksekti ve NİV'deki SpO_2 değeri başlangıç değerine kıyasla önemli ölçüde arttı. Her iki yöntemde de vizüel analog skalaya göre hasta memnuniyeti standart oksijen terapisine (SOT) göre daha iyiydi. Hastaların yüzde sekseni (24/30) orotrakeal entübe edildi; 13 hasta servise sevk edildi (%43,3), 2 hasta taburcu edildi (%6,7), 15 hasta öldü (%50).

Sonuç: COVİD-19 ve diğer nedenlere bağlı AHSY ve ARDS hastalarında solunum desteğine SOT yerine HFNO ve/veya NİV ile başlamak oksijenizasyonu iyileştirmede daha etkilidir. NİV, SpO_2 ve (PaO_2/ FiO_2) P/F oranını artırmada HFNO'dan daha etkilidir.

Anahtar Kelimeler: COVİD-19, yoğun bakım ünitesi, non-invazif ventilasyon, respiratuvar distress sendromu, vizuel analog skalası

Introduction

The coronavirus disease-2019 (COVID-19) is a mortal infection that triggers a new kind of severe acute respiratory syndrome (SARS). A mortality rate of 61% has been reported in those critically ill who have been identified with COVID-19 (1,2). The highest mortality rate was reported as 86% in mechanically ventilated patients (3). Progressive hypoxemia is the main problem in these patients, resulting from lung injury and associated multi-organ damage. Aggressive treatments, such as tracheal intubation and classic mechanical ventilation, which are used to treat lung injury, have been reported to be unhelpful and potentially damaging. Acute respiratory distress syndrome (ARDS) that develops in patients infected with COVID-19 is not typical and is estimated to have a different mechanism; therefore, it is emphasized that different strategies should be used for the treatment of ARDS in these patients (4,5).

Two main strategies used for these patients in the intensive care unit (ICU) are high-flow nasal oxygenation (HFNO) and non-invasive ventilation (NIV). HFNO is a frequently used method for the treatment of hypoxemia in adult patients with acute respiratory failure. It's principle based on administering humidified oxygen to the patient through a nasal cannula in the range between 1-70 L/min. Due to the limited number of mechanical ventilators in many ICUs at the beginning of the COVID-19 pandemic, HFNO was used for a lot COVID-19 patients and also found effective in retrospective analyses. Many studies have reported that HFNO therapy is more effective than conventional mask oxygen therapy (6,7). It is considered beneficial compared to NIV because it is easier to apply and comfortable for the patient.

Classical NIV comprises continuous positive airway pressure (CPAP) or bi-level positive airway pressure ventilation. It has been used as oxygen/ventilation therapy in SARS and H1N1 patients and at a rate of 70% for the treatment of hypoxemia in COVID-19 patients. However, mortality was high in the COVID-19 patients.

HFNO and NIV strategies are the most used strategies for the hypoxemia treatment in patients with a diagnosis of COVID-19 in the ICU. No study has yet compared these two methods in the treatment of COVID-19. In this prospective study, we want to compare the effectivity between these two treatment modalities applied alternately in the same patient. The primary aim was to evaluate the success of the treatment [oxygenation and PaO_2/FiO_2 (P/F ratio)] and to investigate the predictive role of the ROX index [(SpO_2/FiO_2)/ respiratory rate]. The secondary aim was to discharge the patients from the ICU to the ward or home.

Materials and Methods

Ethics approval was obtained from the İstanbul Medipol University Non-Invasive Clinical Research Ethics Committee for this prospective, observational study (decision no: 889, date: 10.12.2020). Permission was obtained for the study from the Ministry of Health of the Republic of Turkey (permission no: 2020-12-22T15_20_37). The clinical trial was registered at clinicaltrials.gov (NCT05137431). This study was conducted in the ICU of İstanbul Medipol University, an academic university hospital, between December 2021 and April 2022. Forty-five patients with COVID-19 ARDS were admitted to the ICU during the study period. Standard oxygen therapy (SOT, mask oxygen) was administered for 1 hour to the patients hospitalized in the ICU with a diagnosis of acute hypoxemic respiratory failure (AHRF) and ARDS due to COVID-19. HFNO and NIV were applied alternately to the patients who met the inclusion criteria, and we evaluated the effects of HFNO and NIV applied to the same patient. All participants provided informed consent.

Standard Oxygen Therapy

Oxygen was administered with a simple face mask in patients who needed oxygen of over 6 L/min. It was started with 5 L/min oxygen and increased to a maximum of 15 L/min after the FiO_2 reached 60% at most.

Study inclusion and exclusion criteria:

Inclusion Criteria

- Polymerase chain reaction (+),
- P/F ratio ≤300 mmHg (despite standard mask oxygen support for 1 hour at 15 L/min),
- Respiratory rate ≥24/min or signs of respiratory failure (intercostal retraction, nasal wing breathing),

Exclusion Criteria

- Chronic respiratory failure,
- Cardiogenic pulmonary edema,
- Aplasia,
- Glasgow coma scale ≤12,
- Hemodynamic instability (use of vasopressors),
- Emergency intubation requirement.

Implementation of NIV and HFNO

The patients who met the criteria received HFNO for 16 hours and NIV for 8 hours in 24 hours; they were treated alternately with 2 hours of HFNO and 1 hour of NIV.

HFNO: The HFNO device (Optiflow, Fisher & Paykel Healthcare, Auckland, New Zealand) contains an air-oxygen mixture. The current in the device was adjusted from 50 to 70 liters during the treatment. The patient's SpO_2 value was maintained at at least 92%. Arterial blood gas (ABG) was evaluated at 1 hour. The blender providing the correct adjustment of FiO_2 was set at between 0.21 and 1.0, and the delivery of the gas flow was provided by a heated humidifier (MR850, Fisher & Paykel Healthcare) at 70 L/min.

NIV: The patients who underwent NIV were placed in a semi-recumbent position. The tidal volume was adjusted to 6-8 mL/kg. The respiratory rate was adjusted to be <30/min. The patient's SpO_2 value was maintained at least 92%. The positive end-expiratory pressure value was set to at least 5 cmH_2O. ABG was evaluated at 1 hour. NIV was administered with a full face mask (Fisher & Paykel Healthcare) connected to a mechanical ventilator (Evita XL, Evita 4 or Evita 2 dura, Dräger, Lübeck, Germany) and a heated humidifier (MR850, Fisher & Paykel Healthcare). FiO_2 was set to keep SpO_2 at its lowest (6).

The patients whose HFNO and NIV application could be followed for at least two cycles (6 hours) were evaluated.

Data Collection

We used STROBE flow chart for our observational study (Figure 1). The patients' demographic characteristics, ARDS criteria, and severity scores were recorded prospectively.

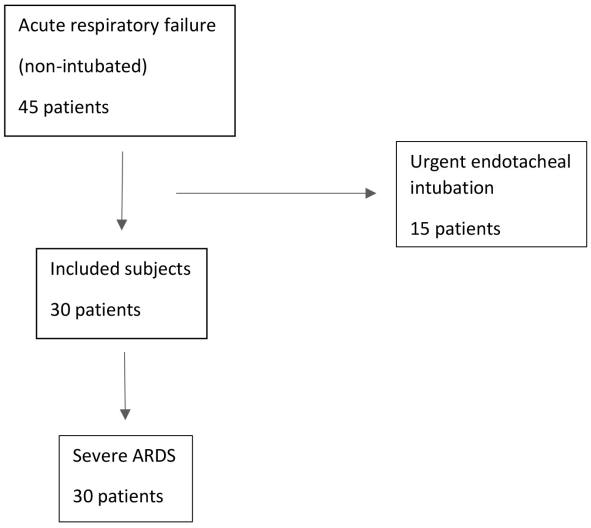

Figure 1. STROBE flow chart of the study
ARDS: Acute respiratory distress syndrome

The ARDS severity was assessed with the Berlin definition according to the oxygenation value in the first hour after treatment: mild (201≤ PaO_2/FiO_2 ≤300 mmHg), moderate (101≤ PaO_2/FiO_2 ≤200 mmHg), or severe (PaO_2/FiO_2 ≤100 mmHg) (8). The respiratory parameters, ventilator settings, tolerance, FiO_2, and blood gas parameters were recorded as baseline values when applying the face mask during spontaneous ventilation and in the first hour after the start of treatment. Tolerance was evaluated by visual analog scale (VAS) scoring (with a scoring system from 0 to10). All values were recorded 1 hour after the start of the second cycle of the HFNO and NIV sequences. NIV and HFNO application continued between NIV sessions until the respiratory distress resolved or the patient was intubated. C-reactive protein (CRP), D-dimer, and ferritin levels were recorded for all the patients, and the ROX index (the ratio of oxygen saturation measured by pulse oximetry/FiO_2 to the respiratory rate) was calculated.

The following criteria were used for endotracheal intubation: Loss of consciousness or psychomotor agitation hindering nursing care; persistent hypotension (defined by systolic arterial blood pressure >90 mmHg or mean arterial blood pressure <65 mmHg) despite fluid resuscitation or need for vasopressors; or two of the following criteria: evident worsening of respiratory distress, breathing frequency of >30 breaths/min, SpO_2 remaining below 80%

despite an FiO_2 of 1.0, or pH <7.30. NIV failure was defined as the need for endotracheal intubation.

Statistical Analysis

All data are expressed as a median with interquartile ranges (25th and 75th percentiles) or as a number with percentages. The data distribution was analyzed using the Kolmogorov-Smirnov test. Non-parametric tests were applied according to the result of the test. The qualitative data were compared using Pearson's chi-square test, and the quantitative data were compared by One-Way analysis of variance (the Friedman test). The Wilcoxon signed-rank test was applied for repeated measures. A p value >0.05 was considered statistically significant. Statistical analysis was performed using IBM SPSS 20.0 software.

Results

Thirty of forty-five patients admitted to the ICU for COVID-19 ARDS met the inclusion criteria for the study. Fifteen patients were intubated urgently, so we excluded them. The characteristics and demographic data of the patients at admission are shown in Table 1. There was no statistical difference in terms of demographic characteristics.

Table 1. Demographic parameters of patients

Variables	Values
Age (age)	61.5 (51-66)
Weight (kg)	82 (76-90)
Height (cm)	169.5 (164-172)
Status (ward/discharge/exitus)	13 (43.3%)/2 (6.7%)/15 (50%)
Female/male	13/17 (43.3%/56.7%)
Intubation rate	24/30 (80%)

According to the first and second ABG values, the P/F ratio was significantly higher during NIV compared to both the baseline and HFNO. In addition, the ROX index was significantly higher during NIV than HFNO, and the SpO_2 in NIV increased significantly compared to the baseline value. The median P/F ratio of the patients was 74, and the median ROX index was 7.61. All the patients met the criteria for severe ARDS (Tables 2-4). In both methods, patient satisfaction according to the VAS was better than SOT. Moreover, a significant improvement in VAS was observed in the HFNO-1 and HFNO-2 measurements (Table 3).

No significant difference was observed in the patients in terms of the laboratory parameters (CRP, D-dimer, and ferritin) (Tables 2-4).

Eighty percent (24/30) of the patients were orotracheally intubated (OTE); 13 patients were transferred to the ward (43.3%), 2 patients were discharged home (6.7%), and 15 patients died (50%) (Table 1).

Discussion

In this study, the P/F ratio and SpO_2 were significantly higher during NIV compared to baseline and HFNO. The VAS score was better for HFNO and NIV-2 than O_2 therapy applied with a standard mask for SOT. It was thought that the increase in saturation and, consequently, the decrease in hypoxic agitation compared to the standard mask application may be the reason. The features of HFNO for patients that make it comfortable (eating, drinking water, and heated-humidified

Table 2. Evolution of arterial blood gases and biochemistry parameters in all patients during HFNO and NIV sessions

Variables	Baseline	HFNO-1	NIV-1	HFNO-2	NIV-2
SpO_2	91 (90-94)	90.5 (84-94)	95 (90-97)[a,b]	91 (86-95)	92 (89-97)[*a,b]
P/F	74 (60-97)	71 (60-119)	106 (72-158.5)[**a,b]	74 (63-117)	117.5 (86-176)[**a,b]
pH	7.43 (7.40-7.45)	7.46 (7.44-7.48)	7.46 (7.41- 7,48)	7.46 (7.41-7.48)	7.44 (7.41-7.47)
ROX	7.61 (5.25-9.07)	4.02 (3.56-6.34)	7.92 (5.27-9.39)[a,b]	5.15 (4.06-6.59)	6.69 (4.61-9.07)[**a,b]
$PaCO_2$	34.5 (31-37)	32.5 (30-35)	34 (32.1-35)	33 (31-38)	34 (31-37)
MRR	30 (22-30)	29 (24-32)	28 (23-30)	26 (22-30)	26.5 (24-30)[b]
VAS	3 (3-4)	3 (2-4)**	3 (2-4)	3 (2-4)**	3 (2-4)**
D-dimer	1063 (689-2089)	1105 (800-1780)	1195.5 (911-1974)[a]	1348 (624-2910)	1348 (636.4-2910)
CRP	80.15 (54.2-117.2)	101.5 (56.1-149)	76 (39.6-142)	77.1 (45-149)	86.5 (33-142)
Ferritin	980 (459-1970)	1005.5 (705-1660)	985 (705-1657)	1111 (606-1660)	1111 (606-1660)

HFNO: High-flow nasal oxygen therapy, NIV: non-invasive mechanical ventilation, P/F: PaO_2/FiO_2, MRR: minute respiratory rate,: VAS: visual analog scale, CRP: C-reactive protein
*p<0.001 versus baseline, **p<0.05 versus baseline, [a]p<0.05 versus HFNO-1, [b]p<0.05 versus HFNO-2

Table 3. Evaluation of arterial blood gases and biochemistry parameters in patients during HFNO sessions				
Variables/ HFNO	Baseline	HFNO-1	HFNO-2	p-value
SpO_2	91 (90-94)	90.5 (84-94)	91 (86-95)	0.974
P/F	74 (60-97)	71 (60-119)	74 (63-117)	0.610
pH	7.43 (7.40-7.45)	7.46 (7.44-7.48)	7.46 (7.41-7.48)	0.500
ROX	7.61 (5.25-9.07)	4.02 (3.56-6.34)	5.15 (4.06-6.59)	0.113
$PaCO_2$	34.5 (31-37)	32.5 (30-35)	33 (31-38)	0.561
MRR	30 (22-30)	29 (24-32)	26 (22-30)	0.547
VAS	3 (3-4)	3 (2-4)**	3 (2-4)**	0.02
D-dimer	1063 (689-2089)	1105 (800-1780)	1348 (624-2910)	0.900
CRP	80.15 (54.2-117.2)	101.5 (56.1-149)	77.1 (45-149)	0.411
Ferritin	980 (459-1970)	1005.5 (705-1660)	1111 (606-1660)	0.513

HFNO: High-flow nasal oxygen therapy, P/F: PaO_2/FiO_2, MRR: minute respiratory rate, VAS: visual analog scale, CRP: C-reactive protein
**p<0.05 versus baseline

Table 4. Evaluation of arterial blood gases and biochemistry parameters in patients during NIV sessions				
Variables/NIV	Baseline	NIV-1	NIV-2	p-value
SpO_2	91 (90-94)	95 (90-97)	92 (89-97)*	0.003
P/F	78 (60-97)	106 (72-158.5)**	117.5 (86-176)**	0.001
pH	7.42 (7.40-7.45)	7.46 (7.41-7.48)	7.44 (7.41-7.47)	0.176
ROX	7.61 (5.25-9.07)	7.92 (5.27-9.39)	6.69 (4.61-9.07)**	0.23
$PaCO_2$	34 (31-37)	34 (32.1-35)	34 (31-37)	0.695
MRR	30 (22-30)	28 (23-30)	26.5 (24-30)	0.361
VAS	3 (3-4)	3 (2-4)**	3 (2-4)	0.01
D-dimer	1146 (760-2089)	1195.5 (911-1974)	1348 (636.4-2910)	0.623
CRP	80.2 (67.1-117.2)	76 (39.6-142)	86.5 (33-142)	0.857
Ferritin	980 (542-1970)	985 (705-1657)	1111 (606-1660)	0.503

NIV: Non-invasive mechanical ventilation, P/F: PaO_2/FiO_2, MRR: minute respiratory rate, VAS: visual analog scale, CRP: C-reactive protein
*p<0.001 versus baseline, **p<0.05 versus baseline

air advantage) may have had a positive psychological effect. Similarly, Frat et al. (6) found that although HFNO showed few useful effects for treatment of hypoxemia and respiratory distress than NIV compared to SOT, HFNO was better tolerated and could be used in transition between NIV sessions without significant oxygenation impairment.

We found no significant difference in the intubation and mortality rates of the NIV and HFNO applications compared to studies that compared patients who underwent OTE after standard mask application. More prospective randomized controlled studies are needed on whether it contributes to the improvement of oxygenation in patients discharged without OTE. In a study focusing on ARDS patients receiving NIV as first-line therapy according to the Berlin ARDS classification, Thille et al. (9) reported an intubation rate of 61%. However, some patients in that study had a diagnosis of severe ARDS. In this study, the rate of intubation was 80% in all the patients with a diagnosis of severe ARDS, which can be attributed to the fact that all the patients had severe ARDS. Despite this, the 50% mortality rate appears to be similar to other clinical studies of deaths from COVID-19-related ARDS (1,2).

In line with this study, Zhu et al. (10) reported that HFNO is more effective in terms of oxygenation than SOT with a nasal cannula or oxygen face mask. In another study, the VAS showed that HFNO was easily tolerated in addition to its ease of application compared to NIV (11). Other studies have concluded that HFNO is recommended because of the

side effects (skin deterioration) associated with the use of NIV (11,12).

The ROX index, defined as the ratio of SpO_2/FiO_2 to the respiratory rate, was evaluated as an indicator of the need for intubation in the patients receiving NIV and HFNO therapy (13). In this study, a significant increase was found in the ROX index during NIV compared to HFNO, and the P/F ratio increased significantly in the NIV group compared to the HFNO application. The reason why the VAS score was higher for HFNO than for SOT may be the higher ROX index and P/F ratio of NIV as well as HFNO's ease of use.

Although it was not possible to evaluate the effect of HFNO and NIV on intubation, since they were applied in the same patient, the mortality and intubation rates were similar compared to the literature, although our patients had severe ARDS. In the study by Koga et al. (14), the risks of treatment failure and 30-day mortality were not significantly different between HFNO and NIV as first-line therapy in respiratory failure. Levy et al. (15) reported in their study that HFNO decreased the intubation rate, while NIV increased the intubation rate in AHSY patients (16). It has been suggested that HFNO should be used before NIV in critically ill COVID-19 patients (17).

In a study by Perkins et al. (18) to determine whether CPAP or HFNO improved clinical outcomes in patients with AHRF due to COVID-19 compared with SOT, the application of CPAP as the first strategy significantly increased the risk of tracheal intubation or mortality compared to SOT However, when HFNO was the first strategy, there was no significant difference with SOT.

A study found that the probability of NIV failure was higher in hypoxemic patients, and the intubation rate could reach 60% in randomly selected patients. Providing a high flow of heated and humidified oxygen, HFNO has been shown to improve oxygenation and comfort of patient and alleviate symptoms of illness. For this reason, intermittent HFNO applications in patients connected to NIV may be a way to maintain long-term NIV sessions while maintaining adequate oxygenation (6).

Ospina-Tascon et al. (7) found that the use of HFNO among severe COVID-19 patients significantly reduced the need for mechanical ventilation support and clinical recovery time compared to SOT. Although there was no significant difference between the rates of HFNO due to COVID-19, HFNO was associated with a lower rate of invasive mechanical ventilation (19). Another study concluded that HFNO was a useful treatment to avoid intubation in ARDS or as a bridge treatment and that mortality did not increase due to a delay in intubation (20).

In the study by Zucman et al. (21), 34% of the patients who presented with deep hypoxemia were successful with HFNO application and were discharged from the ICU, 63% required mechanical ventilation, and 3% died due to the patient's desire not to be intubated while receiving HFNO. The overall ICU mortality was 17%. The authors concluded that the ROX index, measured within the first 4 hours after the onset of HFNO, can be an easy-to-use predictor of early ventilation response (21). In our study, the mortality rate was 50%, and the intubation rate was 80%. The ROX index differed significantly between NIV-1 and NIV-2, but there was no significant difference in HFNO.

As stated by Oczkowski et al. (22) the guidelines published by the European Respiratory Society; It has been suggested to use HFNO instead of NIV in hypoxemic AHRF patients, and HFNO instead of SOT between NIVs in patients with AHRF. Our study also points to results consistent with the guideline (22).

He et al. (23), on the other hand, stated that the use of HFNO for COVID-19 patients was associated with a decrease in mortality and hospital stay at 28 days, and they observed a significant improvement in the P/F ratio at 24 hours. However, it was observed that there was no difference between HFNO and NIV in transition to invasive mechanical ventilation. In our study, although an improvement in the P/F ratio was observed in both strategies, our OTE rate was 80% (23).

The limitations of our study were the lack of a control group to evaluate the effects of a strategy combining HFNO and NIV on outcomes. In addition, because our patient group consisted of severe ARDS patients, the long-term effects of the ROX index could not be evaluated, since only two cycles could be completed in these patients.

Conclusion

Starting respiratory support with HFNO and/or NIV rather than SOT is more effective in improving oxygenation in patients with AHRF and ARDS due to COVID-19 and other causes. NIV is more effective than HFNO in increasing the SpO_2 and P/F ratio. In our study, the fact that the ROX index was high during NIV, which contributes positively to the P/F ratio and SpO_2, seems to be compatible with the literature

data in that it can be used in the evaluation of oxygenation. We conclude that it may be more beneficial to prefer HFNO, where patient compliance is better, to SOT as a transitional treatment in NIV applications.

Ethics

Ethics Committee Approval: Ethics approval was obtained from the İstanbul Medipol University Non-Invasive Clinical Research Ethics Committee for this prospective, observational study (decision no: 889, date: 10.12.2020).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: C.E., D.K., Concept: I.A., Y.D., Design: B.Ç., S.A., Data Collection and Process: D.K., E.C.Ç., T.B.T., Analysis or Interpretation: B.Ç., E.C.Ç., Y.D., Literature Search: I.A., T.B.T., Writing: C.E.

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

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References

1. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020;395:1054-62.
2. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. JAMA 2020;323:1061-69.
3. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med 2020;8:475-81.
4. Gattinoni L, Chiumello D, Caironi P, Busana M, Romitti F, Brazzi L, et al. COVID-19 pneumonia: different respiratory treatments for different phenotypes? Intensive Care Med 2020;46:1099-102.
5. Gattinoni L, Coppola S, Cressoni M, Busana M, Rossi S, Chiumello D. COVID-19 Does Not Lead to a "Typical" Acute Respiratory Distress Syndrome. Am J Respir Crit Care Med 2020;201:1299-300.
6. Frat JP, Brugiere B, Ragot S, Chatellier D, Veinstein A, Goudet V, et al. Sequential application of oxygen therapy via high-flow nasal cannula and noninvasive ventilation in acute respiratory failure: an observational pilot study. Respir Care 2015;60:170-8.
7. Ospina-Tascón GA, Calderón-Tapia LE, García AF, Zarama V, Gómez-Álvarez F, Álvarez-Saa T, et al. Effect of High-Flow Oxygen Therapy vs Conventional Oxygen Therapy on Invasive Mechanical Ventilation and Clinical Recovery in Patients With Severe COVID-19: A Randomized Clinical Trial. JAMA 2021;326:2161-71.
8. ARDS Definition Task Force, Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, et al. Acute respiratory distress syndrome: the Berlin Definition. JAMA 2012;307:2526-33.
9. Thille AW, Contou D, Fragnoli C, Córdoba-Izquierdo A, Boissier F, Brun-Buisson C. Non-invasive ventilation for acute hypoxemic respiratory failure: intubation rate and risk factors. Crit Care 2013;17:R269.
10. Zhu Y, Yin H, Zhang R, Ye X, Wei J. High-flow nasal cannula oxygen therapy versus conventional oxygen therapy in patients after planned extubation: a systematic review and meta-analysis. Crit Care 2019;23:180.
11. Stephan F, Barrucand B, Petit P, Rezaiguia-Delclaux S, Medard A, Delannoy B, et al. High-Flow Nasal Oxygen vs Noninvasive Positive Airway Pressure in Hypoxemic Patients After Cardiothoracic Surgery: A Randomized Clinical Trial. JAMA 2015;313:2331-9.
12. Leone M, Einav S, Chiumello D, Constantin JM, De Robertis E, Abreu MG, et al. Noninvasive respiratory support in the hypoxaemic peri-operative/periprocedural patient: A joint ESA/ESICM guideline. Eur J Anaesthesiol 2020;37:265-79.
13. Roca O, Caralt B, Messika J, Samper M, Sztrymf B, Hernández G, et al. An Index Combining Respiratory Rate and Oxygenation to Predict Outcome of Nasal High-Flow Therapy. Am J Respir Crit Care Med 2019;199:1368-76.
14. Koga Y, Kaneda K, Fujii N, Tanaka R, Miyauchi T, Fujita M, et al. Comparison of high-flow nasal cannula oxygen therapy and non-invasive ventilation as first-line therapy in respiratory failure: a multicenter retrospective study. Acute Med Surg 2019;7:e461.
15. Levy SD, Alladina JW, Hibbert KA, Harris RS, Bajwa EK, Hess DR. High-flow oxygen therapy and other inhaled therapies in intensive care units. Lancet 2016;387:1867-78.
16. Huang HB, Peng JM, Weng L, Liu GY, Du B. High-flow oxygen therapy in immunocompromised patients with acute respiratory failure: A review and meta-analysis. J Crit Care 2018;43:300-5.
17. Alhazzani W, Møller MH, Arabi YM, Loeb M, Gong MN, Fan E. Surviving Sepsis Campaign: Guidelines on the Management of Critically Ill Adults with Coronavirus Disease 2019 (COVID-19). Crit Care Med 2020;48: 440-69.
18. Perkins GD, Ji C, Connolly BA, Couper K, Lall R, Baillie JK, et al. Effect of Noninvasive Respiratory Strategies on Intubation or Mortality Among Patients With Acute Hypoxemic Respiratory Failure and COVID-19: The RECOVERY-RS Randomized Clinical Trial. JAMA 2022;327:546-58.
19. Bonnet N, Martin O, Boubaya M, Levy V, Ebstein N, Karoubi P, et al. High flow nasal oxygen therapy to avoid invasive mechanical ventilation in SARS-CoV-2 pneumonia: a retrospective study. Ann Intensive Care 2021;11:37.
20. Panadero C, Abad-Fernández A, Rio-Ramirez MT, Acosta Gutierrez CM, Calderon-Alcala M, Lopez-Riolobos C, et al. High-flow nasal cannula for Acute Respiratory Distress Syndrome (ARDS) due to COVID-19. Multidiscip Respir Med 2020;15:693.
21. Zucman N, Mullaert J, Roux D, Roca O, Ricard JD; Contributors. Prediction of outcome of nasal high flow use during COVID-19-related acute hypoxemic respiratory failure. Intensive Care Med 2020;46:1924-26.
22. Oczkowski S, Ergan B, Bos L, Chatwin M, Ferrer M, Gregoretti C, et al. ERS clinical practice guidelines: high-flow nasal cannula in acute respiratory failure. Eur Respir J 2022;59:2101574.
23. He Y, Liu N, Zhuang X, Wang X, Ma W. High-flow nasal cannula versus noninvasive ventilation in patients with COVID-19: a systematic review and meta-analysis. Ther Adv Respir Dis 2022;16:17534666221087847.

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ORIGINAL RESEARCH / *ÖZGÜN ARAŞTIRMA*

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Effect of the Timing of Admission Upon Patient Prognosis in the Intensive Care Unit: Off-hours and On-hours

Yoğun Bakım Ünitesine Kabul Zamanının Hasta Prognozu Üzerine Etkisi: Mesai İçi ve Mesai Dışı Yatışlar

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ABSTRACT *Objective:* This study was planned to evaluate the clinical features and outcomes of patients hospitalized in intensive care units (ICUs) on-hours [workdays (WD)] and out of hours [time-off (TO)].

Materials and Methods: Ethics committee approval was obtained for this study. Patients hospitalized in adult ICUs between July 2021 and January 2022 were retrospectively evaluated. The patients were divided into two groups: those who were accepted during on-hours (group WD, WD 08.00 am-05.00 pm) and out of hours (group TO; WD-05.01 pm-07.59 am, weekends, and all public holidays). The groups were compared in terms of patient characteristics and intensive care outcomes.

Results: Of the 173 patients included in the study, 69.94% (n=121) were hospitalized during out-of-hours and 30.05% (n=52) during on-hours. The median age of the patients was 70.3±9.5 years, 58.4% were male and 41.6% were female. The number of patients hospitalized in TO was statistically significantly higher than the number of patients in WD (p=0.04). There was no significant difference between the two groups in terms of demographic data, except that chronic renal failure (18.2%, p=0.024) was more common as a comorbidity in TO patients. The need for continuous renal replacement therapies treatment, which is one of the reasons for ICU admission, was found to be significantly higher in TO patients (p=0.048). The length of stay in the ICU and intubation period was higher in group TO (p=0.006, p=0.022). It resulted in death in 34.1% of the patients. There was no significant difference in mortality and discharge between the groups.

Conclusion: In our study, the clinical outcome was found to be similar in patients followed up in ICUs under WD and TO conditions. This result; This can be attributed to the fact that the shift team is not different in our hospital, the number of experienced health personnel is high, and the necessary diagnostic procedures are not delayed.

Keywords: Intensive care unit, working hours, workdays, time-off, mortality, discharge

ÖZ *Amaç:* Yoğun bakım üniteleri (YBÜ), kritik hastaların 24 saat boyunca dinamik olarak takip edildiği kliniklerdir. Bu çalışma; YBÜ'ye mesai içi (Mİ) ve mesai dışı (MD) zamanlarda yatan hastaların klinik özelliklerini ve sonuçlarını değerlendirmek amacıyla planlanmıştır.

Gereç ve Yöntem: Bu çalışma için etik kurul onayı alındı. Temmuz 2021 ile Ocak 2022 tarihleri arasında erişkin YBÜ'lerinde yatan hastalar geriye dönük olarak değerlendirildi. Hastalar Mİ (grup Mİ; hafta içi 08.00-17.00) ve MD (grup MD; hafta içi 17.01-07.59, hafta sonları ve tatil günleri) kabul edilen olmak üzere iki gruba ayrıldı. Gruplar hasta özellikleri ve yoğun bakım sonuçları açısından karşılaştırıldı.

Bulgular: Çalışmaya dahil edilen 173 hastanın %69,94'ü (n=121) MD, %30,05'i (n=52) Mİ zamanlarda takip edilmişlerdir. Hastaların medyan yaşı 70,3±9,5 yıl olup, %58,4'ü erkek, %41,6'sı kadındır. MD yatan hasta sayısı, Mİ yatan hasta sayısına göre istatistiksel olarak anlamlı daha yüksektir (p=0,04). MD yatan hastalarda komorbidite olarak kronik böbrek yetmezliğinin (%18,2, p=0,024) daha sık görülmesi dışında iki grup arasında demografik veriler açısından anlamlı fark yoktur. YBÜ'ye yatış nedenlerinden sürekli renal replasman terapi tedavisi ihtiyacı MD yatan hastalarda anlamlı daha yüksek olarak bulunmuştur (p=0,048). YBÜ gün sayısı ve entübe gün sayısı grup MD'de daha yüksek bulunmuştur (p=0,006, p=0,022). Hastaların %34,1 eksitus ile sonuçlanmıştır. Gruplar arasında mortalite ve taburculuk açısından anlamlı fark yoktur.

Sonuç: Çalışmamızda YBÜ'lerde Mİ ve MD koşullarda takip edilen hastalarda klinik sonuçların benzer olduğu görüldü. Bu sonuç; hastanemizde nöbet ekibinin farklı olmamasına, deneyimli sağlık personeli sayısının fazla olmasına ve gerekli tanısal işlemlerin geciktirilmemesine bağlanabilir.

Anahtar Kelimeler: Yoğun bakım ünitesi, çalışma saatleri, mesai içi, mesai dışı, mortalite, taburculuk

Introduction

Intensive care units (ICU); are clinics where critically ill patients are treated with a multidisciplinary approach. Situations that require close observation and rapid intervention may develop during patient follow-up. Although mortality rates in the ICUs vary depending on the underlying disease, they are usually higher than in other services of the hospital. Mortality rates tend to decrease in ICUs, especially with the training of qualified personnel and the presence of technological developments (mechanical ventilation, extracorporeal membrane oxygenation, continuous renal replacement, etc.).

In the literature, there are many studies that show that clinics work more effectively during weekdays than weekends (1-3). Some researchers have suggested that this relationship is causal and is due to weekend reductions in hospital staff and/or the fact that out-of-hours staff generally have less seniority and experience than regular-time workers. Others have argued that this correlation is due to unobservable characteristics of hospitalized patients. It is important to provide the same quality of service in ICUs 24/7 for the prognosis of the patient. As a result, in this study, our primary aim is to evaluate the outcomes of patients hospitalized in ICUs out of hours and our secondary aim is to determine the factors affecting mortality.

Materials and Methods

Study Design and Participants

This retrospective cohort study was carried out in a single 10-bed ICU of a city hospital operating with 90 intensive care beds. After obtaining the University of Health Sciences Turkey, Kartal Dr. Lütfi Kırdar City Hospital Clinical Research Ethics Committee approval (decision no: 2022/514/218/8, date: 28.01.2022) and informed consent from all patients, data was started to collect by scanning the electronic system and patient files. The study was carried out in accordance with the ethical principles stated in the Declaration of Helsinki and Good Clinical Practices.

The study included 173 adult patients who were hospitalized in the tertiary level ICU between July/2021 and January/2022. The patients were divided into two groups as those who were accepted during on-hours [group workdays (WD); weekdays 08:00 am-05:00 pm] and those who were accepted out-of-hours [group time-off (TO); weekdays 05.01 pm-07.59 am, weekends and all public holidays].

Data Collection

The clinical and demographic characteristics of the patients, the reasons of hospitalization, accompanying comorbidities, the number of days intubated, the length of stay in ICU, discharge and death status were recorded. Patients hospitalized for postoperative follow-up and patients who were hospitalized for less than 24 hours were excluded from the study. The groups were compared in terms of patient characteristics and intensive care outcomes.

Intervention

The primary predictor was whether the admission was on a during working hours or out of hours.

Measurement

The primary outcome was in ICU mortality and secondary outcomes were discharge and length of stay.

Statistical Analysis

All statistical analyses were performed using the SPSS (Statistical Package for Social Sciences) software, version 21.0 (IBM Corp., Armonk, NY). Quantitative variables expressed as mean ± standard deviation, were compared using the Student's t-test. The qualitative variables were expressed in percentages and compared using either the chi-square test or Fisher's Exact test. A p-value <0.05 was considered significant.

Results

In the study period, 121 (69.94%) patients in group TO and 52 (30.05%) patients from group WD were included into the study. Number of patients hospitalized outside of working hours were significantly higher than hospitalized during working hours (p=0.04). The median age of these 173 patients was 70.3±9.5 years, 58.4% male and 41.6% female. There was no significant difference between the two groups in terms of comorbidity, except that chronic renal failure (CRF). CRF was significantly higher in group TO than in group WD (p=0.024) (Table 1).

The number of patients receiving invasive mechanical ventilation support was similar in the two groups. However, length of stay in ICU and intubated days were found to be significantly higher in group TO (p=0.006, p=0.022) and the

Table 1. Characteristics of patients admitted to the ICU			
	Group workdays (n=52)	Group time-off (n=121)	p-value
Number of patients, n (%)	52 (30.05)	121 (69.94)	**0.04**
Age	70.08±15.2	70.08±15.3	0.856
Gender, n (%)			
Male	34 (65.4)	76 (62.8)	
Female	18 (34.6)	45 (37.2)	0.443
APACHE-II (mean ± SD)	20.1±3.62	21.1±3.3	0.900
SOFA score (mean ± SD)	5.7	6.2	0.534
Comorbidity, n (%)			
Malignancy	14 (26.9)	38 (31.7)	0.345
COPD	4 (7.7)	14 (11.7)	0.319
CHF	10 (19.2)	19 (15.7)	0.358
CRF	3 (5.8)	22 (18.2)	**0.024**
Liver cirrhosis	3 (5.8)	13 (10.8)	0.232
DM	16 (30.8)	25 (20.7)	0.109
CVD	5 (9.6)	18 (14.9)	0.250
Transfer from which clinic, n (%)			
From the outer hospital	0	1 (0.8)	0.805
Emergency service	28 (53.8)	65 (53.7)	
In patient clinics	24 (46.2)	55 (45.5)	
Readmission to ICU, n (%)	1 (1.9)	4 (4.4)	0.709

APACHE-II: Acute Physiological and Chronic Health Evaluation-II, SOFA: Sequential Organ Failure Assessment, COPD: chronic obstructive pulmonary disease, CHF: congestive heart failure, CRF: chronic renal failure, CVD: cerebrovascular diseases, DM: diabetes mellitus, SD: standard deviation, ICU: intensive care unit

need for continuous renal replacement therapies treatment was found to be significantly higher in group TO (p=0.048) (Table 2).

A total of 59 (34.1%) patients died in ICU. Of these, 15 (32.7%) belonged to group WD, 44 (35.5%) belonged to group TO, and there was no significant difference between the groups in mortality (p=0.429). A total of 65.9% of the patients were discharged from ICU. There was no significant difference in the number of discharged patients between the groups (Table 2).

Discussion

In this study, we examined the hospitalization of patients in ICUs for a period of 6 months. We found that the number of patients hospitalized out of hours was higher than those hospitalized during working hours, but there was no significant difference between the two groups in terms of discharge from ICU and mortality. This result may reflect that there is no difficulty in accessing in-hospital care during non-working hours. When the literature is searched, there are many studies showing that hospital admission during out-of-hours is associated with higher in-hospital mortality rates (1-3), but the reasons for this phenomenon is controversial.

As a result of a 10-year study, Bell and Redelmeier (4) concluded that the mortality rate is high in weekend inpatients and that this result is unlikely to be due to chance, with the exact binomial distribution. They attributed the high causes of death to the unpopularity of working on the weekends, the lack of equal numbers and skills of staff working on the weekends, and also the fact that there are fewer supervisors on weekends. In our study; in the ICU, the same team and the same number of ICU staffing work during working hours and on the shifts. We believe that this situation is effective on equalizing the quality of work. Similarly, Fan and Needham (5) supported this conclusion with their study.

Laupland et al. (6), in their study, found that 41% of the patients hospitalized in the ICU were overnight and 49%

Table 2. Comparison of study groups			
	Group workdays (n=52)	Group time-off (n=121)	p-value
Hospitalization, n (%)			
Trauma	2 (3.8)	5 (4.2)	0.647
Cerebrovascular diseases	5 (9.6)	18 (15)	0.243
Cardiac overload	5 (9.6)	9 (7.4)	0.417
Acute renal failure	14 (26.3)	41 (33.9)	0.236
Gastrointestinal bleeding	3 (5.9)	6 (5)	0.542
Infectious diseases	9 (17.3)	9 (7.4)	0.050
Acute respiratory failure	10 (19.2)	22 (18.2)	0.513
Post-CPR	2 (3.8)	8 (6.6)	0.376
CRRT treatment, n (%)	4 (7.7)	21 (17.3)	0.048
Intubated patients, n (%)	28 (53.8)	79 (65.3)	0.106
Intubation periods (days) (mean ± SD)	4.58±7.9	9.2±13.4	0.022
LOS (days) (mean ± SD)	6.62±7.4	11.9±12.9	0.006
Vasopressor need, n (%)	20 (40)	38 (31.7)	0.193
Central catheter need, n (%)	19 (36.5)	40 (33.3)	0.406
Discharge, n (%)	37 (66.4)	77 (64.2)	0.842
Discharge planning, n (%)			
To the surgical clinics	13 (25)	31 (25.6)	
To the internal medicine clinics	22 (42.3)	39 (32.2)	0.187
To the home	2 (3.8)	7 (5.8)	
Death, n (%)	15 (32.7)	44 (35.5)	0.429
LOS: Length of stay in ICU, CRRT: continue renal replacement therapy, CPR: cardioplumober resuscitation, ICU: intensive care unit			

were overnight and/or weekends, and they emphasized that overnight stay was associated with mortality. Similarly, Buck et al. (7) evaluated the relationship between patient admission to the ICU out of hours and on the weekend, and 90-day mortality and showed that the risk of death in adult patients was slightly higher in those hospitalized out of hours; as in our study, emphasized that increasing the out-of-hours services may result in the desired decrease in the inpatient mortality rate.

Halm and Chassin (8) raised the question of why hospital mortality rates are changing, and they argued that this situation is based on medical-social-biological procedural knowledge and therefore deserves careful investigation.

In a meta-analysis of forty-five articles by Honeyford et al. (9) concluded that there is high heterogeneity for the "weekend effect" and further studies are needed. In a comprehensive meta-analysis by Hoshijima et al. (10); they concluded that although weekend admissions were associated with a higher risk of death than weekday admissions, this effect was limited to certain diagnostic groups and admission subtypes. As can be seen, the relationship between patient prognosis and admission time is limited and shows quite heterogeneity. In this study, we observed that a similar population of patients were admitted to our hospital during the day and night. Mitchell et al. (11) examined a similar study on a specific population. They cohort 3,729 adult stroke patients hospitalized in tertiary care between 2001 and 2012. As a result of that study; the effect of weekend ICU-admission for stroke patients appears to be significant for in-hospital mortality, but no significant difference in adjusted ICU-mortality, length-of-stay, or longer-term morbidity and mortality measures (11).

On the other hand, Adıgüzel et al. (12) concluded in their study that full-time staff would improve outcomes in the ICUs. In a recent study, Aiken et al. (13) showed that nurse employment and education are effective on patient mortality.

In our study, only the patients hospitalized in the ICU were evaluated and the training of the personnel as a single unit was based on.

Barnett et al. (14) conducted a study in 38 ICUs in 28 hospitals, reported that the length of stay in the ICU was significantly longer for weekend or Friday admissions. Ko et al. (15) showed that there was a significant increase in weekend hospital admissions, mortality rate, and length of stay. Similarly, in the present study, length of stay in the ICU and intubation period were found to be longer in patients in group TO. This may be associated with unmeasured factors such as patient characteristics and the severity of the disease. This result suggests that the patient risk profile and a difference in severity of illness greatly affect the course of the disease from patient to patient even if it does not change the outcome.

In present study, we aimed to investigate whether there is a difference in patient outcomes in patients admitted to the ICUs out of hours compared to patients hospitalized during working hours, and we found that mortality rates did not change when full care and support can be provided. Discharge rates were also similar. We attributed this situation to the fact that the patients who admitted to the hospital during and out of hours had a similar profile in terms of factors that could affect mortality and that they could receive similar health care independent of working hours. Differences in patient risk factors and disease severity affected the process, but did not change the outcome.

The results of our study need to be interpreted within the context of its limitation. First, our study was a retrospective study and sample size was small. Secondly, our study did not account patient's intrinsic factors and the severity of illness. Finally, we did not attempt to determine whether the outcomes were associated with qualities of care and weekend working staff in this study.

Conclusion

Numerous adverse prognostic factors have been described that affect mortality rates in critically ill patients admitted to the ICU. Our study showed that hospitalization of patients out-of-hours is not one of these reasons. Thus, we wanted to emphasize that the number of full-time personnel should be sufficient and the necessary diagnostic procedures should not be delayed.

Ethics

Ethics Committee Approval: After obtaining the University of Health Sciences Turkey, Kartal Dr. Lütfi Kırdar City Hospital Clinical Research Ethics Committee approval (decision no: 2022/514/218/8, date: 28.01.2022). The study was carried out in accordance with the ethical principles stated in the Declaration of Helsinki and Good Clinical Practices.

Informed Consent: Informed consent from all patients, data was started to collect by scanning the electronic system and patient files.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Y.B., F.C., D.Ç., K.T.S., Concept: Y.B., Design: Y.B., K.T.S., Data Collection and Process: F.C., D.Ç., Analysis or Interpretation: Y.B., F.C., Literature Search: Y.B., D.Ç., K.T.S., Writing: Y.B.

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

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References

1. Bressman E, Rowland JC, Nguyen VT, Raucher BG. Severity of illness and the weekend mortality effect: a retrospective cohort study. BMC Health Serv Res 2020;20:169.
2. Pauls LA, Johnson-Paben R, McGready J, Murphy JD, Pronovost PJ, Wu CL. The Weekend Effect in Hospitalized Patients: A Meta-Analysis. J Hosp Med 2017;12:760-6.
3. Williams A, Powell AGMT, Spernaes I, Basu P, Edwards S, Edwards P. Mode of presentation rather than the 'weekend effect' is a major determinant of in-hospital mortality. Surgeon 2019;17:15-8.
4. Bell CM, Redelmeier DA. Mortality among patients admitted to hospitals on weekends as compared with weekdays. N Engl J Med 2001;345:663-8.
5. Fan E, Needham DM. An intensivist all day, keeps the bad outcomes away. Crit Care Med 2007;35:286-7.
6. Laupland KB, Shahpori R, Kirkpatrick AW, Stelfox HT. Hospital mortality among adults admitted to and discharged from intensive care on weekends and evenings. J Crit Care 2008;23:317-24.
7. Buck DL, Christiansen CF, Christensen S, Møller MH; Danish Intensive Care Database. Out-of-hours intensive care unit admission and 90-day mortality: a Danish nationwide cohort study. Acta Anaesthesiol Scand 2018;62:974-82.
8. Halm EA, Chassin MR. Why do hospital death rates vary? N Engl J Med 2001;345:692-4.
9. Honeyford K, Cecil E, Lo M, Bottle A, Aylin P. The weekend effect: does hospital mortality differ by day of the week? A systematic review and meta-analysis. BMC Health Serv Res 2018;18:870.
10. Hoshijima H, Takeuchi R, Mihara T, Kuratani N, Mizuta K, Wajima Z, et al. Weekend versus weekday admission and short-term mortality: A meta-analysis of 88 cohort studies including 56,934,649 participants. Medicine (Baltimore) 2017;96:e6685.
11. Mitchell WG, Pande R, Robinson TE, Jones GD, Hou I, Celi LA. The weekend effect for stroke patients admitted to intensive care: A retrospective cohort analysis. PLoS One 2020;15:e0234521.
12. Adıgüzel N, Karakurt Z, Moçin ÖY, Takır HB, Saltürk C, Kargın F, et al. Full-Time ICU Staff in the Intensive Care Unit: Does It Improve the Outcome? Turk Thorac J 2015;16:28-32.
13. Aiken LH, Clarke SP, Sloane DM, Sochalski J, Silber JH. Hospital nurse staffing and patient mortality, nurse burnout, and job dissatisfaction. JAMA 2002;288:1987-93.
14. Barnett MJ, Kaboli PJ, Sirio CA, Rosenthal GE. Day of the week of intensive care admission and patient outcomes: a multisite regional evaluation. Med Care 2002;40:530-9.
15. Ko SQ, Strom JB, Shen C, Yeh RW. Mortality, Length of Stay, and Cost of Weekend Admissions. J Hosp Med 2018;13:476-81.

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CASE REPORT / *OLGU SUNUMU*

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Alternative Treatment Method for Crimean Congo Hemorrhagic Fever: Coupled Plasma Filtration and Adsorption

Kırım Kongo Kanamalı Ateşi için Alternatif Tedavi Yöntemi: Birleştirilmiş Plazma Filtrasyonu ve Adsorpsiyon

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ABSTRACT Crimean-Congo hemorrhagic fever (CCHF) is a viral hemorrhagic fever syndrome that can cause multi-organ failure with hyperactivation of the immune system. There is no proven treatment for CCHF, supportive care is essential for management. Extracorporeal depurative techniques have been used to remove inflammatory mediators from the bloodstream. This report aims to present the use of coupled plasma filtration and adsorption (CPFA) in CCHF patients. We performed CPFA on three patients with CCHF, all of which were confirmed with polymerase chain reaction. A 35-year-old female was admitted one week after tick-exposure. Despite supportive treatment, patient developed mucosal and gastrointestinal bleeding due to disseminated intravascular coagulation (DIC). After CFPA, her clinic situation and laboratory results improved. A 54-year-old female was admitted to the intensive care unit due to severe bleeding and had a history of tick bite nine-days-ago. She had multiple organ failure with DIC, we started CPFA. Patient didn't respond to the treatment and died. A 69-year-old male was admitted to the hospital on the seventh-day of exposure to tick. He had diabetes, hypertension and coronary artery disease. Next day, patient developed alveolar hemorrhage and his liver enzymes, coagulation parameters deteriorated. We performed CFPA, however, the patient didn't respond to treatment and died. We suggested that CPFA may have positive effects on the outcome and prognosis of critically ill CCHF patients. Only one patient responded well which can be a result of being young, early admission to the hospital and lack of comorbidity. CPFA may be an option to treat severe CCHF infection with cytokine storm. However,there is a need for further studies on when we should apply this treatment and whether early application prevents mortality.
Keywords: Crimean-Congo hemorrhagic fever, therapeutic plasma adsorption, therapeutic plasmapheresis

ÖZ Kırım-Kongo kanamalı ateşi (KKKA), bağışıklık sisteminin hiperaktivasyonu ile çoklu organ yetmezliğine neden olabilen viral bir hemorajik ateş sendromudur. KKKA için kanıtlanmış bir tedavi yoktur, yönetim için destek tedavisi şarttır. Ekstrakorporeal depuratif teknikler enflamatuvar mediyatörleri kan dolaşımından uzaklaştırmak için kullanılır. Bu rapor, KKKA hastalarında birleştirilmiş plazma filtrasyon ve adsorpsiyon (BPFA) kullanımını sunmayı amaçlamaktadır. Polimeraz zincir reaksiyonu ile tanısı doğrulanmış üç hastaya BPFA uygulandı. Otuz beş yaşında kadın hasta kene temasından bir hafta sonra başvurdu. Destek tedavisine rağmen hastada yaygın damar içi kanama (YİK) nedeniyle mukozal ve gastrointestinal kanama gelişti. BPFA sonrası klinik durumu ve laboratuvar sonuçları düzeldi. Dokuz gün önce kene ısırması öyküsü olan 54 yaşında kadın hasta mukozal kanama ve hipotansiyon nedeniyle yoğun bakıma alındı. YİK'nin eşlik ettiği çoklu organ yetmezliği vardı, BPFA tedavisine rağmen hasta tedaviye yanıt vermedi ve eksitus oldu. Altmış dokuz yaşında erkek hasta kene maruziyetinden bir hafta sonra hastaneye başvurdu. Eşlik eden diabetes mellitus, hipertansiyon ve koroner arter hastalığı vardı. Ertesi gün hastada alveoler hemoraji gelişti, karaciğer enzimleri yükseldi ve pıhtılaşma parametreleri bozuldu. BPFA uygulandı ancak tedaviye yanıt vermeyen hasta öldü. BPFA'ya yalnızca bir hasta olumlu yanıt verdi, bu durum genç olmak, hastaneye erken başvurmuş olmak ve komorbidite olmaması ile ilişkili olabilir. Şiddetli KKKA hastalarında sitokin fırtınasını tedavi etmek için BPFA iyi bir seçenek olabilir. Ancak bu tedaviyi ne zaman uygulamamız gerektiği ve erken uygulamanın mortaliteyi önleyip önlemediği konusunda ileri çalışmalara ihtiyaç vardır.
Anahtar Kelimeler: Kırım-Kongo kanamalı ateşi, terapötik plazma adsorpsiyonu, terapötik plazmaferez

Introduction

Crimean-Congo hemorrhagic fever (CCHF) is a viral hemorrhagic fever syndrome caused by a tick-borne virus from the genus Nairovirus and the family Bunyaviridae. The clinical progression occurs in four phases: incubation, pre-hemorrhagic, hemorrhagic and convalescent period. In severe cases, hemorrhagic manifestations develop 3-6 days after the onset of the disease. Thrombocytopenia, leukopenia, elevated liver enzymes and prolonged coagulation times are the main laboratory features. Endothelial cells damaged by virus and virus-derived mediators play a role in the immunopathogenesis of CCHF (1,2). Pro-inflammatory cytokines released from damaged endothelial cells activate immune cells. Cytokines cause releasing of procoagulant factors, endothelial cell dysfunction and increased vascular permeability resulting in disseminated intravascular coagulation (DIC) and multiple organ failure. Rapid and severe activation of the inflammatory cascade autoamplificate cytokine production,which is called cytokine storm (3). There is no recommended antiviral treatment for CCHF. The clinical and laboratory effect of ribavirin is controversial (4). Supportive therapy is recommended in the management of the disease. Different extracorporeal depurative techniques have been developed to remove inflammatory mediators from the bloodstream thus restore immune homeostasis. Plasmapheresis, one of these techniques, has been shown to have a positive effect on the clinical course of severe CCHF patients (5-7). Coupled plasma filtration and adsorption (CPFA), another depurative technique, is used in intensive care patients with indications such as sepsis, septic shock and multiorgan failure (8). We present the the use of CFPA in management of three patients with CCHF.

Case Reports

CPFA was applied to three patients followed in the intensive care unit (ICU). All of the patients lived in rural areas and were engaged in animal husbandry. The diagnosis of CCHF was confirmed by polymerase chain reaction. Informed consent was obtained for this study.

Case 1

A 35-year-old female patient presented to the emergency department with complaints of fever, malaise and nausea. The patient was biten by a tick seven-days before her admission. Her symptoms started three-days after exposure. She was conscious, cooperative and oriented. She had fever (38 °C), other vitals were normal. She had bilateral conjunctivitis and vaginal bleeding. The laboratory blood results at the admission were as follows: leukocyte count: 810/μL, hemoglobin: 11.4 gr/dL, platelet: 33,000/μL, alanine aminotransferase (ALT): 55U/L, aspartate aminotransferase (AST): 239U/L, lactate dehydrogenase (LDH): 1670U/L, international normalized ratio (INR) 1 and D-dimer >36.2 mg/L. The severity grading score (SGS) was nine (9). On the 4th day of hospitalization, despite supportive treatment refractory thrombocytopenia developed, and intravenous immunoglobulin (IVIG) was administered. The patient whose vaginal bleeding continued had hematochezia. Hemoglobin value decreased (6.6 g/dL). Laboratory values of the patient are given in Table 1. She developed severe mucosal bleeding,

Table 1. Laboratory parameters of Patient-1 during the clinical course

Days after tick exposure	7	9	11	13	15	17	19	25
	Admission to hospital		1st session of CPFA	2nd session of CPFA				Day of discharge
WBC (x10^3/μL)	0.81	0.85	0.91	9.5	8.3	7	7.4	4
Hb (gr/dL)	11.4	9	7.5	7.1	8.7	8.7	8.9	9
Plt (x10^3/μL)	33	14	8	101	67	131	251	235
FIB (mg/dL)	238	230	380	214	375	571	340	300
INR	0.9	1	1.2	0.86	0.8	0.82	0.9	0.9
aPTT (sec)	42	50	50	38	25	20	-	22
D-dimer (mg/L)	>36	1.93	3.26	2.2	2.1	-	2.1	-
ALT (U/L)	55	171	430	275	168	100	92	24
AST (U/L)	239	431	1280	667	230	90	40	21
LDH (U/L)	1670	2160	2250	1057	620	543	483	120

WBC: White blood cells, Hb: hemoglobin, Plt: platelet, FIB: fibrinogen, INR: international normalized ratio, aPTT: activated partial thromboplastin time, ALT: alanine aminotransferase, AST: aspartate aminotransferase, LDH: lactate dehydrogenase, CPFA: coupled plasma filtration and adsorption

tachycardia (n=140/min) and hypotension (90/50 mm/Hg). After the patient became desaturated (SpO_2: 85%) and chest X-ray was consistent with interstitial edema, she transferred to the ICU with oxygen support. By calculating the patient's plasma volume, the total plasma volume was passed through the absorbent (Medisorb, Bellco, Medtronic, IT) once, the blood flow was 100-120 mL/min, and CPFA (Bellco, Medtronic, IT) was administered with heparin infusion for approximately 10-12 hours. The target activated partial thromboplastin time value in heparin infusion was between 45-65 seconds. After nine days in ICU, patient's leukocyte and thrombocyte values returned to normal and bleeding stopped. On the 25th day of admission, her vitals were stable and she was discharged healthy.

Case 2

A 54-year-old female was brought to the hospital with complaints of widespread muscle-joint pain, fever and nausea that started three days after a tick bite. There was no known comorbidities. The patient, who was hospitalized in another center for five days, was referred to our ICU because of increased liver enzymes and deterioration in coagulation parameters. Ten days after tick exposure, the laboratory blood parameters at admission to the hospital were as follows: leukocyte: 5910/µL, hemoglobin: 11.4 gr/dL, platelet: 61,000/µL, ALT: 2153 U/L, AST: 239 U/L, LDH: 116890 U/L, INR: 1, D-dimer: 1.9 mg/L. SGS was nine. When admitted to the ICU, the patient required mechanical ventilation. Patient was treated with CPFA for two days. On the 2nd day at the ICU, she died due to septic shock.

Case 3

A 69-year-old male was admitted to the emergency department with the complaints of chills, fatigue and weakness. He had a history of tick exposure seven days prior to the admission. He had hypertension, diabetes mellitus and coronary artery diseases with the use of anticoagulants. The laboratory blood parameters were as follows: leukocyte: 2510/µL, hemoglobin: 16 gr/dL, platelet: 19,000/µL, ALT: 185 U/L, AST: 390 U/L, LDH: 1120 U/L, INR: 0.9, D-dimer: 0.89 mg/L. SGS was ten. Supportive treatment was started. The patient desaturated on the 2nd day of hospitalization, chest X-ray was consistent with alveolar hemorrhage. The patient was intubated and transferred to the ICU. Patient was treated with CFPA on the 2nd day of his admission for two days. The desaturated, hypotensive patient died on the 5th day of admission.

Discussion

CCHF incidence is increasing due to changes in agricultural and animal practices as well as the effects of global warming on climate. CCHF is among the most fatal zoonotic diseases. There is a need for new treatment modalities to manage severe patients.

All of the three patients presented to clinic one week after the tick exposure were found to have SGS >9, which is a high risk for mortality (9). Case-based management of CCHF patients is required therefore checking complete blood count, coagulation parameters daily to replace blood products such as platelets, fresh frozen plasma (FFP) and erythrocyte preparations is essential. As presented in these cases, vital signs and examination are important since the clinical course of patients can change very rapidly. We did not use ribavirin because there are controversial findings regarding the use of this antiviral in CCHF patients (4).

Clinical progress of all three cases worsened in hemorrhagic period. One of the reasons for this rapid deterioration is cytokine storm. Cytokine storm triggers development of hemophagocytic lymphohistiocytosis, characterized by an overactivation of macrophages causing DIC, liver dysfunction, and endothelial damage. To manage cytokine storm in this particular phase will be effective for decreasing mortality. In a study, methylprednisolone, FFP and IVIG have been shown to be beneficial in the treatment of DIC-associated thrombocytopenia in CCHF patients with hemophagocytosis (10). In patient-1, IVIG was started due to refractory thrombocytopenia, but other patients' vitals were not stable enough to administer IVIG. To fight with overactive immune system, extracorporeal depurative techniques have been developed. Removing inflammatory mediators from the bloodstream restore immune homeostasis. CPFA is a hybrid system combining plasma filtration and adsorption with a resin cartridge that removes cytokines.There are case-based publications on the use of extracorporeal depurative techniques in CCHF patients.A positive effect of plasmapheresis on the prognosis of a pediatric CCHF patient was reported (6). In another study, 119 adult CCHF patients were examined, mortality was significantly reduced in the plasmapheresis group, but the effect on the prognosis could not be demonstrated (5). We performed CPFA to patients with CCHF who had cytokine storm causing multiple organ failure. In average ten days after tick exposure and seven days after onset of symptoms, when patients were in hemorrhagic period, first CPFA session done.Primary goal

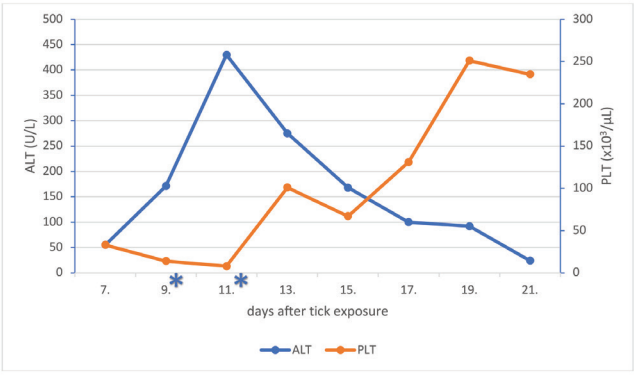

Figure 1. ALT and platelet values of patient-1 during the clinical course
*Indicate days of coupled plasma filtration and adsorption sessions
ALT: Alanine aminotransferase, PLT: platelet

for using CFPA is to reduce overactive inflammation and hemorrhagic complications. The number of CPFA sessions was determined according to the clinical and laboratory improvement. CFPA was used with heparin, considering that there may be an increase in liver toxicity when used with citrate as an anticoagulant. Despite severe thrombocytopenia in patient-1, elimination of inflammatory mediators resulted in rapid improvement in white blood cells and platelet counts (Figure 1). This promising result may indicate that endothelial damage can be prevented by controlling the underlying hyperinflammation with CPFA. Overall, only one patient responded well, which can be a result of being young, early admission to the hospital and lack of comorbidity. Since these treatments were applied to ICU patients improvement of symptoms or decreasing severity of clinical symptoms cannot be optimally assessed. The main question we face is when to apply CFPA. It is not possible to comment on the effect of the early application of CPFA on mortality and which patient should be administered early with small number of patients. Further studies are needed on the indications, application time and duration of CPFA in CCHF patients.

In this case series, for the first time, use of CFPA in CCHF patients and its positive effect on prognosis were demonstrated. More studies are needed using CFPA in CCHF to understand its effect on disease management.

Ethics

Informed Consent: Informed consent was obtained for this study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: D.T., G.Y., Design: D.T., M.P.K., Data Collection and/or Processing: D.T., Analysis and/or Interpretation: A.O.K., M.P.K., Literature Search: D.T., G.Y., Writing: D.T., G.Y., A.O.K., M.P.K.

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

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References

1. Basler CF. Molecular pathogenesis of viral hemorrhagic fever. Semin Immunopathol 2017;39:551-61.
2. Iannetta M, Di Caro A, Nicastri E, Vairo F, Masanja H, Kobinger G, et al. Viral Hemorrhagic Fevers Other than Ebola and Lassa. Infect Dis Clin North Am 2019;33:977-1002.
3. Chousterman BG, Swirski FK, Weber GF. Cytokine storm and sepsis disease pathogenesis. Semin Immunopathol 2017;39:517-28.
4. Ascioglu S, Leblebicioglu H, Vahaboglu H, Chan KA. Ribavirin for patients with Crimean-Congo haemorrhagic fever: a systematic review and meta-analysis. J Antimicrob Chemother 2011;66:1215-22.
5. Beştepe Dursun Z, Korkmaz S, Türe Z, Kaynar L, Dursun A, Çelik İ. Efficacy of therapeutic plasma exchange in patients with Crimean-Congo hemorrhagic fever. J Clin Apher 2021;36:390-7.
6. Perk O, Emeksiz S, Ozcan S, Meral G. Crimean-Congo hemorrhagic fever: A pediatric case responding to plasmapheresis treatment. Transfus Apher Sci 2021;60:103215.
7. Kurnaz F, Metan G, Coskun R, Kaynar L, Eser B, Doganay M. A case of Crimean-Congo haemorrhagic fever successfully treated with therapeutic plasma exchange and ribavirin. Trop Doct. 2011;41:181-2.
8. Garbero E, Livigni S, Ferrari F, Finazzi S, Langer M, Malacarne P, et al. High dose coupled plasma filtration and adsorption in septic shock patients. Results of the COMPACT-2: a multicentre, adaptive, randomised clinical trial. Intensive Care Med. 2021;47:1303-11.
9. Bakır M, Gözel MG, Köksal I, Aşık Z, Günal Ö, Yılmaz H, et al. Validation of a severity grading score (SGS) system for predicting the course of disease and mortality in patients with Crimean-Congo hemorrhagic fever (CCHF). Eur J Clin Microbiol Infect Dis 2015;34:325-30.
10. Erduran E, Bahadir A, Palanci N, Gedik Y. The treatment of crimean-congo hemorrhagic fever with high-dose methylprednisolone, intravenous immunoglobulin, and fresh frozen plasma. J Pediatr Hematol Oncol 2013;35:e19-24.