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CASE REPORT / OLGU SUNUMU

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ORIGINAL RESEARCH / *ÖZGÜN ARAŞTIRMA*

Erbil Türksal,
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Merve Karaşahin,
Esra Onhan Tekoğlu,
Ali Koç

Evaluation of Electrolyte Imbalance on Intensive Care Unit Admission and Its Effect on Prognosis

Yoğun Bakım Ünitesine Kabuldeki Elektrolit İmbalansı ve Prognoza Etkisinin Değerlendirilmesi

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Presented in: This study was presented as an oral presentation at 55th National Congress of Turkish Society of Anesthesiology and Reanimation.

ABSTRACT *Objective:* Electrolyte imbalance is an important factor that is frequently observed in the intensive care unit (ICU) and affects prognosis. We analyzed the type of electrolyte imbalance on ICU admissions and its relation to prognosis, mechanical ventilation day, ICU and hospital stay, and mortality.
Materials and Methods: The electrolyte values of 826 patients admitted to the ICU were analyzed. Demographic data, the type of electrolyte imbalance, mechanical ventilation day, length of stay in the ICU and hospital, acute physiology and chronic health evaluation-II (APACHE-II) scores, and mortality status were recorded.
Results: A total of 826 patients were included. Of the patients, 252 (30.5%) had dysnatremia, 193 (23%) had dyskalemia, 432 (52%) had dyscalcemia, 389 (47%) had dysmagnesaemia, and 625 (75%) had dysphosphatemia. APACHE-II score, mechanical ventilation day, and length of stay in ICU and hospital were significantly higher in hypernatremia than in normonatremia and hyponatremia. In hypokalemia, the length of stay in the ICU and mechanical ventilation day was significantly higher than in normokalemia. The mortality rate was 1.7 and 4.4 times higher in hyponatremia and hypernatremia, respectively, than in normonatremia. Mortality was 1.8 times higher in hypokalemia and 2.2 times higher in hyperkalemia than in normokalemia. Mortality was 11 times higher in hypercalcemia than in normocalcemia.
Conclusion: Electrolyte imbalance is frequently observed among ICU patients. In particular, in patients with dysnatremia and dyskalemia, the prognosis is worse.
Keywords: Water-electrolyte imbalance, critical illness, prognosis

ÖZ *Amaç:* Elektrolit imbalansı, yoğun bakım ünitesinde (YBÜ) sıklıkla görülen ve prognozu etkileyen önemli bir faktördür. YBÜ'ye yatışlardaki elektrolit imbalansı tipini ve bunun prognoz, mekanik ventilasyon günü, YBÜ ve hastanede kalış süresi ve mortalite ile ilişkisini analiz etmeyi amaçladık.
Gereç ve Yöntem: YBÜ'ye kabul edilen 826 hastanın elektrolit değerleri incelendi. Demografik veriler, elektrolit imbalansı tipi, mekanik ventilasyon günü, YBÜ ve hastanede kalış süresi, akut fizyoloji ve kronik sağlık değerlendirmesi-II (APACHE-II) skorları ve mortalite durumu kaydedildi.
Bulgular: Çalışmaya toplam 826 hasta dahil edildi. Hastaların 252'sinde (%30,5) disnatremi, 193'ünde (%23) diskalemi, 432'sinde (%52) diskalsemi, 389'unda (%47) dismagnezemi ve 625'inde (%75) disfosfatemi mevcuttu. APACHE-II skoru, mekanik ventilasyon günü, YBÜ ve hastanede kalış süresi, normonatremi ve hiponatremiye kıyasla hipernatremide anlamlı olarak daha yüksekti. Hipokalemide, YBÜ kalış süresi ve mekanik ventilasyon günü, normokalemiye kıyasla anlamlı derecede yüksekti. Normonatremiye kıyasla ölüm oranı hiponatremi ve hipernatremide sırasıyla 1,7 ve 4,4 kat daha fazlaydı. Normokalemiye göre hipokalemide mortalite 1,8 kat, hiperkalemide ise 2,2 kat daha fazlaydı. Hiperkalsemide, normokalsemiye kıyasla mortalite 11 kat daha fazlaydı.
Sonuç: Elektrolit imbalansı YBÜ hastalarında sıklıkla görülür. Özellikle disnatremisi ve diskalemisi olan hastaların prognozu daha kötüdür.
Anahtar Kelimeler: Sıvı-elektrolit imbalansı, kritik hastalık, prognoz

Introduction

Electrolytes play an important role in many vital functions such as; nerve cell transmission, bone metabolism, fluid balance, acid-base balance, muscle contraction mechanism, hormone function, cell membrane structure and function, metabolic and homeostatic functions. While many studies report the relationship between electrolyte imbalance (EI) and mortality and morbidity; EI is still one of the major problems among intensive care unit (ICU) patients (1-3). The complications of EI include a large variety of clinical disorders ranging from mild symptoms to life-threatening cardiac arrhythmias, and respiratory failure (4,5). Sodium, potassium, magnesium, calcium, and phosphorus are the most responsible electrolytes in regard to these complications in ICU. The main EI types are hypo- and hyper-states of sodium, potassium, magnesium, and calcium (6). Although there are publications analyzing EI in the literature, the studies examining each EI within itself and its effect on prognosis in ICU are rare.

In our study, we aimed to investigate the EI types of ICU patients on admission and the effect of EI type on prognosis in terms of mechanical ventilation day (MVD), length of stay (LOS) in ICU and hospital, acute physiology and chronic health evaluation-II (APACHE-II) scores, and mortality.

Materials and Methods

After the University of Health Sciences Turkey, Ankara Atatürk Sanatory Training and Research Hospital Clinical Research Ethics Committee approval (decision no: 2531, date: 14.06.2022) and clinical trial registration, we assessed retrospectively the charts of the patients hospitalized in our third-level ICU in the period between January 01, 2016 and July 31, 2019. Data were obtained from the hospital's biochemistry database and ICU patient files. Data was searched whether there is an EI on admission blood tests in ICU and if any EI was caught its type and severity were recorded according to ranges depicted in Table 1. Patients' age, sex, MVD, APACHE-II score, LOS in ICU and hospital, and mortality were recorded.

Corrected calcium was calculated according to Corrected Calcium = Total Calcium+ [0.8 × (4.0 – Albumin)] formulation. MVD was defined as the number of days from the first day of intubation to the day he was extubated or died.

Statistical Analysis

Analysis of the data was made in SPSS for Windows 22 package program (Chicago, Illinois, USA). After determining whether the data show normal distribution or not with the Kolmogorov-Smirnov test, all data were given as mean ± standard deviation or the difference between the median value and the quartiles. The correlation between categorical data was demonstrated with the chi-square test or the Fisher's Exact test. In the comparison of the numerical variables, Student-t test or Mann-Whitney U test was used depending on the parametric conditions. The statistical significance level was accepted as $p<0.05$ for all calculations.

Results

A total of 826 patients, 413 (50%) female, and 413 (50%) male were analyzed. The age range was between 16-101 years (69.19±19.33). Four hundred four (48.9%) patients were admitted to ICU from the emergency department, 81 (9.8%) were from the ward and 341 (41.3%) were postoperative patients (Table 2). The types and the numbers of patients with EI are depicted in Table 3. There was no EI in 100 of 826 patients (12%). In hypernatremia, APACHE-II score, MVD, and LOS in ICU and hospital were found to be significantly higher compared to normonatremia and hyponatremia

Table 1. Hypo-hyper reference ranges

	Reference range	Hypo-	Hyper-
Sodium (mmol/L)	136-145	<136	>145
Potassium (mmol/L)	3.5-5.5	<3.5	>5.5
Albumin corrected calcium (mg/dL)	8.8-10.6	<8.8	>10.6
Magnesium (mmol/L)	1.8-2.6	<1.8	>2.6
Phosphate (mmol/L)	2.5-4.5	<2.5	>4.5

Table 2. Demographic data

		n	Percent (%)	Mean ± SD
Age				69.19±19.33
Gender	Male	413	50	
	Female	413	50	
Admission unit	Emergency department	404	48.9	
	Ward	81	9.8	
	Operating room	341	41.3	

SD: Standard deviation

(p<0.05) (Table 4). Mortality in normonatremia, hyponatremia and hypernatremia was 26%, 44% and 71% respectively. In hyperkalemia, APACHE-II score was significantly higher compared to normokalemia and hypokalemia. In hypokalemia, MVD, and LOS in ICU was significantly higher than normokalemia (p<0.05). In dyscalcemia (corrected with albumin), there was no significant difference in terms of APACHE-II score, MVD, and LOS in ICU and hospital. In dysmagnesaemia, no significant difference was found in terms of MVD, and LOS in ICU and hospital. APACHE II score was found to be higher in hypermagnesemia compared to normomagnesaemia and hypomagnesaemia.

APACHE-II score in hyperphosphatemia was found to be significantly higher than normophosphatemia and hypophosphatemia (p<0.05). There was no significant difference between hypo-hyper and normophosphatemia in terms of MVD, and LOS in ICU and hospital.

When the readmission rates were examined, it was revealed that dysnatremia did not affect the readmission rates (p>0.05). Although the readmission was found to be higher in hyperkalemia compared to hypokalemia and normokalemia, the result was not statistically significant (p>0.05). Readmissions in hypocalcemia were higher than hypercalcemia and normocalcemia, but statistically, there was no difference (p>0.05). Similarly, there was no statistical difference in readmission rates of hypo-, hyper-, and normomagnesaemia (p>0.05).

Compared to normonatremia, the rate of mortality was 1.7 times higher in hyponatremia and 4.4 times higher in hypernatremia. The mortality rate was 1.8 times higher in hypokalemia and 2.2 times higher in hyperkalemia compared to normokalemia. While the mortality rate was similar in hypocalcemia compared to normocalcemia, mortality was 11 times higher in hypercalcemia. Mortality was unchanged in dysmagnesemia. Compared with normophosphatemia, mortality was 1.7 times higher in hypophosphatemia and 5.1 times higher in hyperphosphatemia.

Table 3. Type and proportion of EI

Electrolyte	Type of EI	n	Proportion (%)
Sodium	Normonatremia	574	69.5
	Hyponatremia	192	23.2
	Hypernatremia	60	7.3
Potassium	Normokalemia	633	76.6
	Hypokalemia	123	14.9
	Hyperkalemia	70	8.5
Calcium (albumin-corrected)*	Normocalcemia	394	47.7
	Hypocalcemia	419	50.7
	Hypercalcemia	13	1.6
Magnesium	Normomagnesaemia	437	52.9
	Hypomagnesaemia	337	40.8
	Hypermagnesaemia	52	6.3
Phosphate	Normophosphatemia	530	64.2
	Hypophosphatemia	95	11.5
	Hyperphosphatemia	201	24.3

*Corrected Calcium = Total Calcium + [0.8 × (4.0 – Albumin)]
EI: Electrolyte imbalance

Table 4. Analysis of electrolyte imbalance in terms of APACHE-II score, mechanical ventilation day, length of stay in ICU and hospital

	EI	EI	Mean difference	Std. error	Sig.	95% Confidence interval	
						Lower bound	Upper bound
APACHE-II score	Normonatremia	Hyponatremia	-3,057	1,383	0.08	-6.38	0.27
		Hypernatremia	-11,067	2,403	<0.01*	-16.84	-5.29
	Hyponatremia	Hypernatremia	-8,010	2,600	<0.01*	-14.26	-1.76
	Normokalemia	Hypokalemia	-2,602	1,652	0.34	-6.57	1.37
		Hyperkalemia	-9,458	2,294	<0.01*	-14.97	-3.94
	Hypokalemia	Hyperkalemia	-6,856	2,672	<0.05*	-13,28	-0.43
	Normomagnesaemia	Hypomagnesaemia	3,188	1,155	<0.05*	0,41	5.96
		Hypermagnesaemia	-13,856	2,685	<0.01*	-20.31	-7.40
	Hypomagnesaemia	Hypermagnesaemia	-17,044	2,693	<0.01*	-23.52	-10.57
	Normophosphatemia	Hypophosphatemia	-3,180	1,650	0.16	-7.15	0.79
		Hyperphosphatemia	-12,511	1,333	<0.01*	-15.71	-9.31
	Hypophosphatemia	Hyperphosphatemia	-9,331	1,903	<0.01*	-13.90	-4.76

Table 4. Analysis of electrolyte imbalance in terms of APACHE-II score, mechanical ventilation day, length of stay in ICU and hospital

	EI	EI	Mean difference	Std. error	Sig.	95% Confidence interval	
						Lower bound	Upper bound
Mechanical ventilation days	Normonatremia	Hyponatremia	-0,478	1,456	1.00	-3.97	3.02
		Hypernatremia	-8,267	2,370	<0.01*	-13.95	-2.58
	Hyponatremia	Hypernatremia	-7,789	2,584	<0.01*	-13.99	-1.59
	Normokalemia	Hypokalemia	-5,397	1,724	<0.01*	-9.53	-1.26
		Hyperkalemia	-0,793	2,203	1.00	-6.08	4.49
	Hypokalemia	Hyperkalemia	4,604	2,619	0.23	-1.68	10.89
	Normomagnesaemia	Hypomagnesaemia	1,954	1,273	0.37	-1.10	5.01
		Hypermagnesaemia	3,023	2,577	0.72	-3.16	9.20
	Hypomagnesaemia	Hypermagnesaemia	1,070	2,617	1.00	-5.21	7.35
	Normophosphatemia	Hypophosphatemia	-1,053	1,956	1.00	-5.75	3.64
		Hyperphosphatemia	-2,832	1,454	0.15	-6.32	0.66
	Hypophosphatemia	Hyperphosphatemia	-1,779	2,186	1.00	-7.02	3.46
LOS ICU	Normonatremia	Hyponatremia	-0,223	1,486	1.000	-3.79	3.34
		Hypernatremia	-7,825	2,418	<0.01*	-13.62	-2.03
	Hyponatremia	Hypernatremia	-7,602	2,636	<0.05*	-13.92	-1.28
	Normokalemia	Hypokalemia	-5,064	1,758	<0.05*	-9.28	-0.85
		Hyperkalemia	0,690	2,247	1.00	-4.70	6.08
	Hypokalemia	Hyperkalemia	5,754	2,671	0.09	-0.65	12.16
	Normomagnesaemia	Hypomagnesaemia	1,755	1,298	0.53	-1.36	4.87
		Hypermagnesaemia	3,335	2,626	0.61	-2.96	9.64
	Hypomagnesaemia	Hypermagnesaemia	1,580	2,667	1.00	-4.82	7.98
	Normophosphatemia	Hypophosphatemia	-1,359	1,997	1.00	-6.15	3.43
		Hyperphosphatemia	-1,514	1,484	0.92	-5.08	2.05
	Hypophosphatemia	Hyperphosphatemia	-0,155	2,231	1.00	-5.51	5.20
LOS Hospital	Normonatremia	Hyponatremia	-0,213	1,529	1.00	-3.88	3.46
		Hypernatremia	-6,819	2,484	<0.05*	-12.78	-0.86
	Hyponatremia	Hypernatremia	-6,606	2,709	<0.05*	-13.11	-0.11
	Normokalemia	Hypokalemia	-4,501	1,803	<0.05*	-8.82	-0.18
		Hyperkalemia	3,089	2,304	0.54	-2.44	8.62
	Hypokalemia	Hyperkalemia	7,589	2,738	<0.05*	1.02	14.16
	Normomagnesaemia	Hypomagnesaemia	0,073	1,331	1.00	-3.12	3.27
		Hypermagnesaemia	4,719	2,693	0.24	-1,74	11.18
	Hypomagnesaemia	Hypermagnesaemia	4,646	2,735	0.26	-1.91	11.21
	Normophosphatemia	Hypophosphatemia	-0,353	2,049	1.00	-5.27	4.56
		Hyperphosphatemia	0,102	1,524	1.00	-3.55	3.76
	Hypophosphatemia	Hyperphosphatemia	0,455	2,290	1.00	-5.04	5.95

APACHE-II: Acute physiology and chronic health evaluation-II, ICU: intensive care unit, EI: electrolyte imbalance, LOS: length of stay, *p<0.05 statistically significant

Discussion

In different clinics, the prevalence and type of EI may vary. Our study was conducted in a third-level ICU running under the anesthesiology and reanimation department. Tazmini et al. (7) conducted a retrospective study in an emergency department. In their population, the prevalence of hyponatremia was 24%, hypokalemia was 8.6% and hypocalcemia (albumin-corrected) was 1.6%. Our hyponatremia, hypokalemia and hypocalcemia (albumin-corrected) prevalence were 23.2%, 14.7% and 50.7% respectively. While their hypernatremia, hyperkalemia and hypercalcemia prevalence were 1.7%, 3.3% and 10.9%, ours were 7.3%, 8.5% and 1.6% respectively. In our ICU study, the ratios are notably higher except hypercalcemia in comparison to their study. This may be explained by the condition of the critically ill patients who were exposed to many medications, fluid shifts and interventional approaches before ICU admission. Hyponatremia ratios are closer to each other in both studies. The biggest difference is between hypocalcemia ratios which are 50.7% in our study and 1.6% in theirs. One of the reasons for this notable difference may be the different reference values between the centers. Sedlacek et al. (8) reported that electrolyte imbalances in ICU can be prevented by attention to the usage of intravenous fluids and nutrition. In our study we analyzed the admission blood tests in ICU, so we didn't have the chance to prevent the electrolyte disturbances but the initial treatment was done as soon as the ICU team received the blood test results.

In their prospective cohort, Mestrom et al. (9) analyzed ICU-acquired hypernatremia. They enrolled 183 patients including 70 with ICU-acquired hypernatremia. The APACHE-IV scores of hypernatremic and normonatremic patients were 62 and 48, respectively. ICU mortality of hypernatremic and normonatremic patients were 23% and 12%; 90-day mortality were 33% and 14% respectively. Although our study is not about ICU-acquired EI, the comparison of this study with ours may reveal the differences between the admission electrolyte disturbances and the ICU-acquired ones. In our study, while there was no statistically significant difference between APACHE-II scores for hyponatremia and normonatremia, the APACHE-II scores for hypernatremia were significantly higher than the patients with hyponatremia and normonatremia. In their study mortality in hypernatremic patients was 2.35 times higher than normonatremic patients and 4.4 times higher in ours. This difference may be due to the severity of critically ill patients in our study.

A systematic review and meta-analysis reported that hyponatremia is associated with a prolonged LOS in hospital and higher risk of readmissions (10). In our study, the difference in readmission rates of hyponatremia, normonatremia and hypernatremia was not statistically significant. We also found that patients with hypernatremia had a significantly longer ICU stay compared to patients with hyponatremia ($p<0.05$).

In their retrospective cross-sectional study Lindner et al. (11) revealed that there is no significant correlation between serum calcium level and LOS in hospital. In our study, there was no statistically significant difference in patients with dyscalcemia in terms of MVD, and LOS in ICU and hospital. Mortality rates in normocalcemic, hypocalcemic and hypercalcemic patients were 34%, 32% and 84% respectively. In a retrospective cohort, acute medical admissions were evaluated in terms of potassium levels (12). Hospital mortality rates were 3.9%, 5%, and 18% in normokalemic, hypokalemic and hyperkalemic patients respectively. In our ICU, the mortality rates of patients who have potassium imbalance on admission were; 29%, 40% and 68% in normokalemic, hypokalemic and hyperkalemic patients respectively. Our study was performed in a third-level ICU which may be the reason for the big difference between mortality rates in the two studies. In their study, hypokalemic patients had a longer LOS compared to normokalemia which is the same as our results. In our study, we also revealed that hypokalemic patients had longer LOS than hyperkalemic patients ($p=0.017$).

A large study reported that higher serum phosphorus levels influence mortality in patients with normal kidney function (13). In our trial, the mortality rates were 22%, 32% and 67% in normophosphatemic, hypophosphatemic and hyperphosphatemic patients respectively.

Our study has some limitations. In our ICU, the diseases of patients in admission vary, so the patient population is not homogenized. Our patients have many comorbidities, and different therapies and there are many other factors which may affect mortality, LOS, APACHE-II score and readmissions. In addition, the source of the ward patients was lacking.

Conclusion

In conclusion, EI is one of the most frequent diagnoses in ICU admissions. Mortality, LOS, and prognosis differ in EI types. In our study, we revealed that dysnatremic and dyscalcemic patients have more negative prognosis.

Ethics

Ethics Committee Approval: Approval was received from the Clinical Research Ethics Committee of the University of Health Sciences Turkey, Ankara Atatürk Sanatorium Training and Research Hospital (decision no: 2531, date: 14.06.2022).

Informed Consent: For this type of study formal consent is not required.

Authorship Contributions

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

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ORIGINAL RESEARCH / *ÖZGÜN ARAŞTIRMA*

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Initial Vital Signs in Traumatized Children Determine the Length of Stay in Intensive Care Unit

Travma Geçirmiş Çocuklarda İlk Yaşamsal Belirtiler Yoğun Bakım Kalış Süresini Belirliyor

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ABSTRACT *Objective:* Vital signs and trauma scores of pediatric trauma patients affect morbidity and length of stay in the intensive care unit (ICU); treatment and follow-up of appropriate trauma patients in experienced centers is of great importance. This study aimed to determine the demographic data, clinical findings and scoring systems, and respiratory and circulatory support requirements of trauma patients during their follow-up in the pediatric ICU (PICU) and investigate the effects of these factors on the length of PICU and hospital stay and mortality.
Materials and Methods: Demographic and clinical findings of 49 pediatric patients who were hospitalized in the PICU because of trauma were prospectively recorded for 16 months. Data on the length of PICU and hospital stay, trauma mechanisms, and affected organ systems were collected.
Results: The most frequent etiology of trauma was falling from heights in 36.7% of the patients. Mechanical ventilation (MV) was necessary in 18.4% of the cases, and the mean duration for MV was 48 (12-306) hours. When MV need was evaluated concerning vital findings, the findings showed that patients with bradypnea needed MV more (p=0.004). MV was needed in 66.7% of hypotensive patients, and there was a statistically significant difference between blood pressure and MV requirement (p=0.005). Glasgow coma score and length of PICU stay were correlated (p=0.02). PICU (p=0.005, p=0.005, p=0.001) and hospital stay (p=0.02, p=0.01, p=0.04) were statistically significantly longer in patients who had blood products, inotropic agents and MV.
Conclusion: The effects of initial vital signs and trauma scores on morbidity and length of PICU stay of pediatric trauma patients, as well as the importance of treatment and follow-up of appropriate patients in experienced centers, have been shown in our study.
Keywords: Pediatric trauma, trauma scores, vital signs

ÖZ *Amaç:* Pediatrik travma hastalarının vital bulguları ve travma skorları, morbidite ve yoğun bakım ünitesinde (YBÜ) kalış süresine etkisi ile uygun travma hastalarının deneyimli merkezlerde tedavi ve takibi açısından büyük önem taşımaktadır. Bu çalışmada, travma hastalarının çocuk YBÜ'de (ÇYBÜ) izlemleri sırasındaki demografik verileri, klinik bulguları ve skorlama sistemleri, solunum ve dolaşım destek gereksinimlerinin belirlenmesi ve bu faktörlerin hastanede kalış, ÇYBÜ kalış süreleri ve mortalite üzerine etkisinin araştırılması amaçlanmıştır.
Gereç ve Yöntem: Bu çalışmada travma nedeniyle ÇYBÜ'de yatan 49 çocuk hastanın demografik ve klinik bulguları prospektif olarak 16 ay süreyle kaydedildi. ÇYBÜ ve hastanede kalış süreleri, travma mekanizmaları ve etkilenen organ sistemleri hakkında veriler toplandı.
Bulgular: Hastaların %36,7'sinde en sık travma nedeni yüksekten düşme idi. Olguların %18,4'ünde mekanik ventilasyon (MV) uygulanmıştı ve ortalama MV süresi 48 (12-306) saatti. Vital bulgular açısından MV ihtiyacı değerlendirildiğinde, bulgular bradipneli hastaların MV'ye daha fazla ihtiyaç duyduğunu gösterdi (p=0,004). Hipotansif hastaların %66,7'sinde MV ihtiyacı oldu ve kan basıncı ile MV ihtiyacı arasında istatistiksel olarak anlamlı fark vardı (p=0,005). Glasgow koma skoru ve ÇYBÜ kalış süresi arasında istatistiksel olarak anlamlı bir ilişki vardı (p=0,02). ÇYBÜ (p=0,005, p=0,005, p=0,001) ve hastanede kalış süresi (p=0,02, p=0,01, p=0,04) kan ürünleri, inotropik ajan ve MV bulunan hastalarda istatistiksel anlamlı olarak daha uzundu.
Sonuç: Çalışmamızda pediatrik travma hastalarında başlangıç vital bulguları ve travma skorlarının morbidite ve ÇYBÜ kalış süresine etkisi ile uygun hastaların deneyimli merkezlerde tedavi ve takibinin önemi gösterilmiştir.
Anahtar Kelimeler: Pediatrik travma, travma skorları, yaşamsal belirtiler

Introduction

Physical trauma is one of the most important causes of mortality and morbidity in childhood, especially in children older than one year of age (1,2). Trauma is a public health problem that needs to be solved, as trauma-related injuries and deaths in childhood outstrip other major diseases (2,3). According to the 2017-2018 data of the Turkish Statistics Institute, the death rates due to accidents, injuries and poisonings are in the first place for deaths between the ages of 0 and 14 years (4,5).

The most common causes of trauma-related death in children in all age groups are in-car or out-of-car motor vehicle accidents. Falling from heights, drowning, abuse, and fires are among the other causes of death. Adolescent deaths are mostly due to gunshot wounds (1-4). Risky trauma mechanisms may cause multiple trauma in children, paving the way for serious multi-systemic complications (6). Injuries due to trauma are the leading causes of emergency department and pediatric intensive care unit (PICU) admissions (7). The present study aimed to reveal the demographic data of trauma patients followed up in the PICU, evaluate the correlation of clinical findings with a length of PICU stay, respiratory and circulatory support requirements, and prognosis.

Materials and Methods

During the 16-month period between July 2018 and June 2019, 49 critically ill children were included in this study. The trauma mechanisms exposed, the organ systems affected by the trauma, demographic characteristics, clinical findings, vital signs, need for respiratory support, lengths of PICU, and hospital stays were prospectively recorded. Glasgow coma score (GCS) (mild head trauma was considered 15-14 points, moderate head trauma as 13-9 points, and severe head trauma as ≤8 points). Pediatric trauma score (PTS), the patient's airway patency, state of consciousness, body weight, systolic blood pressure, presence of an open wound and roughly the presence of any skeletal system trauma are evaluated and scored. The total score ranges between -6 and +12, <8 points identifies a potential significant trauma and indicates that follow up in a trauma center would be appropriate. PTS is an important scoring system in predicting patient triage and mortality (6-12). Pediatric Risk of Mortality (PRISM III) and pediatric logistic organ dysfunction (PELOD) scores were calculated and recorded to determine the risk of morbidity and organ failure in trauma patients (13,14).

The use of inotropes and blood products and the type of hyperosmolar therapy administered to patients with head trauma were recorded. Serial intravesical pressure measurements were made in patients with risk factors for intra-abdominal hypertension (IAH). Intra-abdominal pressure (IAP) was measured through a Foley bladder catheter as defined in the final pediatric consensus definitions section of the 2013 updated The World Society of the Abdominal Compartment Syndrome (WSACS, www.wsacs.org) consensus (15). Briefly, in a complete supine position, 1 mL/kg of normal saline, with a minimal instillation volume of 3 mL and a maximum installation volume of 25 mL, was instilled in to the bladder through a Foley catheter. The end of the urinary catheter was connected to a transparent, open-ended plastic tube, which was then connected to a transducer set and monitoring lines. The IAP level was automatically measured by the monitor in mmHg units. The procedure was repeated every 6 hours (h), with four serial measurements per day.

In patients with head trauma, optic nerve sheath diameter (OSD) was measured with ultrasonography (USG), to detect and monitor the presence of high intracranial pressure. Mindray M7 ultrasound device and L14-6s linear probe were used for measurements. While the patients were in the supine position, ultrasound gel was applied over the closed eyelids, and they were examined with orbital USG, holding the probe in a straightforward position. OSD measurement was performed by obtaining images in the longitudinal and transverse axes from the area between the hyper echoic dural sheaths located at the edge of the hypo echoic subarachnoid area surrounding the optic nerve (16). In addition, cerebral monitoring was performed with near infrared spectroscopy (NIRS), a non-invasive method, to monitor regional tissue oxygenation (17). For cerebral measurement, self-adhesive pediatric probes were placed in the right and left frontal regions after skin cleansing. Cerebral oxygenation monitoring was performed with NIRS (INVOS somanetics, 5100C, Covidien, Mansfield, MA, USA) device. The patients who underwent electroencephalography (EEG) monitoring were recorded.

Ethical approval to conduct this study was obtained from the Non-Invasive Ethics Committee of the Faculty of Medicine of Çukurova University (decision no: 30, date: 07.12.2018). The data were recorded after obtaining written informed consent from the families of the patients included in the study.

Statistical Analysis

Statistical Package for Social Sciences (SPSS for Windows 20.0 version) was used for statistical analysis. Categorical variables are expressed as numbers and percentages. In numerical continuous data, it was stated that the mean ± standard deviation was given for those with normality distribution, and the median [minimum (min)-maximum (max)] value was given for those without normality distribution. Friedman's test was used to compare more than two dependent groups that did not show normal distribution. Kolmogorov-Smirnov test was used to test the normality of continuous data. The Mann-Whitney U test was used to compare two independent groups that did not show normal distribution. Conformity to the normal distribution was evaluated using the Shapiro-Wilk test. Fisher's Exact test was used to compare categorical variables according to groups. Linear regression analysis was used to analyze the independent variables affecting the duration of intensive care. The statistical significance level was $p<0.05$.

Results

We enrolled 49 pediatric patients (11 female), with a mean age of 90.78±59.70 months (min: 6 months, max: 17 years). Age group classification was made as follows: infant age group (younger than ≤24 months, 16.3%, n=8), toddlers (24-72 months, 28.5%, n=14) and school-age children (≥72 months, 55.2%, n=27). According to the age groups, the most common etiology of trauma was falling from heights (75%) in infants and out-of-car traffic accidents in toddlers (43%). In the group ≥72 months, which constituted the majority of the patients, falling from heights was the most common etiology. The classification of the patients according to their demographic and clinical characteristics is shown in Table 1.

Mortality did not develop in any of our cases during this study. The mean PRISM III score was 6.61±4.97 (min: 0, max: 21), while the mean PELOD score was 5.69±5.09 (min: 0, max: 22). When the need for mechanical ventilation (MV) was evaluated according to the vital findings, the need for MV was higher in patients with bradypnea (p=0.004). While 66.7% of hypotensive patients needed MV, this rate was 11.6% in non-hypotensive patients (p=0.001) (Table 2). Surgery was performed in 51% (n=25) of our trauma patients. When the relationship between vital signs and the need for surgery was examined, it was seen that there was no significant relationship between respiratory rate, blood pressure and

Table 1. Demographic and clinical characteristics of the pediatric trauma patients

Characteristics of the patients	**% (n)**
Mechanism of injury	
Falling from high	36.7% (n=18)
Non-vehicle traffic accident	34.7% (n=17)
In-vehicle traffic accident	8.2% (n=4)
Blunt trauma	6.2% (n=3)
Penetrating trauma	4.1% (n=2)
Firearm injury	4.1% (n=2)
Falling-crash on same ground	2% (n=1)
Hanging	2% (n=1)
Electric shock	2% (n=1)
Glasgow coma scores (GCS)	
GCS ≥12	73.5% (n=36)
GCS 9-11	10.2% (n=5)
GCS ≤8	16.3% (n=8)
Pediatric trauma scores (PTS)	
PTS >8	30.6% (n=15)
PTS ≤8	69.4% (n=34)
According to trauma mechanism need for mechanical ventilation	
Falling from high	22.2% (n=2)
Non-vehicle traffic accident	33.4% (n=3)
In-vehicle traffic accident	11.1% (n=1)
Firearm Injury	11.1% (n=1)
Others	22.2% (n=2)
Respiratory support	
No respiratory support	26.5% (n=14)
Oxygen support with reservoir mask	53.1% (n=26)
Need for mechanical ventilation	18.4% (n=9)
According to injured organ systems need for mechanical ventilation	
Head injury	53.4% (n=8)
Extremity injury	20% (n=3)
Thoracic injury	13.3% (n=2)
Abdominal injury	13.3% (n=2)
According to head trauma types need for mechanical ventilation	
Isolated skull fracture	25% (n=2)
Isolated parenchymal injury	50% (n=4)
Fracture and parenchyma injury	25% (n=2)
Mechanical ventilation indications	
Low Glasgow coma score	10.2% (n=5)
Hemorrhagic shock	4.1% (n=2)
Post-operation	4.1% (n=2)
Blood transfusions	
Transfused	36.7% (n=18)
Not transfused	64.3% (n=31)

body temperature values and surgery. However, patients with tachycardia needed surgery more (Table 2). Trauma etiologies and affected systems were evaluated according to the need for surgery, and no significant difference was found between them. A total of 18 patients (36.7%) were administered blood and blood products, and a massive blood transfusion was needed in one patient. After excluding the urethral and bladder injury, urinary catheters were placed in 33 (67.3%) patients to monitor urine output and/or monitor IAP. Intra-abdominal pressure measurement was performed in 15 patients (30.6%). The mean IAP was 9.0±2.4 (min: 5, max: 14) mmHg. IAH was detected in seven of 15 patients. Symptomatic treatment with nasogastric decompression and appropriate fluid management was applied to patients with IAH. Abdominal compartment syndrome and requirement of surgical decompression did not occur any of the patients with intraabdominal hypertension. There was no significant difference between the lengths of PICU and hospital stay between those with and without IAH. There was no statistically significant difference between the distributions of mechanical ventilator needs between those with and without IAH (p=1.000). MV was needed in 20% of those without IAH, and 10% of those with IAH.

The mean time between trauma and admission to the pediatric ICU was 31.6±98.7 h, with a median of six h. The mean hospital stay was eight (min: 2, max: 30) days, and the mean PICU stay was four (min: 1, max: 13) days. The median follow-up time on the mechanical ventilator was 48 (min: 12, max: 306) h. 18.4% (n=9) of the patients needed MV. There was no significant difference between trauma etiologies, affected organ systems and head trauma types in terms of MV (p=0.399). When the hospital and PICU stay of the patients who needed and did not need MV were compared, it was found that the need for MV had a statistically significant effect on the duration of PICU stay and hospitalization (p=0.01, p=0.04) (Table 3).

The critically ill children included in this study were grouped according to their PTS and GCS scores. Five patients with GCS below 8 had surgery, and all of them needed MV. When the lengths of PICU stay were compared between the patients with mild and moderate brain injury and no statistically significant difference was found (p=0.66). There was no difference between the cases with severe and moderate brain damage for the length of PICU stay (p=0.35). When the lengths of PICU stay were compared between the children with severe and mild brain injury, and the difference was statistically significant (p=0.02). According to the PTS, there was no correlation between the lengths of stay in hospital and PICU between the groups. The lengths of PICU stay were similar in patients who fell from heights and in

Table 2. Classification of patients according to their vital signs recorded within the first hour of admission to the pediatric intensive care unit; comparison in terms of mechanical ventilation and operation requirement

	Patients n (%)	**Mechanical ventilation n (%)**	**p-value**	**Operation n (%)**	**p-value**
Pulse					
Bradicardia Normal Tachycardia	- 21 (42.9%) 28 (57.1%)	- 3 (14.2%) 6 (21.4%)	0.520	- 6 (28.6%) 19 (67.9%)	0.01
Respiratory rate					
Bradypnea Normal Tachypnea	3 (6.1%) 30 (61.2%) 16 (32.7%)	3 (100%) 5 (16.6%) 1 (6.2%)	0.004	2 (66.7%) 14 (46.7%) 9 (56.2%)	0.70
Blood pressure					
Hypotension Normotension Hypertension	6 (12.2%) 32 (65.3%) 11 (22.4%)	4 (66.6%) 4 (12.5%) 1 (9%)	0.005	6 (100%) 14 (43.8%) 5 (45.5%)	0.83
Body temperature					
Hypothermia Normothermia Hyperthermia	2 (4.1%) 40 (81.8%) 7 (14.6%)	1 (50%) 6 (15%) 2 (28.5%)	0.346	1 (50.0%) 21 (52.5%) 3 (42.9%)	0.89

Table 3. Comparison of pediatric intensive care and hospital stays according to the clinical characteristics of the patients				
	Length of hospital stay (days) Mean ± SD Median (min-max)	**p-value**	**Length of pediatric intensive care (days) Mean ± SD Median (min-max)**	**p-value**
PTS >8 (n=15)	10.73±7.13 9 (3-30)	0.77	3.80±2.78 3 (1-12)	0.26
PTS ≤8 (n=34)	12.26±8.80 8 (2-30)		4.71±2.96 4 (1-13)	
Falling from high (n=18)	8.56±6.00 7.5 (2-25)	0.01	15.41±9.26 12 (4-30)	0.08
Non-vehicle traffic accident (n=17)	15.41±9.26 12 (4-30)		5.35±3.23 4 (2-13)	
Need for MV (n=9)	18.11±10.26 16 (6-30)	0.04	7.11±3.75 7 (2-13)	0.01
No need for MV (n=40)	10.38±7.17 8 (2-30)		3.83±2.34 3.5 (1-12)	
Transfused (n=18)	16.78±9.69 13 (5-30)	0.02	6.00±3.25 6.5 (2-13)	0.005
Not transfused (n=31)	8.9±5.73 7 (2-30)		3.52±2.28 3 (1-12)	
Inotrope support (n=6)	22.00±9.52 25.50 (7-30)	0.01	7.17±2.04 7.50 (4-10)	0.005
Not receiving inotropic support (n=43)	10.37±7.11 8 (2-30)		4.05±2.82 3 (1-13)	
SD: Standard deviation, min-max: minimum-maximum, PTS: pediatric trauma score, MV: mechanical ventilation				

those who had out-of-car traffic accidents, but the hospital stay was longer in the patients who had traffic accidents (p=0.01). The lengths of PICU stay (p=0.005, p=0.005, p=0.001) and hospitalization (p=0.02, p=0.01, p=0.04) were statistically significantly longer in patients who had blood products or inotropes and in the ones who needed MV support (Table 3).

The independent variables affecting the length of stay in the ICU were analyzed by linear regression analysis. The establish linear regression model was found to be statistically significant (F=7.554, p<0.001). In the established linear regression model, the independent variables and the dependent variable are explained at a rate of 48.9%. Those with blood products were 2,208 more times than those without PICU (p=0.005). The application period also has a positive effect on the duration of the application, and the duration of the application increases by 0.013 when the application period increases by one unit (p<0.001). There was no statistically significant effect of other variables (p>0.050) (Table 4).

Head trauma was present in 73.5% (n=36) of all cases, and all of these patients had hyperosmolar therapy for high intracranial pressure. Hypertonic saline was the agent chosen in the first step of hyperosmolar therapy. In addition, 10 (27.7%) patients had mannitol in addition to hypertonic saline. Barbiturates were administered to one (2%) patient due to a persistent high intracranial pressure. OSD was measured in those 36 (73.4%) patients with head trauma, 21 (42.9%) patients were followed up with NIRS, and 11 out of 14 (28.5%) patients who had EEG were treated with antiepileptic (all with levetiracetam and 3 with additional phenytoin).

Discussion

Trauma-related injuries are one of the most important causes of mortality, morbidity and health expenditures in childhood. While trauma takes the second place after infection among the causes of death between the ages of one and four in underdeveloped and developing countries, it takes

Table 4. Examination of the factors affecting the length of stay in the pediatric intensive care unit by linear regression analysis

	β_0 (95% CI)	SE	β_1	t	p	r^1	r^2	VIF
Static	3.461 (-0.37-7.292)	1.897	0.000	1.824	0.075	0.000	0.000	0.000
Transfused (reference: no)	2.208 (0.701-3.714)	0.746	0.370	2.960	**0.005**	0.416	0.420	1.465
Inotropic support (reference: no)	1.106 (-1.377-3.589)	1.230	0.126	0.899	0.374	0.355	0.139	1.841
MV (reference: no)	1.249 (-0.852-3.35)	1.040	0.168	1.201	0.237	0.442	0.184	1.838
BMI	-0.122 (-0.341-0.097)	0.108	-0.124	-1.127	0.266	-0.042	-0.173	1.144
Application deadline (h)	0.013 (0.007-0.02)	0.003	0.456	4.300	**<0.001**	0.458	0.557	1.057
Heart beat (reference: normokardi)	0.86 (-0.441-2.16)	0.644	0.148	1.335	0.189	0.301	0.204	1.150
Intracranial pressure treatment (reference: no)	1.345 (-0.098-2.788)	0.715	0.206	1.882	0.067	0.154	0.282	1.128

F=7.554. p<0.001. R^2=0.563. Corrected R^2=0.489. β_0: non-standardized beta coefficient, β_1: standardized beta coefficient, r^1: zero-order correlation, r^2: partial correlation, CI: confidence interval, BMI: body mass index, MV: mechanical ventilation, SE: standard error, VIF: variance inflation factor

the first place after the age of four in these countries and the period between 1-14 years in developed countries (2,3).

Wohlgemut et al. (18) examined the demographic and geographic characteristics of pediatric trauma patients, and the median age of the patients was 9.0 (4-12) years. In the İzmir region of our country, Öztan et al. (19) reported the median age as 16.0 (2-11) years. Yousefzadeh Chabok et al. (20) reported that the median age of the patients was 7.3 years (3 months-14 years). In our study, the youngest patient was six months old, the oldest was 17 years old, and the median age was 6.3 years.

When the etiologies of trauma were examined, falling from heights was the most common etiology (36.7%) in our study. This was followed by out-of-car traffic accidents with 34.7% and in-car traffic accidents with 8.2%. When the trauma etiologies in the pediatric age group are examined in the literature, it is evident that falling from heights and out-of-car traffic accidents are the most frequent etiologies for trauma, similar to our patient group (21). Yousefzadeh Chabok et al. (20) studied 588 patients aged 0-14 years in Iran, and the most common trauma etiologies were traffic accidents at a rate of 42.2% and falls at a rate of 39.8%. In the study conducted by Korkmaz et al. (22), it was determined that traffic accidents (50.4%) and falls (18.3%) were more frequent, followed by sharp object injuries (10.9%).

Tambay et al. (1) reported the mean hospital stay as 5.54±6.42 days and the longest hospital stay as 50 days. In another study, the length of PICU stay was 5.8±6.4 (1-34) days and the length of hospital stay was 5.8±7.2 (2-50) days (19). In our study, the mean length of hospital stay was 11.8±8.2 days, the longest length of hospital stay was 30 days, and the mean PICU stay was 4.4±2.9 days. Since ours is a tertiary healthcare institution, better intensive care services in our unit, early diagnosis and treatment of complications, such as possible organ failure and sepsis, increased survival and enable patients to receive longer treatment. The median length of stay in PICU was four (1-13) days, while the median length of hospital stay was eight (2-30) days in our study. Simon et al. (23) reported the length of hospitalization between one and 72 days, with a mean of 9.7±13.1 and a median of four days. In the study of Atike Ongun and Dursun (24), the median duration of PICU stay was four (1-22) days, and the median duration of hospitalization was 10.5 (1-96) days, similar to our study.

Thirty to fifty percent of trauma-related deaths occur at the accident site, and 30% occur within h or days after the accident, usually in the first h. Mortality rates can be reduced by rapid transport to a suitable hospital, rapid evaluation and resuscitation, and recognition of patients requiring surgical intervention. In addition, managing trauma patients in the emergency and PICU and a multidisciplinary approach are important to reduce mortality and morbidity (25,26). The fact that the 49 patients included in our study did not die is probably because the deaths occurred at the time of the accident while reaching the accident site or in the emergency room. In addition, eight patients with GCS scores below 8 were extubated during their follow-up in PICU and were transferred to the clinics where their follow-up will continue without any sequelae.

MV was needed in 18.4% of the patients we followed up in our PICU due to trauma. The indication for MV was a low GCS in five (10.2%) patients, hemorrhagic shock in two (4.1%) patients, and surgery in two (4.1%) patients. In a study involving a larger patient population, the MV rate of the

patients was reported as 12.2%, with similar characteristics (27). The median follow-up period of our patients on the mechanical ventilator was 48 h. Atike Ongun and Dursun (24), on the other hand, found the median follow-up period on a mechanical ventilator as three days.

Surgical intervention was performed in 51% of our patients. Tambay et al. (1) reported that 43.3% of their patients had surgery. In our study, blood transfusion was administered to 18 (36.7%) patients. In their study, Anıl et al. (27) evaluated blunt high-energy trauma patients and reported a blood transfusion rate of 7%. The higher rate in our study may be explained by the inclusion of penetrating injuries and the need for blood transfusion more frequently in such injuries.

One of the best-known scoring systems is GCS. It has been widely used in triage scoring and for predicting mortality. Admission GCS has been found useful in predicting injury severity and the motor component is the most reliable and strongest predictor. In our country, Atike Ongun and Dursun (24) evaluated GCS in relation to traumatic brain injury, and 35.2% of the included patients had mild, 17.7% had moderate, and 47.7% had severe traumatic brain injury. In our study, 16.3% of patients had GCS <8 and had a severe traumatic brain injury. In the same study, when the lengths of PICU and hospital stays were compared according to the GCS of the patients, the mean PICU stay was 7.33±5.78 days in patients with severe traumatic brain injury, and the median length of hospital stay was 16.5 (1-96) days (24). On the other hand, we found the mean PICU stay as 7.00±4.00 days and the median length of hospital stay as 15 (6-30) days in patients with severe traumatic brain injury. In our study, when the lengths of PICU and hospital stays were compared between the patients with severe and mild traumatic brain injury, the mean PICU stay was 3.66±2.45 days in patients with mild traumatic brain injury, and a statistically significant difference was found between the lengths of PICU stay in these two groups.

Head trauma is the most common form of pediatric trauma and is the most common cause of trauma-related mortality and morbidity (28). Mayer et al. (25) reported head injuries as the most common (78.8%) type of injury in the pediatric population. In their study conducted in Tanzania in 2013, Simon et al. (23) found that head and neck injuries were the most common form of trauma in children. In a study conducted by Doğan et al. (29) in our country, in which 1293 pediatric trauma patients aged 0-16 years were examined, the most common injury sites were head and neck (41.9%) and extremities (33.4%). In our study, 73.5% of the patients had head trauma. Extremity (30.6%) and thoracic (26.5%) injuries were the second and third most common injuries. In our study, 73.5% of the patients had head trauma and intracranial pathologies detected on their cranial tomography were subdural hemorrhage in 22.4%, epidural hemorrhage in 16.3%, cerebral edema in 16.3%, and a parenchymal hemorrhage in 10.2% of the patients. In the study of Atike Ongun and Dursun (24), 28.4% of the patients had a subarachnoid hemorrhage, 14.8% had a subdural hemorrhage, 12.6% had an epidural hemorrhage, and 10.3% had a parenchymal hemorrhage. Unlike our study, Atike Ongun and Dursun (24) detected brain edema in 48.9% of their patients. All of the patients (73.5%) in our study, who were followed up for head trauma, had hyperosmolar therapy for high intracranial pressure. Hypertonic saline was the agent chosen in the first step of hyperosmolar treatment. Ten (27.7%) patients had mannitol in addition to hypertonic saline. In our study, none of the patients were administered mannitol alone. Atike Ongun and Dursun (24) reported that 67% of the patients followed in their pediatric ICU due to traumatic brain injury were treated for high intracranial pressure, 10.2% of them were treated with mannitol alone, 14.8% were treated with hypertonic saline alone, and the remaining patients were administered both hyperosmolar agents.

The pediatric trauma scores is used to assess the severity and extent of injury accurately (30). Using the pediatric trauma score, Simon et al. (23) determined the severity of the injury as 0-5 for severe injury, 6-8 for moderate injury, and 9-12 for mild injury. Most of the patients had a mild injury; 40% and 3.3% of the patients had moderate and severe injuries, respectively (23). In our study, 30.6% of the patients had PTS >8 and had trauma caused by minor injuries. The remaining 69.4% had PTS ≤8 and severe trauma. This score is a physiological scoring system developed especially for the triage of pediatric trauma patients, and we suppose that the high rate of severe trauma patients in our study is because our clinic is a tertiary center. Anıl et al. (27) reported that patients with PTS ≤8 had a longer hospital stay and longer follow-up in the emergency department. In our study, no significant difference was found between the lengths of hospital and PICU stay according to the PTS of our patients. We explain this with the small number of patients included in our study.

The limitations of our study are the lack of examining the factors affecting mortality in critically ill children followed up due to trauma, due to the small number of cases followed

in the PICU due to trauma in the specified period and the absence of any mortality.

Conclusion

Pediatric patients are vulnerable to trauma due to their different anatomical and physiological characteristics than adults; therefore, the prevention of trauma should be aimed first. It is very important to identify critically ill children with appropriate triage and scoring systems in case of trauma and transport them to the centers that can provide appropriate treatment as soon as possible and monitor them by making the necessary interventions in a timely manner. As a result, the main goal is to reduce mortality and morbidity. In our study, the effects of vital signs and trauma scores on morbidity and length of stay in PICU are evident in pediatric trauma patients. The importance of treatment and follow-up of appropriate patients in experienced centers has been demonstrated.

Ethics

Ethics Committee Approval: Ethical approval to conduct this study was obtained from the Non-Invasive Ethics Committee of the Faculty of Medicine of Çukurova University (decision no: 30, date: 07.12.2018).

Informed Consent: The data were recorded after obtaining written informed consent from the families of the patients included in the study.

Authorship Contributions

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

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ORIGINAL RESEARCH / *ÖZGÜN ARAŞTIRMA*

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Secondary Infection and Co-infection in COVID-19 Patients Receiving Tocilizumab

Tocilizumab Alan COVİD-19 Hastalarında Sekonder Enfeksiyon ve Ko-enfeksiyon

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ABSTRACT *Objective:* Tocilizumab (TCZ) is a recombinant humanized anti-interleukin-6 receptor monoclonal antibody that is beneficial in critically ill coronavirus disease-2019 (COVID-19) patients. However, the clinical efficacy and safety of immunosuppressants (including TCZ, sarilumab and anakinra) in COVID-19 patients are not yet known. These treatments may predispose patients to infection. The aim of this study was to find any connection between the use of TCZ and increased secondary bacterial infections.
Materials and Methods: In this study, we conducted retrospective analyses of secondary bacterial infections in COVID-19 patients in the intensive care unit (ICU). This study included patients with laboratory-confirmed COVID-19 infection or clinically and radiologically confirmed COVID-19 infections who were admitted to the university hospital adult ICUs between March 2020 and January 2022. Demographic data, recent exposure and travel history, clinical symptoms or signs, laboratory findings, and comorbidities were recorded. Microbial cultures from tracheal aspirates, blood, and urine were obtained at admission and throughout the hospital stay. The patients who received TCZ treatment noted and analyzed for seconder infections. Blood cultures were taken at least 48 hours after the first dose of TCZ.
Results: We found that 80 patients (%37) had positive culture samples at admission, and most of these cases were admitted to the ICU from various hospital wards. The analyzed data showed that the TCZ group had a higher incidence of positive culture samples (75% vs. 35%, p=0.0001). The results showed that culture of TCZ taken patients had more incidence with methicillin resistance *Staphylococcus aureus*, *Klebsiella* spp., and *Acinetobacter* spp. (p=0.0001). Infection and mortality rates were much higher than those in the usual care group.
Conclusion: Secondary infections and sepsis are major risk factors for mortality. The pathogens detected were drug resistant and had a lower chance of treatment. The benefit of TCZ treatment was lost in these patients because of secondary infections. Future studies are needed to help determine the risks of TCZ treatments.
Keywords: Seconder infection, COVID-19, tocilizumab

ÖZ *Amaç:* Tocilizumab (TCZ), kritik durumdaki koronavirüs hastalığı-2019 (COVİD-19) hastalarında fayda sağlayan, rekombinant bir anti-interlökin-6 reseptörü monoklonal antikordur. Bununla birlikte, COVİD-19 hastalarında immünosüpresan tedavilerin (TCZ, sarilumab ve anakinra dahil) klinik etkinliği ve güvenliği henüz bilinmemektedir. Bu tedaviler hastaları enfeksiyona yatkın hale getirebilir. Bu çalışmanın amacı, TCZ kullanımı ile artmış sekonder bakteriyel enfeksiyonlar arasında herhangi bir bağlantı bulmaktır.
Gereç ve Yöntem: Bu çalışmada yoğun bakım ünitesindeki (YBÜ) COVİD-19 hastalarında sekonder bakteriyel enfeksiyonların retrospektif analizlerini yaptık. Bu çalışmaya Mart 2020 ile Ocak 2022 tarihleri arasında üniversite hastanesinin yetişkin YBÜ'lerine kabul edilen laboratuvarca doğrulanmış COVİD-19 enfeksiyonu veya klinik ve radyolojik olarak doğrulanmış COVİD-19 enfeksiyonu olan hastalar dahil edilmiştir. Demografik veriler, yakın zamandaki maruziyet ve seyahat öyküsü, klinik semptomlar veya bulgular, laboratuvar bulguları ve eşlik eden hastalıklar kaydedildi. Trakeal aspiratlardan, kan ve idrardan mikrobiyal kültürler, hastaneye yatışta ve hastanede kaldıkları süre boyunca alındı. TCZ tedavisi alan hastalar sekonder enfeksiyonları not etmiş ve analiz etmişlerdir. Kan kültürleri ilk TCZ dozundan en az 48 saat sonra alınmıştır.

Bulgular: Seksen hastada (%37) başvuru sırasında kültür örneğinin pozitif olduğunu ve bu olguların çoğunun çeşitli hastane servislerinden YBÜ'ye kabul edildiğini saptadık. Analiz edilen veriler, TCZ grubunun pozitif kültür örnekleri insidansının daha yüksek olduğunu gösterdi (%75'e karşı %35, p=0,0001). Sonuçlar, TCZ kültürü alan hastalarda metisilin direnci insidansının daha yüksek olduğunu göstermiştir. *Staphylococcus aureus*, *Klebsiella* spp. ve *Acinetobacter* spp. (p=0,0001). Enfeksiyon oranı ve ölüm oranı normal bakım grubundan çok daha yüksekti.
Sonuç: Sekonder enfeksiyonlar ve sepsis mortalite için önemli bir risktir. Tespit edilen patojenler ilaca dirençliydi ve tedavi şansı daha düşüktü. Bu hastalarda sekonder enfeksiyonlar nedeniyle TCZ tedavisinin yararı kaybolmuştur. TCZ tedavilerinin risklerini belirlemeye yardımcı olmak için gelecekteki çalışmalara ihtiyaç vardır.
Anahtar Kelimeler: Sekonder enfeksiyon, COVİD-19, tocilizumab

Introduction

Most of the coronavirus disease-2019 (COVID-19) patients are asymptomatic or have symptoms that don't need hospitalization. However, there are patients who develop a respiratory failure requiring oxygen support and hospital care. Many of them need intensive care unit (ICU) admission and ventilator support (1). In these patients, COVID has a progressive clinical characteristic. The disease usually begins as an upper respiratory tract infection. Following days, patients have rapid deterioration and increased oxygen support. This results acute respiratory distress syndrome (ARDS), multi-organ failure and death (2).

The pathogenesis of COVID-19 is thought a dysregulated inflammatory response causing clinical manifestations in patients (3). This systemic response includes massive releasing of cytokines such as interleukin (IL)-1, IL-6 (4). This process causes alveolar damage and microvascular thrombosis (5). Treatment of COVID-19 focuses on stopping hyperinflamation response using corticosteroids and immune suppressive agents.

Tocilizumab (TCZ) is a recombinant humanized anti-IL-6 receptor monoclonal antibody that inhibits the binding of IL-6 to both membrane and soluble IL-6 receptors, blocking IL-6 signaling and reducing inflammation. The drug is used in rheumatoid arthritis, juvenile inflammatory arthritis and refractory giant cell arteritis (6). TCZ is also approved for systemic inflammatory response caused by the massive release of proinflammatory cytokines (7,8). TCZ was tested in many COVID-19 cases due to these characteristics and shown that many laboratory parameters improved such as C-reactive protein, lactate dehydrogenase, ferritin and total leukocyte count. TCZ usage in severe COVID-19 patients causes less complications, decreased duration of hospitalization, decreased needs for ICU admission (9).

Secondary infections are common in viral respiratory diseases. There are studies that shows secondary bacterial infection (SBI) is seen 5-15% of patients with COVID-19. According to reports, 50% of COVID-19 deaths had history of SBIs. SBIs have a higher risk of mortality (10). Using immune suppressive treatment makes patients proned to SBI. In most cases, benefit of avoiding pulmonary fibrosis due to COVID infection more beneficial then avoiding SBI.

In this study, we conducted a retrospective analysis of SBIs in COVID-19 patients at ICU. The aim of this study is to find any connection between usage of TCZ and increased SBI in these patients. This connection may lead better clinical follow-up and making health providers aware of SBI risk.

Materials and Methods

The permission for this retrospective study had taken from Non-invasive Clinical Research Ethics Committee of Pamukkale University (no: E-60116787-020-14359, date: 02.02.2021).

This research involved individuals who were admitted to the adult ICUs at the university hospital between March 2020 and January 2022, with confirmed cases of COVID-19 either through laboratory tests or clinical and radiological examinations. COVID-19 diagnosis relied on either a positive outcome from a reverse-transcriptase–polymerase-chain reaction test or antibody Rapid Test using samples collected from nasopharyngeal swabs or endotracheal aspirates. Patient information was retrieved from electronic records stored in the hospital's computer system.

Data Collection

We gathered information on demographics, recent exposure, travel history, clinical symptoms, laboratory results, and existing health conditions. Additionally, we calculated and documented scores for acute physiology and chronic health evaluation-II and sequential organ failure assessment. Parameters related to invasive mechanical ventilation were also noted. Radiological evaluations, including chest X-rays or computed tomography scans, were conducted upon admission and as necessary. We recorded arterial partial

pressure of oxygen (PaO_2), PaO_2/FiO_2 ratio, and occurrences of ARDS. Sepsis and septic shock were defined and treated according to established guidelines and recommendations from the Turkey Ministry of Health for managing COVID-19 patients (11,12). Microbial cultures from tracheal aspirates, blood, and urine were obtained at admission and throughout the hospitalization period. The patients evaluated with infection diseases departments and rheumatology departments for TCZ treatment. The patients who took TCZ treatment had noted and analyzed for seconder infections. The blood cultures had taken at least 48 hours after first dose of TCZ. The patients discharge status (dead, alive), and length of stay in the ICU were also recorded.

Statistical Analysis

All statistical analyses were performed using SPSS 25.0 (IBM SPSS Statistics 25 software (Armonk, NY: IBM Corp.). Continuous variables were defined by the mean ± standard deviation and categorical variables were defined by number and percent. Difference between categorical variables were analyzed with chi-square analysis. Statistical significance was determined as $p<0.05$.

Results

Two hundred and sixteen patients admitted to ICU with laboratory confirmed COVID-19 infection between March 2020 and January 2022.

66.7% of the patients were male. Mean age was 65.93±14.45 years. 49.1% of the patients admitted to ICU from emergency service and the others were from COVID-19 wards and other wards. One or more comorbidities was found in 192 patients. Twenty-four patients had no comorbidity. Three hundred thirty eight comorbidities had detected in these patients. Hypertension was the most common comorbidity in these patients (44.4%). Diabetes mellitus (38%) and oncological diseases (17.6%) followed hypertension (Table 1). The infection parameters at admission are shown at Table 1.

Sixty patients were intubated at beginning of admission (27.7%). Forty patients were intubated in course of admission. One hundred and sixteen patients were followed with high-flow nasal oxygen (HFNO) and non-invasive mechanic ventilation (NIMV) (53.7%). HFNO and NIMV administered alternately. Sixteen patient who received TCZ were intubated which only one of them survived and discharged.

At the admission, empiric antibiotics were started by infection diseases department according to laboratory and clinical findings. Thirty-three patients didn't receive any empiric treatment. Tigecycline, piperacillin-tazobactam and ceftriaxone were the most chosen options in treatment. The microbial samples of patients had taken at admission. Eighty patients had positive culture. 94% of these cultures were blood samples. Most common pathogens were coagulase negative *staphylococcus*, methicillin resistant *Staphylococcus aureus* and *Enterococcus* spp. After positive culture samples, empiric treatment had changed according to antimicrobial resistance testing in 28 patients (13%). The microbiological findings and treatments at admission is shown at Table 2.

Patients with macrophage activation syndrome who have no or little response to glucocorticoids had treated with TCZ (humanized monoclonal antibody against the IL-6 receptor). The dosage used for TCZ is 8 mg/kg (patients ≥30 kg) or 12 mg/kg (patients <30 kg) as a single dose (maximum: 800 mg/dose). TCZ treatment was decided with the cooperation of infection diseases department and rheumatology department. Twenty four of 216 patients has taken TCZ treatment with approvement of Turkish Health Ministry.

Table 1. Demographics and clinical characteristics of the patients

Age (mean ± SD)	65.93±14.45
Sex (M/F)	144 (66.7%)/72 (33.3%)
SOFA score (mean ± SD)	2.6±1.32
Admission service (emergency/other wards)	106 (49.1%)/110 (50.9%)
Length of ICU stay (day) (mean ± SD)	11.17±9.77
Exitus	94 (43.5%)
Comorbidities	
Hypertension	96 (44.4%)
Diabetes mellitus	82 (38%)
Oncological diseases	38 (17.6%)
Cardiac failure	20 (9.3%)
Coronary artery disease	19 (8.8%)
Hematological disease	13 (6%)
Laboratory findings at admission	
Procalcitonin (mean ± SD)	2.9±10.51
C-reactive protein (mean ± SD)	123.83±86
Ferritin (mean ± SD)	1023.33±1335.09

SD: Standard deviation, ICU: intensive care unit, SOFA: sequential organ failure assessment

Eighteen of 24 patients who taken TCZ treatment, had worsened clinical conditions and increased level of infection markers. Culture samples were taken. Methicillin resistance *S. aureus* (n=11) *Klebsiella* spp. (n=6) and *Acinetobacter* spp. (n=6) were most common in these patients.

Almost all of the patients needed to repeat cultures due to clinical and laboratory worsening. Fifty seven of patients who didn't receive anti-cytokine treatment had positive result in their cultures. The pathogens were methicillin resistance *S. aureus* (n=28) *Klebsiella* spp. (n=10) and *Acinetobacter* spp. (n=10), *Enterococcus* spp. (n=8), *Pseudomonas* spp. (n=6), *Candida* spp. (n=3).

The difference of clinical and microbiological characteristics is shown at Table 3. The results have compared between patients who received TCZ and who didn't. There was no statistical difference in cultures at admission. There was an increased positive rating in cultures that were utilized after clinical worsening (p=0.0001). The results showed that culture of TCZ taken patients had more incidence with methicillin resistance *S. aureus*, *Klebsiella* spp. and *Acinetobacter* spp. (p=0.0001). Death was more common in TCZ group. There was no difference in admission service.

Table 2. Microbiological findings at admission and antimicrobial treatment characteristics

Positive culture samples (positive/negative) (total n=216)	80 (37%)/136 (63%)
Pathogens at culture positive patients	
Coagulase negative *Staphylococcus*	35 (43.8%)
Methicillin resistant *Staphylococcus aureus*	33 (41.3%)
Enterococcus spp.	7 (8.8%)
Klebsiella spp.	3 (3.8%)
Corynebacterium spp.	3 (3.8%)
Candida spp.	2 (2.5%)
Acinetobacter spp.	1 (1.3%)
Pseudomonas spp.	1 (1.3%)
Other pathogens	5 (6.3%)
Positive sample location	
Blood	78 (97.5%)
Tracheal aspiration	4 (5%)
Urine	1 (1.3%)
Empiric treatment at admission	
Tigecycline	66 (12%)
Piperacillin-tazobactam	50 (9.1%)
Ceftriaxone	42 (7.6%)
Meropenem	17 (3.1%)
Teicoplanin	14 (2.5%)
No antibiotics	33 (6%)

Discussion

After COVID-10 outbreak, many immunocompromised patients were admitted to ICUs. There has been an increased need of ICUs. Many of these patients had SBIs and ICU specialists fought with sepsis and co-infection beside COVID-19. There are many studies, reviews and case report about secondary infections in COVID. The mechanism of increased SBI thought to be the failure of the adaptive immune reaction toward viral infection against bacterial infection (13).

In one study, researchers utilized the data of 1,495 cases and 6.8% of these cases had secondary bloodstream infections. The pathogens in these cases were mostly Gram-negative bacteria such as *Acinetobacter baumanii* (35.8%) and *Klebsiella pneumoniae* (%30.8) (10). In a study, Zhang et al. (14) analyzed 148,221 patients with severe acute respiratory syndrome coronavirus-2 pneumonia were admitted to Zhongnan Hospital, Wuhan, China. 25.8% (57/221) patients had co-infections, 29.8% (17/57) of these cases were co-infected with bacteria (14).

In our study, secondary infection rate was higher like these studies. Eighty patients (37%) had positive culture sample at admission and most of these cases was admitted to ICU from various hospital wards. The reason for high rate of positive cultures at admission is thought to be long duration of hospital admission. Most patients had come to ICU after being in infection wards for days. Most of the positive cultures had the pathogens such as coagulase negative *Staphylococcus*, methicillin resistant *S. aureus* and *Enterococcus* spp. Most of our patients had worsened clinically (fever, decreased consciousness) and had cultures repeated. Seventy five of these patients (35%) had SBI with positive cultures. These results are consistent with other studies.

There are limited studies about secondary infections in patients who take anti-cytokine, anti-inflammatory treatment. It is known that these treatments cause predisposition with secondary infections. TCZ is most used immunomodulatory treatment in our ICU. These patients evaluated about infections, immunosuppressive conditions, tuberculosis, human immunodeficiency virus. After this evaluation, TCZ admitted.

Table 3. Comparison of clinical and microbiological characteristics				
		Tocilizumab group	**Non-tocilizumab group**	**p-value**
Admission service	Emergency	12 (50%)	94 (48.96%)	0.923
	Wards	12 (50%)	98 (51.04%)	
Outcome	Discharge	9 (37.5%)	113 (58.85%)	0.047*
	Death	15 (62.5%)	79 (41.15%)	
Cultures	Negative	6 (25%)	153 (79.69%)	0.0001*
	Positive	18 (75%)	39 (20.31%)	
Coagulase negative *Staphylococcus*	Negative	209 (96.76%)	187 (97.4%)	0.176
	Positive	7 (3.24%)	5 (2.6%)	
Methicillin resistance *S. aureus*	Negative	13 (54.17%)	175 (91.15%)	0.0001*
	Positive	11 (45.83%)	17 (8.85%)	
Corynebacterium	Negative	22 (91.67%)	187 (97.4%)	0.176
	Positive	2 (8.33%)	5 (2.6%)	
***Klebsiella* spp.**	Negative	18 (75%)	188 (97.92%)	0.0001*
	Positive	6 (25%)	4 (2.08%)	
***Acinetobacter* spp.**	Negative	18 (75%)	188 (97.92%)	0.0001*
	Positive	6 (25%)	4 (2.08%)	
***Enterococcus* spp.**	Negative	20 (83.33%)	188 (97.92%)	0.006*
	Positive	4 (16.67%)	4 (2.08%)	
***Pseudomonas* spp.**	Negative	22 (91.67%)	188 (97.92%)	0.135
	Positive	2 (8.33%)	4 (2.08%)	
***Candida* spp.**	Negative	23 (95.83%)	190 (98.96%)	0.299
	Positive	1 (4.17%)	2 (1.04%)	
*p<0.05 statistically significant; chi-square test				

The analyzed data showed that TCZ group has a higher incidence of positive culture samples (75% vs. 35%, p=0.0001). Methicillin resistance *S. aureus*, *Klebsiella* spp. and *Acinetobacter* spp. had increased incidence in TCZ group's cultures against usual care group's (respectively, 45-8%, 25-2% and 24-2%; p=0.0001 for each).

Giacobbe et al. (15), studied secondary bloodstream infections among critically ill patients with COVID-19. They found the cumulative risk of SBI was 25% after 15 days and 50% after 30 days of ICU stay. The study also showed that TCZ was associated with an increased risk of secondary infection (p=0.003) (15). Our data is consistent with these ratios.

RECOVERY study showed that the patients receiving TCZ has higher chance for discharge at 28 day of admission and lower rates for mortality and MV needs. RECOVERY study didn't analyze infection situation in patients (6).

In one study, receiving TCZ was associated with a higher risk of secondary bacterial (48.1% vs. 28.1%; p=0.029 infections and higher mortality (35.2% vs. 19.3%; p=0.020) (16). Our mortality rate is higher in TCZ group consistent with higher positive culture rates (62% vs. 41%, p=0.004). Our results are similar with this study.

In our study, infection rate and mortality rate were much higher than usual care group. Secondary infections and sepsis are a major risk for mortality. The pathogens detected were drug-resistance and had a lower chance of treatment. The benefit of TCZ treatment lost in these patients because of secondary infections.

Another reason for higher mortality is thought to need of MV. Our data showed that 66% of the patients who received TCZ were intubated. Only one of them survived and discharged while other patients were lost. MV is a major risk for both infection and mortality. This is also a controversial point. TCZ prones to infection but TCZ is given to patients

who are in severe condition like need of MV. Further studies are needed in more specific groups on this subject.

In an ongoing study, the mortality rate in TCZ-treated patients was 24.1%. There was an association between mortality and seniority, the need for mechanic support, the presence of critical COVID-19 and severe lung parenchymal disease. The same study found that invasive MV support, immunosuppression and extended lung injury may increase the risk for SBIs (17).

This study has several limitations: small sample size, retrospective nature (selection and information biases) and single-center nature (contamination and flora of the same ICU).

Conclusion

The incidence rate of SBI is higher in critically ill patients in COVID-19. TCZ is a promising treatment for COVID patients who has overactive immune system due to cytokines. In response to this, TCZ can create predisposition to infection which causes sepsis and mortality. These risks cast a suspicion of benefit in TCZ treatment. These findings should be confirmed with a larger randomized clinical trial with longer follow-up. Future studies are needed to help determine about risks of TCZ treatments.

Ethics

Ethics Committee Approval: The permission for this retrospective study had taken from Non-invasive Clinical Research Ethics Committee of Pamukkale University (no: E-60116787-020-14359, date: 02.02.2021).

Informed Consent: Retrospective study.

Authorship Contributions

Concept: Ç.E., H.S., Design: Ç.E., H.S., Data Collection and Process: Ç.E., M.K., B.Ş., Analysis or Interpretation: Ç.E., M.K., H.S., Literature Search: Ç.E., M.K., Writing: Ç.E.

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ORIGINAL RESEARCH / *ÖZGÜN ARAŞTIRMA*

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Predicting Mechanical Ventilation, Intensive Care Unit Admission, and Mortality in COVID-19 Patients: Comparison of Seven Different Scoring Systems

COVİD-19 Hastalarında Mekanik Ventilasyon, Yoğun Bakım Ünitesine Yatış ve Mortalite Tahmini: Yedi Farklı Skorlama Sisteminin Karşılaştırılması

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ABSTRACT *Objective:* In this study, we investigated whether scoring systems determine coronavirus disease-2019 (COVID-19) severity.
Materials and Methods: COVID-19 patients hospitalized between 01.09.2020 and 31.04.2021 were retrospectively assessed. The national early warning score (NEWS), modified early warning score, rapid emergency medicine score, quick sequential organ failure assessment score (q-SOFA), CURB-65, MuLBSTA, and ISARIC-4C scores on admission day were calculated. Scoring systems' ability to predict mechanical ventilation (MV) need, intensive care unit (ICU) admission, and 30-day mortality were assessed.
Results: A total of 292 patients were included; 137 (46.9%) were female, and the mean age was 62.5±15.4 years. 69 (23.6%) patients required ICU admission, 45 (15.4%) needed MV, and 49 (16.8%) died within 30 days. No relationship was found between q-SOFA and MV need (p=0.167), but a statistically significant relationship was found between other scoring systems and MV need, ICU admission, and 30-day mortality (p<0.05). ISARIC-4C (optimal cut-off >5.5) and NEWS (optimal cut-off >3.5) had the highest area under the curve in receiver operating characteristic curve analyses, whereas q-SOFA had the lowest.
Conclusion: The severity of COVID-19 could be estimated by using these scoring systems, especially ISARIC-4C and NEWS, at the first admission. Thus, mortality and morbidity would be reduced by making the necessary interventions earlier.
Keywords: COVID-19, ISARIC-4C, mortality, NEWS, scoring systems

ÖZ *Amaç:* Çalışmada skorlama sistemlerinin koronavirüs hastalığı-2019 (COVİD-19) şiddetini belirleyip belirlemediğini araştırdık.
Gereç ve Yöntem: 01.09.2020 ve 31.04.2021 tarihleri arasında yatan COVİD-19 hastaları retrospektif olarak incelendi. Başvuru günündeki ulusal erken uyarı skoru (NEWS), modifiye erken uyarı skoru, hızlı acil tıp skoru, tekrarlanan-sepsis ilişkili organ yetmezliği hızlı değerlendirmesi skoru (q-SOFA), CURB-65, MuLBSTA ve ISARIC 4C skorları hesaplandı. Skorlama sistemlerinin mekanik ventilasyon (MV) ihtiyacını, yoğun bakım ünitesine (YBÜ) yatışını ve 30 günlük mortaliteyi öngörme kapasitesi incelendi.
Bulgular: Toplam 292 hasta dahil edildi, 137'si (%46,9) kadındı, yaş ortalaması 62,5±15,4 yıldı. Hastaların 69'unun (%23,6) YBÜ yatışı gerekti, 45 (%15,4) hastada MV'ye ihtiyaç duyuldu ve 49 (%16,8) hasta 30 gün içinde öldü. Q-SOFA ile MV ihtiyacı arasında bir ilişki bulunmadı (p=0,167) ancak diğer tüm skorlama sistemleri ile MV ihtiyacı, YBÜ yatış ve 30 günlük mortalite arasında istatistiksel olarak anlamlı bir ilişki bulundu (p<0,05). Alıcı işletim karakteristik eğrisi analizlerinde eğri altında kalan alanı en yüksek olanlar ISARIC-4C (optimal cut-off >5,5) ve NEWS (optimal cut-off >3,5) iken en düşük q-SOFA idi.
Sonuç: İlk başvurularında ISARIC-4C ve NEWS başta olmak üzere mevcut skorlama sistemleri kullanılarak COVİD-19'un şiddeti tahmin edilebilecektir. Böylece gerekli müdahalelerin daha erken yapılarak mortalite ve morbiditenin azaltılabilecektir.
Anahtar Kelimeler: COVİD-19, ISARIC-4C, mortalite, NEWS, skorlama sistemleri

Introduction

The coronavirus disease-2019 (COVID-19) has been diagnosed in over 750 million people, and more than 6.8 million people have died due to this disease to date (1). The disease can be asymptomatic or mild with a flu-like syndrome. However, in some cases, it progresses more severely, and pneumonia and acute respiratory distress syndrome (ARDS) can be seen (2). In severe cases, the patient may require mechanical ventilation, admission to the intensive care unit (ICU), and even die. Many studies have examined the correlation between the severity of COVID-19 and markers such as blood type (3), blood inflammation and coagulation biomarkers, and viral load (4). In addition, it is reported that various scoring systems can predict worsening and mortality in COVID-19 patients (5-10). We aimed to investigate whether the scoring systems that can be easily calculated during the emergency admissions of COVID-19 patients determine the requirement for mechanical ventilation, ICU admission, and mortality that may occur in the follow-up of the patients.

Materials and Methods

The research is a single-center, retrospective descriptive study. Patients aged 18 years and over and hospitalized in the infectious diseases clinic and pulmonary diseases clinic with a diagnosis of COVID-19 confirmed by positive severe acute respiratory syndrome-coronavirus-2 polymerase chain reaction between 01.09.2020 and 31.04.2021 in a secondary care hospital were included in our study. The patients' epidemiological data, chronic diseases, clinical signs, laboratory values detected at the emergency admission, and outcomes were evaluated retrospectively from the patient files. National early warning score (NEWS), modified early warning score (MEWS), rapid emergency medicine score (REMS), quick sequential organ failure assessment score (q-SOFA), CURB-65, MuLBSTA and ISARIC-4C scores were calculated using MDCalc online calculator (https://www.mdcalc.com) at admissions to the hospital (Table 1). The primary endpoint of the study was 30-day mortality. Secondary endpoints were the need for mechanical ventilation and ICU admission.

Statistical Analysis

The statistics of the study were made with the IBM Statistical Package for the Social Sciences (SPSS) Version 22.0 (Armonk, NY: IBM Corp) program. Analytical tests (Kolmogorov-Smirnov/Shapiro-Wilk) were used to check variables for normal distribution. Descriptive analyses were presented using means (± standard deviation) for the normally distributed variables and medians (minimum-maximum) for the non-normally distributed. The Mann-Whitney U test was used to evaluate the association between scoring systems and the endpoints of the study since none of the scoring systems were normally distributed. The capacity of scoring systems in predicting the need for mechanical ventilation, ICU admission, and 30-day mortality were analyzed using receiver operating characteristic (ROC) curve analysis. Significant cut-off values were dedicated, and the sensitivity and specificity values were presented. A power analysis was conducted with a power of 95%, a margin of error of 0.05, and an effect size of 0.8, using the G*Power 3.1.9.2 program.

Table 1. Scoring systems evaluated in the study and the parameters they contain

Scoring system	Parameters
NEWS	Respiratory rate, oxygen saturation, any supplemental oxygen temperature, systolic blood pressure, heart rate, AVPU†
MEWS	Systolic blood pressure, heart rate, respiratory rate, temperature, AVPU†
REMS	Age, mean arterial pressure, heart rate, respiratory rate, peripheral oxygen saturation, Glasgow coma scale
q-SOFA	Glasgow coma scale, respiratory rate, systolic blood pressure
CURB-65	Confusion, BUN, respiratory rate, systolic or diastolic blood pressure, age
MuLBSTA	Multilobe infiltrate, absolute lymphocyte count, bacterial coinfection smoking history, history of hyper-tension, age
ISARIC-4C	Age, male sex, number of comorbidities‡, respiratory rate peripheral oxygen saturation on room air, Glasgow coma scale Urea, C-reactive protein

NEWS: National early warning score, MEWS: modified early warning score, REMS: rapid emergency medicine score, q-SOFA: quick sequential organ failure assessment score, †AVPU; A: Alert, V: Response to voice, P: Response to pain, U: Unresponsive

‡Comorbidities include chronic cardiac disease, chronic respiratory disease (excluding asthma), chronic renal disease (estimated glomerular filtration rate ≤30), mild to severe liver disease, dementia, chronic neurological conditions, connective tissue disease, diabetes mellitus (diet, tablet, or insulin controlled), human immunodeficiency virus or acquired immunodeficiency syndrome, and malignancy

The analysis revealed that a minimum sample size of 108 and 22 participants for groups was required to achieve adequate statistical power. A p-value of less than 0.05 was considered statistically significant.

Ethics

Ethics committee approval of the study was received from the Non-invasive Clinical Research Ethics Committee of Recep Tayyip Erdoğan University Faculty of Medicine on 19/08/2021 with decision number 2021/149. The principles of the Helsinki Declaration were followed in the study.

Results

The data of 445 patients followed up due to COVID-19 within the specified date range were analyzed, and 153 of them did not meet the research criteria due to missing data. Thus, 292 patients were included in the study. The mean age was 62.5±15.4 years, and 137 patients (46.9%) were female.

During the follow-up of the patients, 69 (23.6%) required ICU admission, 45 (15.4%) needed mechanical ventilation, and 49 (16.8%) died within 30 days. The median values of the scoring systems and the distribution of these values according to the outcomes are shown in Table 2. While no statistically significant relationship was found between

Table 2. Distribution of median (minimum-maximum) values of the scoring systems according to the need for mechanical ventilation, intensive care unit admission, and 30-day mortality

	All patients	Mechanical ventilation		p*	Intensive care unit admission		p*	30-day mortality		p*
		No	Yes		No	Yes		No	Yes	
NEWS	3 (0-11)	2 (0-10)	5 (1-11)	<0.001	2 (0-10)	4 (0-11)	<0.001	2 (0-9)	5 (1-11)	<0.001
MEWS	1 (0-5)	1 (0-4)	2 (1-5)	<0.001	1 (0-4)	2 (1-5)	<0.001	1 (0-4)	2 (1-5)	<0.001
REMS	5 (0-14)	4 (0-10)	6 (0-14)	<0.001	4 (0-10)	6 (0-14)	<0.001	4 (0-11)	6 (1-14)	<0.001
q-SOFA	1 (1-3)	1 (1-2)	1 (1-3)	0.167	1 (1-2)	1 (1-3)	0.033	1 (1-2)	1 (1-3)	0.008
CURB-65	1 (0-5)	1 (0-4)	1 (0-5)	0.002	1 (0-4)	1 (0-5)	<0.001	1 (0-3)	2 (0-5)	<0.001
MuLBSTA	9 (0-16)	9 (0-16)	9 (0-16)	0.009	9 (0-16)	9 (0-16)	<0.001	9 (0-16)	9 (7-16)	<0.001
ISARIC-4C	3 (0-17)	2 (0-16)	10 (4-17)	<0.001	2 (0-11)	10 (4-17)	<0.001	2 (0-16)	10 (2-17)	<0.001

*Data with a p-value below 0.05 were considered statistically significant. NEWS: national early warning score, MEWS: modified early warning score, REMS: rapid emergency medicine score, q-SOFA: quick sequential organ failure assessment score

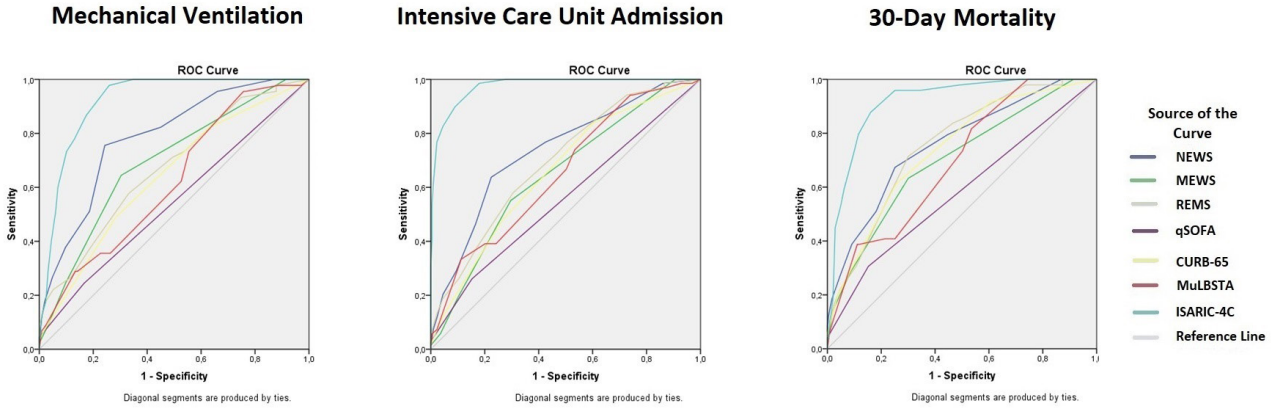

Figure 1. ROC curves of the scoring systems according to the need for mechanical ventilation, intensive care unit admission, and 30-day mortality

NEWS: National early warning score, MEWS: modified early warning score, REMS: rapid emergency medicine score, q-SOFA: quick sequential organ failure assessment score, ROC: receiver operating characteristic

q-SOFA and the need for mechanical ventilation (p=0.167), a statistically significant relationship was found between all scoring systems except this one and the need for mechanical ventilation, ICU admission, and 30-day mortality (Table 2). When the ROC curve was examined for the outcomes, ISARIC-4C (0.919, 0.974, and 0.918, respectively) and NEWS (0.785, 0.735, and 0.759, respectively) scores were found to have the highest area under the curve (AUC), while q-SOFA (0.543, 0.556, and 0.580, respectively) have the lowest (Figure 1, Table 3). The optimal cut-off values determined for outcomes were found to be >5.5 in the ISARIC-4C score and >3.5 in the NEWS. The percentages of sensitivity and specificity according to the determined optimal cut-off values are shown in Table 3.

Table 3. The median values of the areas under the ROC curve (AUC) of the scoring systems according to the need for mechanical ventilation, intensive care admission, and 30-day mortality, and sensitivity, and specificity results according to the optimal cut-off values

	Mechanical ventilation					Intensive care unit admission					30-day mortality				
	AUC (95% CI)*	p†	Cut-off	Sensitivity (%)	Specificity (%)	AUC (95% CI)*	p†	Cut-off	Sensitivity (%)	Specificity (%)	AUC (95% CI)*	p†	Cut-off	Sensitivity (%)	Specificity (%)
NEWS‡	0.785 (0.716-0.854)	<0.001	3.5	75.6	75.7	0.735 (0.667-0.803)	<0.001	3.5	63.8	77.6	0.759 (0.684-0.833)	<0.001	3.5	67.3	74.9
MEWS‡	0.692 (0.610-0.775)	<0.001	1.5	64.4	69.6	0.649 (0.577- 0.721)	<0.001	1.5	55.1	70.4	0.701 (0.619-0.783)	<0.001	1.5	63.3	70
REMS‡	0.670 (0.585- 0.756)	<0.001	5.5	57.8	66.8	0.694 (0.626- 0.763)	<0.001	5.5	58	69.5	0.756 (0.688-0.825)	<0.001	5.5	71.4	70
q-SOFA‡	0.543 (0.447-0.638)	0.360		NA		0.556 (0.476- 0.637)	0.157		NA		0.580 (0.487-0.673)	0.077		NA	
CURB-65	0.639 (0.552-0.727)	0.003	1.5	48.9	71.7	0.657 (0.585- 0.729)	<0.001	1.5	47.8	73.5	0.739 (0.665-0.813)	<0.001	1.5	61.2	74.5
MuLBSTA	0.620 (0.535-0.705)	0.010	8.5	62.2	47.4	0.653 (0.581- 0.725)	<0.001	8.5	66.7	49.8	0.694 (0.620-0.769)	<0.001	8.5	73.5	49.8
ISARIC-4C	0.919 (0.887-0.951)	<0.001	5.5	86.7	82.6	0.974 (0.959- 0.989)	<0.001	5.5	89.9	91.0	0.918 (0.881-0.955)	<0.001	5.5	87.8	84

*Data with a p-value below 0.05 were considered statistically significant. NEWS: National early warning score, MEWS: modified early warning score, REMS: rapid emergency medicine score, q-SOFA: quick sequential organ failure assessment score, AUC: area under the curve, CI: confidence interval, ROC: receiver operating characteristic

Discussion

COVID-19 can be presented with a wide spectrum from asymptomatic to severe disease which may result in death. It is important to be able to predict how the prognosis will progress at the first admission of patients. In our study, the performance of scoring systems, which can be easily calculated during the first admission of COVID-19 patients, to determine the requirement for mechanical ventilation, ICU admission, and 30-day mortality was examined. Especially in patients with ISARIC-4C score >5.5 and NEWS >3.5, COVID-19 disease was found to be more severe, while CURB-65 and MuLBSTA scores had the lowest performance.

During the course of COVID-19, the need for mechanical ventilation with endotracheal intubation may develop

due to ARDS (5). Similar to our study, in determining the requirement for mechanical ventilation in COVID-19 patients, Ocho et al. (6) reported that ISARIC-4C (AUC =0.85) was better than CURB-65 (AUC =0.82) and q-SOFA (AUC =0.67), and in another study (7), NEWS (AUC =0.69) was better than q-SOFA (AUC =0.61). Kuroda et al. (8) found that the ISARIC-4C predicts the composite outcome of the need for mechanical ventilation and mortality better than REMS in COVID-19 patients. Chang et al. (9) reported that the detection of NEWS >7 at the first admission to the hospital can determine the need for mechanical ventilation with 72.3% sensitivity and 92.5% specificity. However, it has been reported that the MuLBSTA score (AUC =0.836) is better than CURB-65 and q-SOFA in determining the need for mechanical ventilation (10). In our study, ISARIC-4C [AUC =0.919, 95% confidence interval (CI) 0.887-0.951] and NEWS (AUC =0.785, 95% CI 0.716-0.854) were the best performing scores in line with the literature in demonstrating the requirement for mechanical ventilation of COVID-19 patients while q-SOFA and MuLBSTA performed poorly.

Severe COVID-19 patients may need to be admitted to the ICU for close monitoring and supportive treatment. Studies are reporting that especially the NEWS score is good at predicting ICU admission (11,12). In a study that compares scoring systems in COVID-19 patients, the NEWS (AUC =0.73) showed the best performance for predicting ICU admission, but good results were not obtained in the q-SOFA, CURB-65, and REMS scores (11). In another study, early warning scores were evaluated and it was reported that the NEWS (AUC =0.783) was more successful in predicting ICU hospitalization within 7 days compared to MEWS, REMS, and q-SOFA scores (12). However, unlike our study, it was reported that CURB-65 (AUC =0.898) was better than ISARIC-4C (AUC =0.797) (13) and MuLBSTA was better than CURB-65 and q-SOFA (10) in predicting ICU admission. In our study, the most successful scores in predicting ICU admission were ISARIC-4C (AUC =0.974, 95% CI 0.959-0.989), NEWS (AUC =0.735, 95% CI 0.667-0.803) and REMS (AUC =0.694, 95% CI 0.626-0.763) while q-SOFA did not show the expected performance.

COVID-19 may have a severe course and be mortal due to reasons such as pneumonia, sepsis, ARDS, and pulmonary thromboembolism (2,14). It is crucial to identify these patients in the early period for the chance to prevent mortality. Similar to our findings, previous research has shown that the ISARIC-4C and NEWS scores are reliable indicators of mortality in COVID-19 patients (7,8,15-17). However, studies are reporting that REMS is better than the q-SOFA, NEWS, MEWS, and CURB-65 scores (11,12), and CURB-65 is better than the ISARIC-4C (13) in the prediction of mortality. Moreover, MEWS, CURB-65, and q-SOFA scores have also been reported to be successful in predicting mortality (18,19). Kalani et al. (20) reported that MuLBSTA (AUC =0.832) and CURB-65 (AUC =0.809) scores performed well in predicting 30-day mortality. In our study, ISARIC-4C (AUC =0.918, 95% CI 0.881-0.955), NEWS (AUC =0.759, 95% CI 0.684-0.833), and REMS (AUC =0.756, 95% CI 0.688-0.825) scores were found to be reliable predictors of 30-day mortality, but the q-SOFA did not show promising results.

Our research has limitations. First of all, it is a retrospective study. Secondly, other factors that may cause the need for mechanical ventilation, ICU admission, and mortality such as co-infections were not investigated.

Conclusion

Especially ISARIC-4C and NEWS scores showed high performance in predicting the requirement for mechanical ventilation, ICU admission, and 30-day mortality, but good results were not obtained in q-SOFA. With the early use of these scoring systems in COVID-19 patients, it will be possible to distinguish patients with a risk of clinical worsening. In this way, it was thought that necessary interventions could be made earlier and a decrease in mortality rate could be achieved.

Ethics

Ethics Committee Approval: Ethics committee approval of the study was received from the Non-invasive Clinical Research Ethics Committee of Recep Tayyip Erdoğan University Faculty of Medicine on 19/08/2021 with decision number 2021/149.

Informed Consent: Retrospective study.

Authorship Contributions

Concept: T.İ., S.M.Ç., K.A., G.Ç.O., S.K., Ö.Y., Design: T.İ., Ö.Y., Data Collection and Process: T.İ., S.M.Ç., K.A., G.Ç.O., S.K., A.Ö., A.T., Analysis or Interpretation: T.İ., S.M.Ç., A.Ö., A.T., Ö.Y., Literature Search: T.İ., K.A., G.Ç.O., S.K., A.Ö., A.T., Writing: T.İ.

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ORIGINAL RESEARCH / *ÖZGÜN ARAŞTIRMA*

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The Effect on the Work Ability of Intensive Care Nurses of Psychological Distress During the COVID-19 Pandemic: Descriptive and Cross-sectional Study

COVİD-19 Pandemi Sürecindeki Psikolojik Sıkıntıların Yoğun Bakım Hemşirelerinin İş Yeterliliklerine Etkisi: Tanımlayıcı ve Kesitsel Çalışma

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ABSTRACT *Objective:* This study aims to determine the effects of psychological distress on the work ability of intensive care nurses during the coronavirus disease-2019 (COVID-19) pandemic in Turkey.
Materials and Methods: This study is descriptive and cross-sectional design. The sample consisted of 233 intensive care nurses. Data were collected via online Google forms with the Participant Information form, the COVID-19-related Psychological Distress scale (PDS), and the Work Ability index (WAI). In the analysis of data, Pearson and Spearman correlation analysis was used along with descriptive statistics.
Results: A statistically significant positive correlation was found between the nurses' length of time working in the profession and their WAI scores (r=0.132, p=0.043), and a negative correlation was found with their COVID-19 PDS scores (r=-0.162, p=0.013). A statistically significant difference was found about WAI total scores in the effect on work ability of the working conditions of the COVID-19 pandemic (p<0.001). A statistically significant positive correlation was found between the WAI total score and the COVID-19 PDS sub-section of doubt (r=0.128, p=0.049).
Conclusion: It was found that the work abilities and COVID-19 psychological distress levels of nurses were medium and there are relationship between them. It is recommended that the many factors affecting work ability and psychological distress be taken under control.
Keywords: Anxiety, COVID-19, work ability, pandemic, psychological distress, doubt, intensive care nurses

ÖZ *Amaç:* Bu çalışmanın amacı Türkiye'de koronavirüs hastalığı-2019 (COVİD-19) pandemi sürecindeki psikolojik sıkıntıların yoğun bakım hemşirelerinin iş yeterliliklerine etkisini belirlemektir.
Gereç ve Yöntem: Bu çalışma tanımlayıcı ve kesitsel tiptedir. Örneklemi 233 yoğun bakım hemşiresi oluşturdu. Veriler, Katılımcı Bilgi formu, COVİD-19 Psikolojik Sıkıntı ölçeği (PSÖ) ve İş Yeterliliği ölçeği (İYÖ) ile Google formlar aracılığıyla online olarak toplandı. Verilerin analizinde tanımlayıcı istatistiklerin yanında Pearson ve Spearman korelasyon analizleri yapıldı.
Bulgular: Hemşirelerin meslekte çalışma süreleri ile İYÖ (r=0,132, p=0,043) puanı arasında pozitif yönde, COVİD-19 PSÖ (r=-0,162, p=0,013) puanı arasında ise negatif yönde istatistiksel olarak anlamlı ilişki olduğu saptandı. COVİD-19 pandemisindeki çalışma koşullarının iş yeterliliğine etkisine İYÖ toplam puanları bakımından istatistiksel olarak anlamlı fark olduğu bulundu (p<0,001). İYÖ toplam puanı ile COVİD-19 PSÖ şüphe (r=0,128, p=0,049) alt boyut puanı arasında pozitif yönde istatistiksel olarak anlamlı ilişki olduğu belirlendi.
Sonuç: Hemşirelerin iş yeterliliklerinin ve COVİD-19 psikolojik sıkıntı düzeylerinin orta düzeyde olduğu ve aralarında ilişki olduğu saptandı. İş yeterliliği ve psikolojik sıkıntıları etkileyen birçok faktörün kontrol altına alınması önerilmektedir.
Anahtar Kelimeler: Anksiyete, COVİD-19, iş yeterliliği, pandemi, psikolojik sıkıntılar, şüphe, yoğun bakım hemşireleri

Introduction

All over the world, whenever there are outbreaks of disease, natural disasters or war, important responsibilities fall to nurses especially (1). One very special branch of nursing is intensive care nursing, and these nurses work in a physically and psychosocially high risk environment (2). At the same time, the intensive care nurse performs complex duties which include critical situations such as facing unforeseen events, rapid decision making under time stress, and dealing with aggressive relatives (3). In addition to these problems, the coronavirus pandemic appeared in China and rapidly spread over the whole world, infecting a very large number of people, resulting in a large number of people in need of intensive care, and intensive care nurses taking a major role in treatment and care. This increased their workload and caused intense stress, leaving them at risk of mental health problems such as exhaustion, depression and anxiety (4,5). Studies have shown that the coronavirus disease-2019 (COVID-19) pandemic has increased the risk of mental disorders such as schizophrenia, anxiety, depression and acute stress disorder in both health workers and the general population, leading to an increase in fear of illness, anger, the misuse of alcohol and tobacco, divorce and suicide (6,7). According to a report by the World Health Organization in 2020, there is not enough nursing workforce in the world to maintain universal health (8); the nursing workforce should remain healthy and not be worn out (9). Particularly during COVID-19, it is necessary to evaluate the difficulties experienced by intensive care nurses-working long hours without a break caring for and treating patients, both putting themselves at risk and living with the fear of infecting their families and friends-their workload, their psychological and mental health, and their work ability levels (2,9).

The concept of work ability, which is frequently used in the field of work health, is an important element in work health services, where greater physical and psychosocial working capacity is needed, and the risk of disabling injury and illness is high (2), and is defined as how a person meets work-related difficulties, or in other words the ability of a worker to cope physically and mentally with difficulties at work (10). This concept is an indicator of how well a person's physical, mental, social and interpersonal abilities match their personal capacities, but also of how well they match their work needs and improvement in their working environment and working conditions, job satisfaction, performance, health, knowledge, skill, attitude and motivation with the necessities of the work they do (10,11). Studies have reported that an intensive care nurse's work ability is affected by factors such as body mass index, age, personal characteristics, physical and mental fatigue, lack of sleep, disappointment, shift working and workload (2,12,13). Inadequate work ability in nurses causes poor quality of life (14), leaving the profession early (15), cardiovascular diseases in obese individuals, an increase in the risk of mental disorders or diseases such as those of the musculo-skeletal system and resulting disability (16). Taking all of these factors into consideration, it is necessary to improve the work ability levels of nurses, because a person whose work ability is high is predicted to be able to continue doing his or her job for longer (17). In a systematic review and meta-analysis study by Romero-Sánchez et al. (9) evaluating the prevalence of the work inadequacy of nurses working in a hospital, it was concluded that in the world in general, approximately one nurse in four working in a hospital had work inadequacy and that there was an imbalance between individual resources and work, and for this reason nurses were at risk of various negative results throughout their working lives.

The literature shows that very little is known about work ability in a group of health care personnel who are very much needed throughout the world (2). At the same time, although there are studies on the work ability of intensive care nurses during the COVID-19 pandemic, no studies were found evaluating their work ability and psychological distress together. Thus, this study was aimed at investigating the effects on the work ability of intensive care nurses of psychological distress during the COVID-19 pandemic. It is thought that the conclusions of the research will make a contribution to the literature.

Research Questions

1. What are the levels of work ability in intensive care nurses?
2. What is the psychological distress on intensive care nurses in the COVID-19 pandemic?
3. Is there a correlation between the psychological distress on intensive care nurses in the COVID-19 pandemic and their work ability levels?

Materials and Methods

Type of Study

The study is descriptive and cross-sectional.

Study Design and Sample

The population of this study consisted all of nurses living in Turkey and working in an intensive care unit between March and September 2021, regardless of period of time, when the research was conducted. OpenEpi v.3, a statistics program available for general use, was used in calculating the size of the sample (http://www.openepi.com), and this was found to be at least 220 nurses, for a significance level of 0.05, a confidence interval of 99%, and an ability to represent the population of 80%. The research was completed with 233 nurses who were selected from the population by the non-probability random sampling method, and who participated willingly and voluntarily in the study. The inclusion criteria were working in an intensive care unit, voluntarily and willingly participating in the study, not having a problem with vision or hearing, having access to the internet and actively using social media (Facebook, Instagram or WhatsApp).

Data Collection

After obtaining the necessary permissions and before beginning the research, written and oral approvals were obtained from the nurses who met the inclusion criteria, and data was collected online between March and September 2021. The data collection forms created on Google Forms were sent to the nurses by email or to their social media accounts (Facebook, Instagram or WhatsApp), and they were asked to complete them.

Data Collection Tools

Data was collected using a Participant Information form created in line with the literature, the COVID-19 Related Psychological Distress scale (CPDS), and the Work Ability index (WAI).

Participant Information Form: This form, created by the researchers according to the literature 15 with the objective of determining the participants' personal characteristics, contained questions on age, gender, education level, marital status, place of residence, years of work, length of time working in the intensive care unit, and the effects on physical and mental health of the COVID-19 pandemic.

CPDS: This scale was developed in 2020 by Feng et al. (18) and Turkish validity and reliability were performed by Ay et al. (19). It measures the level of psychological distress in uninfected people. The scale consists of a total of 14 items, and has two sub-sections, doubt, and anxiety or fear. The items on the scale are of five-way Likert type: 1-I definitely disagree, 5-I definitely agree. On the original scale, the Cronbach alpha consistency values were as follows: scale total 0.88, anxiety or fear sub-section 0.74, and doubt sub-section 0.87. In the present study, these values were 0.81, 0.62 and 0.78 respectively. Higher scores reflect a higher severity of psychological distress (19).

WAI: This scale began to be used in 1980 in Finland, and it was developed to prevent problems arising from work or the work environment in 1998 under the leadership of Prof. Juhani Ilmarinen at the Finnish Institute of Occupational Health (20). Turkish validity and reliability were performed by Das Gecim and Esin (21). The WAI is a Likert type scale with a total of seven items, intended to assess individuals' work load and performance. Possible scores range between 7 and 49. According to the scale's scoring system, a score of 7-27 represents low work ability, 28-36 medium work ability, 37-43 good work ability, and 44-49 excellent work ability. The Cronbach internal consistency value of the original scale is 0.72, and it is 0.67 in the present study. According to the score obtained on the scale, interventions are made to increase an individual's physical or mental or both physical and mental capacities (20,21).

Ethical Approval

During the research, the Helsinki Declaration on Human Rights was followed. Before commencing the research, approval was obtained from Amasya University Non-Interventional Ethics Committee dated 04 March 2021, decision no: 37, and written permission was obtained from the Turkish Health Ministry Pandemic Research Permission Portal.

Statistical Analysis

The program R version 2.15.3 was used for the statistical analyses (R Core Team, 2013). In reporting study data, minima, maxima, means, standard deviations, medians, first quartile, third quartile, frequencies and percentages were used. Conformity of quantitative data to normal distribution was assessed with the Shapiro-Wilk test and graphical inspections. In evaluating variables showing normal distribution between two groups, the independent groups t-test was used, in evaluating between more than two groups, One-Way variance analysis was used, and if significance was observed, the Bonferroni test was used to determine the source of the significance. In evaluating variables which did not show normal distribution between two groups, the Mann-Whitney U test was used; in evaluating between more than two groups, the Kruskal-Wallis test was used, and when

significance was observed, the Dunn-Bonferroni was used to determine the source of the significance. In determining the level of correlation between quantitative variables, Pearson and Spearman analysis was used. In determining the levels of internal consistency of the scale, the Cronbach alpha coefficient was used. Statistical significance was taken as $p<0.05$.

Results

Participants' General Characteristics

The ages of the nurses in the study ranged from 21 to 49 years (Table 1).

The findings of the research can be grouped under three headings:

Table 1. Nurses' sociodemographic characteristics		
	Min-max (median)	**Avg ± SD**
Age (years)	21-49 (27)	29.39±6.44
Time working in the profession (years)	0.17-30 (4)	7.42±7.23
Time working in intensive care (years)	0.17-24 (3)	5.06±5.20
Number of patients cared for per shift	0-9 (3)	2.78±1.22
	n	**%**
Gender		
Female	186	79.8
Male	47	20.2
Marital status		
Married	80	34.3
Single	153	65.7
Education		
High school	175	75.1
University	41	17.6
Postgraduate	17	7.3
Children		
Yes	64	27.5
No	169	72.5
Income level		
Very bad	39	16.7
Bad	33	14.2
Medium	153	65.7
Good	8	3.4
Very good	0	0.0
General state of health		
Very bad	117	50.2
Bad	91	39.1
Medium	9	3.9
Good	16	6.9
Very good	0	0.0
Regularly used medication/chronic illness		
Yes	55	23.6
No	178	76.4
Level of your intensive care unit		
Level 1	10	4.3
Level 2	30	12.9
Level 3	189	81.1
Level 4	4	1.7
Willingness to work in ICU		
Yes	202	86.7
No	31	13.3
Position		
Nurse	197	84.5
Charge nurse	25	10.7
Mentor nurse	4	1.7
Head nurse	3	1.3
Other	4	1.7
Do you think the unit where you work is suitable for its workforce or capacity?		
Yes	132	56.7
No	101	43.3
Shift type		
08-16	40	17.2
08-20	22	9.4
16-08	45	19.3
Other	126	54.1
Satisfaction with work and working conditions		
Yes	61	26.2
No	172	73.8
Effect of COVID-19 pandemic on work satisfaction		
Very bad	5	2.1
Bad	97	41.6
Medium	43	18.5
Good	86	36.9
Very good	2	0.9

Table 1. Continued		
	Min-max (median)	Avg ± SD
Health problem from work or working environment		
Yes	149	63.9
No	84	36.1
Effect of COVID-19 pandemic on physical health		
Very bad	94	40.3
Bad	76	32.6
Medium	35	15.0
Good	27	11.6
Very good	1	0.4
Effect of COVID-19 pandemic on mental health		
Very bad	91	39.1
Bad	109	46.8
Medium	21	9.0
Good	9	3.9
Very good	3	1.3
Effect of COVID-19 pandemic on adequacy of working conditions		
Very bad	92	39.5
Bad	81	34.8
Medium	29	12.4
Good	24	10.3
Very good	7	3.0
Have you had a coronavirus infection?		
Yes	109	46.8
No	124	53.2
Have you had a COVID-19 test?		
Yes	216	92.7
No	17	7.3
COVID-19 test result		
Positive	67	31.0
Negative	149	69.0
Fear of coronavirus infection		
Yes	141	60.5
No	92	39.5
Are you caring for patients with a diagnosis of COVID-19?		
Yes	199	85.4
No	34	14.6

COVID-19: Coronavirus disease-2019, ICU: intensive care unit, Avg ± SD: average ± standard deviation, min-max: minimum-maximum

Intensive Care Nurses' Work Ability and COVID-19 Psychological Distress Levels

The nurses scored the following: WAI total score mean 31.41±6.97 [minimum (min): 11-maximum (max): 47]; COVID-19 PDS anxiety and fear sub-section score mean 10.06±3.78 (min: 5-max: 25); COVID-19 PDS doubt sub-section score mean 20.13±5.86 (min: 7-max: 35), and COVID-19 PDS total scale mean 30.18±8.42 (min: 12-max: 60) (Table 2).

Correlation Between Intensive Care Nurses' Work Ability and COVID-19 Psychological Distress Levels

A statistically significant positive correlation was found between the nurses' WAI total score mean and their COVID-19 PDS doubt sub-section score mean (r=0.128, p=0.049). A statistically significant positive correlation was found between the COVID-19 PDS total score mean and the anxiety and fear and the doubt sub-sections (r=0.799, p<0.001; r=0.922, p<0.001), and a statistically positive correlation was found between the COVID-19 PDS anxiety and fear sub-section and the doubt sub-section (r=0.503, p<0.001) (Table 3).

Table 2. Nurses' work ability and COVID-19 Psychological Distress scale score means

	No of items	Min-max (median)	Avg ± SD
WAI total	7	11-47 (32)	31.41±6.97
COVID-19 PDS anxiety and fear	5	5-25 (10)	10.06±3.78
COVID-19 PDS doubt	7	7-35 (21)	20.13±5.86
COVID-19 PDS total	12	12-60 (30)	30.18±8.42

COVID-19: Coronavirus disease-2019, PDS: Psychological Distress scale, WAI: Work Ability index, Avg ± SD: average ± standard deviation, min-max: minimum-maximum

Table 3. Correlation between nurses' Work Ability index and COVID-19 Psychological Distress scale

		WAI total	COVID-19 PDS anxiety and fear	COVID-19 PDS doubt	COVID-19 PDS total
WAI total	r	1.000			
	p	-			
COVID-19 PDS anxiety and fear	r	0.025			
	p	**0.710**	-		
COVID-19 PDS doubt	r	0.128	0.503		
	p	**0.049***	**<0.001***	-	
COVID-19 PDS total	r	0.100	0.799	0.922	
	p	**0.126**	**<0.001***	**<0.001***	-

COVID-19: Coronavirus disease-2019, PDS: Psychological Distress scale, WAI: Work Ability index
*p<0.05, r = Pearson correlation analysis,

Factors Affecting the Intensive Care Nurses' Work Ability and their COVID-19 Psychological Distress Levels During the Pandemic

A statistically significant positive correlation was found between the nurses' length of time in the profession and WAI total score (r=0.132, p=0.043), and a statistically significant negative correlation was found with the COVID-19 PDS total score (r=-0.162, p=0.013). In other words, it was seen that the level of COVID-19 PDS decreased as the time spent in the profession increased. A statistically significant difference was found with regard to the nurses' COVID-19 PDS total scores according to their gender (p<0.001). It was found that the COVID-19 PDS scores of the males were higher than those of the females (Table 4).

Table 4. Correlation between nurses' sociodemographic characteristics and Work Ability index and COVID-19 Psychological Distress scale

		WAI	COVID-19 PSD
Age (years)	r	0.118	-0.118
	p	0.072	0.072
Time working in the profession (years)	r	0.132	-0.162
	p	**0.043***	**0.013***
Time working in intensive care (years)	r	0.068	-0.127
	p	0.302	0.054
	n	**Avg ± SD**	**Avg ± SD**
Gender			
Female	186	31.51±7.07	29.12±8.36
Male	47	31.00±6.61	34.38±7.30
Test value (t)		0.448	-3.947
[a]p		0.655	**<0.001***
Income			
Very bad	39	34 (29, 40)	32 (23, 40)
Bad	33	32 (27, 34)	31 (23, 35)
Medium	153	32 (27, 36)	30 (24, 34)
Good	8	28 (26, 28.5)	39.5 (35, 43.5)
Test value (χ^2)		8.178	10.581
[b]p		**0.042***	**0.014***
General health			
Very bad	117	34 (29, 38)	31 (24, 36)
Bad	91	29 (24, 32)	29 (24, 35)
Medium	9	28 (20, 30)	25 (21, 31)
Good	16	36 (28.5, 41.5)	30.5 (29, 42)
Test value (χ^2)		40.014	4.429
[b]p		**<0.001***	0.219
Regularly used medication/chronic illness			
Yes	55	29.29±7.16	28.45±8.00
No	178	32.06±6.80	30.72±8.49
Test value (t)		-2.609	-1.752
[a]p		**0.010***	0.081

Table 4. Continued

		WAI	COVID-19 PSD
Level of your ICU			
Level 1	10	30 (28, 34)	29.5 (26, 33)
Level 2	30	28.5 (25, 34)	30.5 (22, 33)
Level 3	189	32 (28, 37)	30 (24, 36)
Level 4	4	29.5 (24, 36.5)	27.5 (22.5, 33)
Test value (χ^2)		4.122	1.450
[b]p		0.249	0.694
Willingness to work in ICU			
Yes	202	31.91±6.86	30.30±8.18
No	31	28.13±6.86	29.45±9.93
Test value (t)		2.856	0.520
[a]p		**0.005***	0.604
Position			
Nurse	197	32 (27, 36)	31 (24, 36)
Charge nurse	25	34 (28, 39)	25 (21, 31)
Mentor nurse	4	28.5 (19.5, 31)	29.5 (27, 35.5)
Head nurse	3	40 (37, 42)	36 (20, 49)
Other	4	30 (24.5, 33.5)	27.5 (23, 34.5)
Test value (χ^2)		10.437	5.695
[b]p		**0.034***	0.223
Do you think the unit where you work is suitable for its workforce or capacity?			
Yes	132	33.42±6.49	29.92±8.62
No	101	28.77±6.72	30.53±8.18
Test value (t)		5.340	-0.555
[a]p		**<0.001***	0.580
Satisfaction with work and working conditions			
Yes	61	36.79±5.28	29.18±8.68
No	172	29.50±6.49	30.54±8.32
Test value (t)		7.887	-1.085
[a]p		**<0.001***	0.279

Table 4. Continued			
		WAI	**COVID-19 PSD**
Effect of COVID-19 pandemic on work satisfaction			
Very bad/bad	102	31.77±5.98	30.57±8.38
Medium	43	35.86±5.71	30.67±9.04
Good/very good	88	28.81±7.45	29.50±8.19
Test value (F)		17.136	0.468
[c]p		**<0.001***	0.627
Health problem from work or working environment			
Yes	149	29.93±6.75	29.07±8.27
No	84	34.04±6.60	32.17±8.36
Test value (t)		-4.497	-2.737
[a]p		**<0.001***	**0.007***
Effect of COVID-19 pandemic on physical health			
Very bad	94	31.86±5.24	29.51±7.92
Bad	76	27.58±7.02	28.99±8.49
Medium	35	35.51±7.24	31.17±9.06
Good/very good	28	35.14±6.46	34.46±7.93
Test value (F)		17.628	3.390
[c]p		**<0.001***	**0.019***
Effect of COVID-19 pandemic on mental health			
Very bad	91	33 (29, 38)	31 (24, 35)
Bad	109	29 (24, 34)	28 (24, 35)
Medium	21	37 (32, 39)	34 (28, 41)
Good/very good	12	34 (29.5, 39)	33 (31.5, 38.5)
Test value (χ^2)		27.953	7.416
[b]p		**<0.001***	**0.060**
Effect of COVID-19 pandemic on adequacy of working conditions			
Very bad	92	31.88±5.54	29.75±9.13
Bad	81	28.05±7.34	28.33±7.20
Medium	29	34.10±6.85	33.62±8.60
Good/very good	31	36.26±5.70	33.10±7.59
Test value (F)		15.225	4.425
[c]p		**<0.001***	**0.005***
Have you had a coronavirus infection?			
Yes	109	30.29±7.36	28.71±8.17
No	124	32.39±6.48	31.48±8.44
Test value (t)		-2.309	-2.543
[a]p		**0.022***	**0.012***

Table 4. Continued			
		WAI	**COVID-19 PSD**
Have you had a COVID-19 test?			
Yes	216	32 (27, 36.5)	30 (24, 35.5)
No	17	32 (28, 36)	26 (22, 36)
Test value (z)		-0.224	-0.185
[d]p		0.822	0.853
COVID-19 test result			
Positive	67	29.57±6.95	28.52±7.19
Negative	149	32.19±6.86	30.88±8.20
Test value (t)		-2.594	-2.028
[a]p		**0.010***	**0.044***
Fear of coronavirus infection			
Yes	141	30.59±7.09	27.77±7.43
No	92	32.66±6.63	33.88±8.54
Test value (t)		-2.240	-5.781
[a]p		**0.026***	**<0.001***
Are you caring for patients with a diagnosis of COVID-19?			
Yes	199	31.22±6.83	30.18±8.39
No	34	32.53±7.74	30.21±8.67
Test value (t)		-1.015	-0.016
[a]p		0.311	0.987

COVID-19: Coronavirus disease-2019, PDS: Psychological Distress scale, WAI: Work Ability index, Avg ± SD: average ± standard deviation, ICU: intensive care unit r = Pearson correlation analysis. [a]Independent groups t-test. [b]Kruskal-Wallis test results are given as median (first quartile, third quartile). [c]One-Way variance analysis. [d]Mann-Whitney U test results are given as median (first quartile, third quartile). *p<0.05

A statistically significant difference was found regarding WAI and COVID-19 PDS total scores according to whether the participants has had a coronavirus infection (p=0.022 and p=0.012 respectively). The scores of those who had had a coronavirus infection were lower (Table 4). A statistically significant difference was found regarding WAI and COVID-19 PDS total scores according to the test results of participants who had had a COVID-19 test (p=0.010 and p=0.044 respectively). The scores of those whose test results were positive were lower. A statistically significant difference was found regarding WAI and COVID-19 PDS total scores according to whether they were afraid of being infected by coronavirus (p=0.026 and p<0.001 respectively). Those who were afraid of coronavirus infection had lower scores (Table 4).

Discussion

In this research, an investigation was made of the effect of psychological distress on intensive care nurses' work abilities during the COVID-19 pandemic.

Work Ability

It was found in the study that the work ability of nurses living in Turkey and working in intensive care units was at a medium level. There are also other studies in the literature which similarly state that nurses' work abilities are at a medium level (22,23). In contrast to the results of our research, Vasconcelos et al. (24) found that nurses' work abilities were low, and in studies with nurses by Milosevic et al. (14) and Rotenberg et al. (12) it was found that nurses' work abilities were at a good level. In international studies, inadequate or low work ability has been correlated with advanced age, female gender, difficulties with place of work, having another job, doing repetitive or monotonous work, inadequate personnel, and various morbidities (23,25). Evaluating work ability is frequently used in work health services, and both helps to improve workers' health, to ensure the continuation of people's ability to work, and for correct measures to be taken, and also allows the determination of which worker needs which work health service, and of whether there is a decline in people's working conditions (26). At the same time, it allows negative situations for work and workers to be noticed earlier and the necessary measures to be taken, so that its assessment is important (19). According to the literature, studies on work ability among intensive care nurses are insufficient (2). Work ability can be disrupted by such work-related factors as excessive use of muscle strength, lifting and carrying loads, repeated movements, inadequate or wrong standing positions, exposure to accidents related to work or the work environment and the risks which these create, conflicting roles and the lack of opportunity development and recognition in the workplace (24). It was found in this study that intensive care nurses' work abilities were affected by income status, general health level, regularly used medication or chronic illness, willingness to work in intensive care, whether they thought that the work strength or the capacity of the unit where they worked was suitable, their satisfaction with their work or working conditions, the effect of the COVID-19 pandemic on their work satisfaction, experiencing health problems arising from their work or working environment, the state of participants' satisfaction with their work or working conditions, the effect of the COVID-19 pandemic on physical and mental health, and the fear of infection or of infecting others with the coronavirus. It was found in a study by Tuomi et al. (27) that an excessive work load together with symptoms of a high level of stress cause low work ability, and a study by Rostamabadi et al. (2) found that factors such as individual characteristics, illness, tiredness and an excessive work load affected the work ability of intensive care nurses. It has also been found that age is one of the factors reducing work ability both in nurses (15) and in other professions (13). In order to improve the negative factors affecting the skill; It can be recommended to improve the clinical physical environment, to develop and maintain in-service training programs, to make learner-centered education programs, to adopt lifelong learning approaches, and to develop and implement a peer-mentoring system for nurses.

COVID-19 Psychological Distress

The outbreak of COVID-19 has significantly affected the psychological, social and mental health of health workers on the front line, including nurses caring for and treating patients. It is reported in the literature that nurses, who are exposed to infection or the risk of infection and to intense stress, experience stress, anxiety, insomnia and psychosocial problems (28,29). In a study by Da Rosa et al. (4) it was found that the prevalence of emotional distress in nurses was high. For this reason, it is of great importance to understand the effects of the COVID-19 pandemic on psychological health (30). It was found in our research that the psychological distress levels of intensive care nurses relating to the COVID-19 outbreak were at a medium level. Similarly, Kackin et al. (28) found in a study conducted with nurses in Turkey that nurses caring for patients with a diagnosis of COVID-19 were negatively affected both psychologically and socially by the pandemic, and that nurses used short-term coping strategies and needed psychosocial support and resource management. It was found in a study by Zonp et al. (31) that nurses were at a high risk of developing mental health problems during the COVID-19 pandemic. It was found in our study that the intensive care nurses' total COVID-19 PDS scores were affected by factors such as length of time working in the profession, gender, income, health problems arising from work or the work environment, the effect of the COVID-19 pandemic on physical health, and fear of infection or of infecting others with coronavirus. It was also found that the psychological stress levels of male intensive

care nurses were higher than those of female nurses. In contrast to these research results, it was found in studies conducted with various different sample groups evaluating psychological distress during the COVID-19 pandemic that the psychological distress of females was higher (32,33).

Correlation Between Work Ability and COVID-19 Psychological Distress

It was found in the study that the mean scores on the COVID-19 PDS sub-sections of anxiety and fear and doubt were at a medium level, and that there was a positive correlation between the WAI total score and these sub-sections. In other words, nurses with high work ability are more fear of COVID-19 and experience more anxiety than other nurses. It has been found in the literature that during the COVID-19 pandemic, there was a feeling of not being prepared for the pandemic, emotional distress, anxiety, concern, depression, stress and worry caused by a deterioration in mental health conditions, dissatisfaction with work, and a fear of the workplace being infected because of the number of COVID-19 cases (28,29). It was concluded in a study by Da Rosa et al. (4) that health professionals worried about being infected or infecting their families or others. Sampaio et al. (34) found a positive correlation between the fear of being infected and depression, anxiety and stress, and Said and El-Shafei (35), in a study conducted in Egypt during the pandemic, found that a very stressful work environment resulted in dissatisfaction with work and a tendency to leave work. Considering all of this, it is an expected result that doubts or worries connected to psychological distress experienced by intensive care nurses in the COVID-19 pandemic should be parallel to their work ability. The COVID-19 pandemic has affected health workers' mental health with increased stress, worry, depressive symptoms and insomnia (29). Also, the COVID-19 pandemic has led to a high incidence of COVID-19 infections in health workers who are on the front line, and a high prevalence of post-infection symptoms (36). The fact that all of these conditions have a negative effect on work ability suggests that low work ability will increase in the pandemic, and that the situation will remain for some time afterwards (9). Also, it is necessary to increase awareness of how important work in the intensive care unit is, and for nurses working in these units who have a heavy work load and are at risk to have work ability and working capacity in accordance with their work demands (2).

Limitations of the research are that the research results can only be generalized to the sample group, and because it was a cross-sectional study, cause and effect relationships cannot be established. Also, the difficulty of contacting the intensive care nurses and the collection of data online during the COVID-19 pandemic are a further limitation of the study.

Conclusion

In the research, it was determined that the work abilities and the COVID-19 psychological distress levels of intensive care nurses living in Turkey were at a medium level. In order to reduce or eliminate factors such as having had coronavirus, length of time working, or general health condition, it is recommended that suitable work health services be implemented. Also, in order to eliminate all physical and mental factors which cause a decline in work strength and performance by reducing work ability in intensive care nurses, the implementation of programs to improve work health is of importance.

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Ethics

Ethics Committee Approval: Before commencing the research, approval was obtained from Amasya University Non-Interventional Ethics Committee dated 04 March 2021, decision no: 37.

Informed Consent: Written permission was obtained from the Turkish Health Ministry Pandemic Research Permission Portal.

Authorship Contributions

Concept: G.Y.D.G., B.T., Design: G.Y.D.G., B.T., Data Collection and Process: G.Y.D.G., B.T., Analysis or Interpretation: G.Y.D.G., B.T., Literature Search: G.Y.D.G., B.T., Writing: G.Y.D.G., B.T.

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ORIGINAL RESEARCH / *ÖZGÜN ARAŞTIRMA*

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Could SARS-CoV-2 Sepsis Be a Different Phenotype of Sepsis? COVID-19 Pneumosepsis with Its Similarities and Differences

COVİD-19 Sepsisi Farklı Bir Sepsis Fenotipi Olabilir mi? Benzerlikleri ve Farklılıkları ile COVİD-19 Pnömosepsisi

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ABSTRACT *Objective:* By comparing viral sepsis caused by severe acute respiratory syndrome coronavirus-2 with pneumosepsis caused by other pathogens, we aimed to compare the pathogen-host relationship, organ damage affecting the clinic, and similar and different features of the two types of sepsis.
Materials and Methods: A total of 414 patients diagnosed with critical coronavirus disease-2019 (COVID-19) between 2019 and 2021 and 303 pneumosepsis cases that met the diagnostic criteria for sepsis-3 between 2016 and 2019 admitted to the anesthesiology and reanimation intensive care unit (ICU) were retrospectively screened. The patient's demographic data, mortality rates, length of stay in the ICU, development of secondary organ dysfunction, presentation values of laboratory and mechanical ventilation, and changes within the 1-week follow-up were compared.
Results: The sequential organ failure assessment scores were significantly higher in the COVID-19 sepsis group at presentation (8.2±2.9 vs. 7.2±3.7; p<0.0001) and during follow-up (8.9±4.9 vs. 7.8±3.7; p=0.002). The mean age of the patients was 65.4±17.2 years in the non-COVID-19 sepsis group and 57.9±17.1 years in the COVID-19 sepsis group (p<0.0001). The number of days on mechanical ventilation was significantly higher in the COVID-19 sepsis group (p=0.018). Mortality was detected in 299 patients (41.7%) in total, with no significant difference being observed between the two groups (p=0.592).
Conclusion: Despite the patient population having a lower mean age and fewer comorbidities, organ dysfunction was higher in COVID-19 sepsis patients during admission to the ICU and follow-up. While the pathogen causing sepsis can be brought under control with rapid diagnosis and appropriate antimicrobial treatment, organ damage cannot be controlled with appropriate antiviral treatment in COVID-19 sepsis. In COVID-19 sepsis, secondary organ damage may be more evident as a result of damage and immunomicrothrombosis, which causes high mortality and morbidity, the mechanism of which has not yet been fully elucidated.
Keywords: COVID-19 sepsis, SOFA score, pneumosepsis, organ damage

ÖZ *Amaç:* Şiddetli akut solunum yolu yetersizliği koronavirüs sendromu-2 etkenli viral sepsisi diğer patojenlere bağlı gelişen pnömosepsis ile karşılaştırarak; patojen-konak ilişkisi, kliniği etkileyen organ hasarı, iki sepsis türünün benzer ve farklı özelliklerinin karşılaştırılması amaçlandı.
Gereç ve Yöntem: 2019 ve 2021 yılları arasında kritik koronavirüs hastalığı-2019 (COVİD-19) tanısı alan toplam 414 hasta ve 2016 ve 2019 yılları arasında anesteziyoloji ve reanimasyon yoğun bakım ünitesine (YBÜ) başvuran ve sepsis-3 tanı kriterlerini karşılayan 303 pnömopsis olgusu retrospektif olarak tarandı. Hastaların demografik verileri, mortalite oranları, yoğun bakımda kalış süreleri, sekonder organ disfonksiyonu gelişimi, laboratuvar ve mekanik ventilasyon başvuru değerleri ve bir haftalık takipteki değişimleri karşılaştırıldı.
Bulgular: Sıralı organ yetmezliği değerlendirmesi skorları COVİD-19 sepsis grubunda başvuruda (8,2±2,9'a karşı 7,2±3,7; p<0,0001) ve takipte (8,9±4,9'a karşı 7,8±3,7; p=0,002) anlamlı olarak yüksekti. Hastaların ortalama yaşı COVİD-19 olmayan sepsis grubunda 65,4±17,2, COVİD-19 sepsis grubunda 57,9±17,1 idi (p<0,0001). Mekanik ventilatörde geçirilen gün sayısı COVİD-19 sepsis grubunda anlamlı olarak yüksekti (p=0,018). Toplam 299 hastada (%41,7) mortalite saptandı ve iki grup arasında anlamlı fark görülmedi (p=0,592).

Sonuç: Yaş ortalaması daha düşük ve komorbiditeleri daha az olan hasta popülasyonuna rağmen, COVİD-19 sepsis hastalarında YBÜ'ye yatış ve takiplerinde organ disfonksiyonunun daha fazla olduğu görüldü. Hızlı tanı ve uygun antimikrobiyal tedavi ile sepsise neden olan patojen kontrol altına alınabilirken, COVİD-19 sepsisinde uygun antiviral tedavi ile organ hasarı kontrol altına alınamamaktadır. COVİD-19 sepsisinde mekanizması henüz tam olarak aydınlatılamayan yüksek mortalite ve morbiditeye neden olan hasar ve immünomikrotromboz sonucunda sekonder organ hasarı daha belirgin olabilmektedir.
Anahtar Kelimeler: COVİD-19 sepsis, SOFA skor, pnömosepsis, organ hasarı

Introduction

Sepsis, one of the leading causes of infection-related mortality, is defined as a life-threatening organ dysfunction associated with an irregular host response due to infection (1). Sepsis agents are heterogeneous and can often develop due to bacterial, fungal, and viral pathogens (2). The most common infections in the intensive care unit (ICU) are those originating from the lungs (60%), abdomen (18%), and bloodstream (15%) (2). However, it has also recently been emphasized that respiratory viruses are often overlooked in sepsis and septic shock.

The coronavirus disease-2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) rapidly spread across the world, causing the death of millions of people, with 490 million cases and 6 million deaths being reported over two years (3,4). Many clinicians consider severe COVID-19 as a viral sepsis caused by SARS-CoV-2 and use bacterial sepsis as a prototype to better understand its pathogenesis (5,6). Although many studies have been conducted on sepsis, a heterogeneous syndrome, there is only limited research comparing COVID-19 sepsis and pneumosepsis due to other pathogens (non-COVID-19 sepsis) (7). In this study, we retrospectively investigated clinical changes in the host caused by COVID-19-related sepsis and other non-COVID-19 pneumosepsis agents with a primary focus on infection in the lungs, evaluated the data recorded during the intensive care follow-up, and compared the similarities and differences between these two groups.

Materials and Methods

Study Design and Patient Population

After receiving approval from the Local Ethics Committee (decision no: 2021-20-17, date: 18.10.2021), the patients followed up in the ICU of University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital between April 2019 and May 2021 with a COVID-19 and sepsis diagnosis and those that met the diagnostic criteria for sepsis-3 between October 2016 and January 2019 were retrospectively screened.

According to the diagnosis guidelines of the Turkish Ministry of Health COVID-19 Scientific Committee, patients who were found to be positive for COVID-19 in the real-time polymerase chain react test and met the criteria of the World Health Organization (WHO) were considered to have COVID-19. The diagnosis of sepsis was using the sepsis-3 electronic early warning system [an increase of 2 or more points in the sequential organ failure assessment (SOFA) score] and the presence of clinical suspicion of infection.

Patients with a diagnosis of non-COVID-19 pneumosepsis followed up in ICU and met the diagnostic criteria for sepsis-3 and those admitted to ICU due to severe COVID-19 according to the WHO guidelines were included in the study. Patients who had an ICU follow-up of fewer than 24 hours, cases in which acute physiology and chronic health evaluation-II (APACHE-II) and SOFA scores were not calculated, pregnant women, patients with missing data, those with an autoimmune disease or history of immunomodulatory treatment, those with secondary infections during the follow-up, postoperative patients, and those younger than 18 years were excluded.

The patients' demographic and laboratory parameters were obtained at the time of admission to the ICU, and the mean laboratory and hemodynamic parameters were instantly recorded during the seven-day follow-up period. The acceptance values of prognostic scores, such as APACHE-II and SOFA, as well as changes in the seventh-day SOFA scores, were evaluated. For the calculation of the SOFA score, respiratory, hepatic, hematological, neurological, renal, and cardiovascular system evaluations were made. Each organ system score was evaluated separately, and organ dysfunctions were separately compared between the two sepsis groups. The SOFA parameters were obtained using structured query language queries. In addition, mortality rates, length of ICU stay, number of days without mechanical ventilation, and continuous venovenous hemodiafiltration requirement were compared between the two groups. The follow-up period was determined as seven

days in both groups. The data of the patients were recorded using the electronic clinical decision support system (ImdSoftMetavision/QlinICU).

Due to the pandemic condition, verbal informed consent was obtained from the relatives of the patients included in the study. This study was not financially supported.

Statistical Analysis

The Shapiro-Wilk test was used to evaluate the normality of the distribution of numerical data. The Independent-sample t-test was conducted to compare normally distributed numerical data, and the Mann-Whitney U test was for comparisons between two groups in terms of data that did not have a normal distribution. The Pearson chi-square or Fisher's Exact test was used to examining the difference between categorical data. The descriptive statistics of the data were expressed as mean ± standard deviation for normally distributed numerical variables, median (interquartile range) for non-normally distributed numerical variables, and frequency (percentage) for categorical variables. All statistical analyses were performed and reported using IBM SPSS Statistics v. 22.0 software at α=0.05 significance and 95% confidence levels.

Results

After applying the inclusion and exclusion criteria, 717 patients were included in the study. There were 303 (42.3%) patients in the non-COVID-19 sepsis group (group 1) and 414 (57.5%) patients in the COVID-19 sepsis group (group 2). The mean age was 65.4±17.2 years in group 1 and 57.9±17.1 years in group 2, indicating a significant difference between the two groups (p<0.0001). Body mass index was significantly lower in group 1 (p=0.005). The demographic data of the groups are shown in Table 1. Comorbidities were detected in 273 (90%) patients in group 1 and 301 (72.7%) patients in group 2, and there was a significant difference was detected between the two groups (p<0.0001). Table 2 presents the comorbidities of the groups.

Table 1. Demographic data

Parameters (mean ± SD)	Total n=717	Non-COVID-19 sepsis n=303 (42.3%)	COVID-19 sepsis n=414 (57.5%)	p-value
Age (year)	61.1±17.5	65.4±17.2	57.9±17.1	<0.0001
Gender, n (%)				
Female	300 (41.8)	135 (44.6)	165 (39.4)	0.221
Male	417 (58.2)	168 (55.4)	249 (60.1)	
BMI (kg/m^2)	27.5±6.2	26.7±6.9	28±5.6	0.005

SD: Standard deviation, COVID-19: coronavirus disease-2019, BMI: body mass index

Table 2. Comorbidities

Parameters n (%)	Total n=717	Non-COVID-19 sepsis n=303 (42.3%)	COVID-19 sepsis n=414 (57.5%)	p-value
Comorbidity	574 (80)	273 (90)	301 (72.7)	<0.0001
Hypertension	319 (44.4)	138 (45.5)	181 (43.7)	0.594
Diabetes mellitus	217 (30.2)	77 (25.4)	140 (33.8)	0.021
COPD	130 (18.1)	70 (23.1)	60 (14.4)	0.003
CRF	111 (15.4)	58 (19.1)	53 (12.8)	0.021
Hepatitis	26 (3.6)	9 (2.9)	17 (4.1)	0.545
CAD	200 (27.8)	103 (33.9)	97 (23.4)	0.002
CVE	84 (11.7)	61 (20.1)	23 (5.5)	<0.0001
Dementia	38 (5.2)	30 (9.9)	8 (1.9)	<0.0001
Malignancy	118 (16.4)	68 (22.4)	50 (12)	<0.0001
Other	93 (12.9)	45 (14.8)	48 (11.5)	0.215

COVID-19: Coronavirus disease-2019, COPD: chronic obstructive pulmonary disease, CRF: chronic renal failure, CAD: coronary artery disease, CVE: cerebrovascular event

When the admission hemogram parameters were examined, the white blood cell (WBC) count was significantly higher in group 1 (p<0.0001), and the hemoglobin and hematocrit levels were significantly higher in group 2 (p<0.0001 and p=0.001, respectively). There was also a significant difference between the two groups in terms of the neutrophil count (p<0.0001).

The admission biochemistry sodium values were found to be significantly higher in group 1 (p=0.008). Group 2 had significantly higher glucose, lactate dehydrogenase, albumin, triglyceride, and C-reactive protein (CRP) values (p<0.0001, p=0.006, p=0.013, p=0.003, and p=0.001, respectively). In group 1, significantly higher creatine kinase and procalcitonin levels were detected (p=0.049 and p<0.0001, respectively). The international normalized ratio (INR) was significantly higher in group 1, and the fibrinogen value was significantly higher in group 2 (p=0.002 and p<0.0001, respectively). The admission values of the laboratory parameters and comparisons between the two groups are shown in Table 3.

The admission data on the mechanical ventilation parameters are given in Table 4.

According to the comparison of the first week averages of the hemodynamic parameters, group 1 had a significantly higher mean heart rate and significantly lower systolic, diastolic, and mean blood pressure values. The amounts of all vasopressor and inotropic agents, such as adrenaline, noradrenaline, dopamine, and dobutamine used during the first-week follow-up were found to be significantly higher in group 1 (p<0.0001, p<0.0001, p<0.0001, and p=0.047, respectively). No significant difference was observed between the two groups in relation to the APACHE-II admission and mortality values. Continuous renal replacement therapy (CRRT) requirement was significantly higher in group 2 (p<0.0001). There was no significant difference between the two groups in terms of the length of ICU stay. When the duration of mechanical ventilation was compared, the median value was 6.6 (11.8) days in group 1 and 8.3 (10.3) days in group 2, with a significantly higher value being observed in the latter (p=0.018). There was no significant difference in the mortality rates of the two groups. Mortality was detected in a total of 299 patients (41.7%) (Table 5).

Table 3. Comparison of the ICU admission parameters between the groups

Parameters (mean ± SD)	Total n=717	Non-COVID-19 sepsis n=303 (42.3%)	COVID-19 sepsis n=414 (57.5%)	p-value
Hemogram				
WBC (10^3/uL)	16.4±8.1	19.3±6.5	15.5±8.3	<0.0001
Hemoglobin (g/dL)	10.9±2.2	10.2±1.9	11.1±2.2	<0.0001*
Hematocrit (%)	34.1±6.9	32.2±6.2	34.8±7	0.001
Platelet+ (10^3/uL)	226.5 (137.7)	213.5 (145)	228.5 (141.6)	0.234*
Lymphocyte+ (10^3/uL)	0.8 (0.7)	0.9 (0.8)	0.8 (0.7)	0.002*
Neutrophil (10^3/uL)	14.5±7.5	16.9±6.1	13.7±7.8	<0.0001
Neutrophil/lymphocyte+	15.3 (15)	16.8 (18)	14.7 (15)	0.397*
Biochemical				
Glucose+ (mg/dL)	175.5 (84.8)	159 (81)	186 (86.6)	<0.0001*
Sodium (mmol/L)	139.4±6.8	140.7±6.5	138.9±6.9	0.008
LDH+ (IU/L)	517 (382.5)	436.2 (401.7)	540 (373.2)	0.006*
Amylase+ (IU/L)	81.7 (104.2)	82 (87)	81.5 (106.5)	0.877*
Lipase+ (IU/L)	26.5 (58.3)	23.7 (45.6)	27.5 (58.2)	0.067*
Ferritin+ (mg/dL)	752.3 (1156.7)	566.5 (1407.6)	752.3 (1137.2)	0.522*
CK+ (IU/L)	132 (258)	210.7 (265.7)	124 (247)	0.049*
Albumin (g/dL)	2.7±0.4	2.6±0.5	2.8±0.4	0.013
Procalcitonin+ (ng/dL)	3.2 (6.1)	5.4 (14.2)	1.1 (4.4)	<0.0001*
CRP+ (mg/dL)	120 (152)	86.3 (130.2)	132 (148)	0.001*

*Values presented as median (interquartile range) and comparisons made using the Mann-Whitney U test.
COVID-19: Coronavirus disease-2019, SD: standard deviation, ICU: intensive care unit, WBC: white blood cell, LDH: lactate dehydrogenase, CK: creatine kinase, CRP: C-reactive protein

Table 4. Comparison of the mechanical parameters at ICU admission				
Parameters (mean ± SD)	**Total n=717**	**Non-COVID-19 sepsis n=303 (42.3%)**	**COVID-19 sepsis n = 414 (57.5%)**	**p-value**
Mechanical ventilation				
$ETCO_2$ (mmHg)	50.7±16	47.2±15.6	52.3±16	0.033
Horowitz⁺ (PaO_2/FiO_2)	174 (125)	168.5 (148.6)	175.6 (110.4)	0.543*
RR_{set} (min)	14.2±1.9	13.9±2.1	14.4±1.7	0.001
PEEP (cmH_2O)	8.2±2	7.8±2	8.6±1.8	<0.0001
P_{mean} (cmH_2O)	14.3±3.1	13.5±3	15±3	<0.0001
Tidal volume/ideal weight	6.9±1.4	7.3±1.6	6.6±1.2	<0.0001
P_{peak} (cmH_2O)	24.1±4.7	22.8±4.8	25±4.4	<0.0001
$P_{plateau}$ (cmH_2O)	24.1±4.4	24.4±4.2	23.9±4.5	0.700
WOB (j/L)	1.2±0.2	1.1±0.2	1.2±0.2	0.001
I/E	0.6±0.2	0.5±0.2	0.7±0.2	<0.0001
DP (cm H_2O)	15.2±3.6	14.8±3.5	15.5±3.6	0.018

*Comparisons made using the Mann-Whitney U test. ICU: Intensive care unit, SD: standard deviation, PaO_2: partial arterial oxygen pressure, $ETCO_2$: end-tidal carbon dioxide, FiO_2: fraction of inspired oxygen, RR_{set}: set respiratory rate, PEEP: positive end-expiratory pressure, P_{mean}: mean airway pressure, P_{peak}: peak airway pressure, $P_{plateau}$: plateau airway pressure, WOB: work of breathing, I/E: inspiratory/expiratory ratio, DP: driving pressure

Table 5. Comparison of the first-week averages of the hemodynamic parameters				
Parameters (mean ± SD)	**Total n=717**	**Non-COVID-19 sepsis n=303 (42.3%)**	**COVID-19 sepsis n=414 (57.5%)**	**p-value**
Peak heart rate (beat/min)	90.2±19.8	95±21.8	86.6±17.4	<0.0001
ABP_{sys} (mmHg)	118.6±17.5	116.2±22.4	119.9±14	0.026
ABP_{dias} (mmHg)	59±10.9	56.7±13.3	60.3±9.1	<0.0001
ABP_{mean} (mmHg)	78.1±11.6	75.5±14.9	79.6±9.1	<0.0001
Adrenalin⁺	20 (17.3)	30.5 (37.6)	14.2 (9.4)	<0.0001*
Noradrenalin⁺	45 (49.3)	78.9 (63.5)	35.2 (43.5)	<0.0001*
Dopamine⁺	1394.6 (1194.4)	2000 (2147)	1128.4 (738.6)	<0.0001*
Dobutamine⁺	675 (1266)	1150 (3057)	375 (250)	0.047*
Urine volume (cc/day)	1292.4 (1228.2)	1440 (1373)	1254.6 (1077)	0.037*
APACHE-II, admission⁺	22 (10)	22 (11)	22 (10)	0.449*
APACHE-II, mortality⁺	42 (34)	42 (37)	42 (34)	0.448*
CRRT	199 (27.8)	40 (13.2)	159 (38.4)	<0.0001
ICU stay⁺ (day)	9.9 (13)	9.7 (15.3)	10 (11.8)	0.823*
Number of days on MV⁺	7.5 (11.1)	6.6 (11.8)	8.3 (10.3)	0.018*
Number of days without MV⁺	1.2 (3.6)	1.7 (4)	1.1 (3.4)	0.001*
Mortality, n (%)	299 (41.7)	130 (42.9)	169 (40.8)	0.592*

*Comparisons made using the Mann-Whitney U test. Values presented as median (interquartile range). ABP_{sys}: Systolic arterial blood pressure, ABP_{dias}: Diastolic arterial blood pressure, ABP_{mean}: Mean arterial blood pressure, APACHE-II: acute physiology and chronic health evaluation-II, CRRT: continuous renal replacement therapy, ICU: intensive care unit, MV: mechanical ventilation

In parallel to the admission parameters, the comparison of the first-week averages of the hemogram parameters also revealed that the WBC and neutrophil values were significantly higher in group 1 (p<0.0001 for both), and the mean hemoglobin and hematocrit values were significantly higher in group 2 (p<0.0001 and p=0.001, respectively). The mean platelet level was significantly higher in group 2, and the neutrophil/lymphocyte ratio was significantly higher in

group 1 (p=0.002 and p=0.008, respectively), despite no significant difference at the time of ICU admission. Similar to the evaluation at admission, the mean lymphocyte count was significantly higher in group 1 (p=0.008).

As in the evaluation of laboratory parameters at ICU admission, the mean glucose value over the seven-day follow-up was significantly higher in group 2 (p<0.0001). When the averages of the electrolyte parameters were examined, group 1 had significantly higher sodium and chlorine values, and group 2 had a significantly higher calcium value (p<0.0001, p=0.002, and p=0.006, respectively). Comparing the first-week averages of bilirubin, aspartate transaminase (AST), and alanine aminotransferase (ALT), which did not differ significantly at the time of ICU admission, significantly higher values were found in group 2 (p=0.002, p=0.035, and p<0.0001, respectively). There was also a significant difference between the two groups in terms of the mean values of the lipase parameters, which did not show a significant difference at ICU admission (p=0.009). The comparison of the mean values of the lipid profile is shown in Table 6. Similar to the ICU admission parameters, the follow-up CRP was significantly higher in group 2 and the procalcitonin valuewas significantly higher in group 1 (p<0.0001 for both).

When the averages of the coagulation parameters were compared, the INR and D-dimer values were significantly higher in group 1, and the fibrinogen value was significantly higher in group 2 (p=0.002, 0.017, and 0.011, respectively). These data are detailed in Table 6.

Among the mean blood gas parameters, the lactate value was significantly higher in group 2 (p=0.028). In addition, significant differences were observed in the set respiratory rate (RR_{set}), positive end-expiratory pressure (PEEP), P_{mean}, minute ventilation, respiratory index, P_{peak}, work of breathing, inspiratory/expiratory ratio (I/E), and driving pressure (DP) values. When the first-week averages of the RR_{set} parameters were compared, significantly higher values were detected in group 2 (p=0.015). The PEEP value was determined as 7.8±2 mm H_2O in group 1 and 8.3±1.6 mm H_2O in group 2, showing a significantly higher result for group 2 (p<0.0001). The P_{mean} value was 13.5±2.9 mm H_2O in group 1 and 14.9±2.8 mm H_2O in group 2, indicating a significantly higher value in the latter (p<0.0001). When the first-week averages of the I/E values were compared, the result was significantly higher in group 2 (p<0.0001). The DP values of groups 1 and 2 were found to be 15±3.3 and 15.6±3.4 mm H_2O in group 2, respectively, and the difference between the group was statistically significant (p=0.018) (Table 7).

The mean SOFA score at the time of ICU admission was 8.2±2.9 in group 2 and 7.2±3.7 in group 1, indicating a significant difference (p<0.0001). The hematological and cardiovascular parameters were significantly higher in group 1, and the Glasgow coma scale (GCS) score was significantly higher in group 2 (p<0.0001, p<0.0001, and p=0.001, respectively).

When the follow-up SOFA scores were compared, there was a significant increase in group 2 (p=0.002). Group 2 also had significantly higher seven-week averages of hepatic system scores (p=0.024) and neurological, renal, and cardiovascular scores (p=0.005, p=0.014, and p<0.0001, respectively) (Table 8).

Discussion

COVID-19 disease, caused by SARS-CoV-2, is a multisystemic syndrome that emerged in December 2019 and has, since then, had serious consequences on a global scale related to the development of acute respiratory distress syndrome (ARDS) and multiorgan failure, especially the lungs (3). In addition to meeting the criteria for sepsis-3 and being associated with high mortality rates, clinical findings specific to COVID-19 sepsis suggest that this disease may be a different phenotype of sepsis (8).

In our study, when the hemodynamic parameters were compared between the two groups, it was determined that vasoplegia was more pronounced at ICU admission, and the need for inotropic and vasopressor agents was higher during the follow-up in the non-COVID-19 sepsis group, which is consistent with the literature (7-9). The vasopressor requirement in COVID-19 patients may be associated with stronger sedation, high airway pressures, right ventricular dysfunction, and secondary infections rather than cytokine storm and sepsis-induced vasodilation (10).

The neutrophil and procalcitonin levels being significantly higher in the non-COVID-19 sepsis group of our study is consistent with the characteristics of bacterial infections. Although lymphocytes, which are cellular immunity elements, were found to be at a low level in both sepsis groups, lymphopenia was significantly more pronounced in the COVID-19 sepsis group during admission and follow-up, which is similar to the studies in the literature comparing bacterial and COVID-19 sepsis cases (11,12).

Table 6. Comparison of the first-week averages of the laboratory parameters				
Parameters (mean ± SD)	**Total n=717**	**Non-COVID-19 sepsis n=303 (42.3%)**	**COVID-19 sepsis n=414 (57.5%)**	**p-value**
Hemogram				
WBC (10^3/uL)	16.1±7.9	19.5±7.4	15±7.7	<0.0001*
Hemoglobin (g/dL)	10.5±2	9.9±1.9	10.7±2	<0.0001
Hematocrit (%)	32±6.3	31.4±6.2	33.5±6.3	0.001
Platelet+ (10^3/uL)	226.7 (154.3)	200 (155.6)	231.3 (162.8)	0.002*
Lymphocyte+ (10^3/uL)	0.9 (0.7)	0.9 (0.8)	0.8 (0.7)	0.008*
Lymphocyte percentage+	6.9 (5.8)	5.9 (5.6)	7.3 (5.9)	0.004*
Neutrophil (10^3/uL)	14.9±7.1	17±6.8	12.9±6.9	<0.0001
Neutrophil/lymphocyte+	13.3 (13.4)	16.6 (15.6)	12.3 (12.4)	<0.0001*
Biochemical				
Glucose+ (mg/dL)	164 (58)	148.8 (59.6)	169.7 (58.3)	<0.0001*
Calcium (mg/dL)	8.1±0.6	8±0.7	8.2±0.5	0.006
Sodium (mmol/L)	138.9±5.7	140.7±6.4	138.2±5.2	<0.0001
Potassium (mmol/L)	4.3±0.6	4.3±0.7	4.3±0.5	0.504
Chloride (mmol/L)	101.1±5.5	102.6±6.5	100.6±5	0.002
Creatinine+ (mg/dL)	1.1 (1.3)	1.3 (1.2)	1 (1.3)	0.171*
Bilirubin+(mg/dL)	0.7 (1)	0.7 (0.8)	0.8 (1.1)	0.002*
AST+ (IU/L)	50.4 (75.1)	44 (86.6)	55.8 (71.7)	0.035*
ALT+ (IU/L)	37.2 (73.2)	25.4 (56.7)	45.7 (77.8)	<0.0001*
LDH+ (IU/L)	466.8 (375)	439 (440)	474.8 (364.1)	0.083*
Amylase+ (IU/L)	82.5 (104.9)	73 (91)	87 (112.7)	0.173*
Lipase+ (IU/L)	32 (68.8)	25.5 (62.6)	36.5 (68.8)	0.009*
Ferritin+ (g/L)	740 (1304.2)	823.4 (1646)	696.6 (1301)	0.896*
CK+ (IU/L)	192 (437)	181 (414)	196.5 (438.2)	0.408*
Albumin (g/dL)	2.6±0.4	2.5±0.5	2.6±0.3	0.077
Triglyceride+ (mg/dL)	164.5 (141.2)	131 (115.3)	190 (152.1)	0.002*
LDL+ (mg/dL)	77 (64.7)	79.1 (87)	74 (61.7)	0.988*
HDL+ (mg/dL)	26 (17.4)	25 (29)	27 (14)	0.757*
Cholesterol+ (mg/dL)	140.5 (63)	125 (55)	144.2 (55.9)	0.028*
CRP+ (mg/dL)	105.4 (122.2)	79.5 (119)	120.7 (113.1)	<0.0001*
Procalcitonin+ (ng/mL)	3 (6.4)	5.4 (14.7)	1.3 (4.7)	<0.0001*
Coagulation				
aPTT+ (sec)	40.2 (16.5)	40.8 (18.4)	39.9 (15.3)	0.943*
PT+ (sec)	1.2 (0.3)	1.2 (0.3)	1.2 (0.2)	0.163*
INR+	1.2 (0.3)	1.3 (0.4)	1.2 (0.2)	0.002*
Fibrinogen+ (mg/dL)	455 (267.2)	392 (343.7)	491.3 (260.3)	0.011*

*Comparisons made using the Mann-Whitney U test. Values presented as median (interquartile range). SD: Standard deviation, WBC: white blood cell, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, CK: creatine kinase, LDL: low-density lipoprotein, HDL: high-density lipoprotein, CRP: C-reactive protein, aPTT: active partial thromboplastin time, PT: prothrombin time, INR: international normalized ratio, sec: second

Table 7. Comparison of the first-week averages of blood gas and mechanical ventilation parameters				
Parameters (mean ± SD)	**Total n=717**	**Non-COVID-19 sepsis n=303 (42.3%)**	**COVID-19 sepsis n=414 (57.5%)**	**p-value**
Blood gas				
Lactate+ (mmol/L)	1.6 (1)	1.5 (1.1)	1.7 (0.9)	0.028*
PaO_2+	92.1 (31.7)	90.3 (49.3)	92.2 (24.5)	0.170*
SO_2	94.4±4.6	94.4±5.5	94.4±3.9	0.931
Mechanical ventilation				
$ETCO_2$ (mmHg)	49.9±13.4	49±15.3	50.2±12.7	0.480
FiO_2 (%)	53.3±12.9	52.6±13	53.8±12.8	0.229
Horowitz+ (PaO_2/FiO_2)	187.2 (113.2)	183.7 (148.9)	187.6 (101.9)	0.338*
RR_{set} (min)	14.3±1.9	14.1±2.2	14.5±1.6	0.015
PEEP (mm H_2O)	8.1±1.8	7.8±2	8.3±1.6	<0.0001
P_{mean} (mm H_2O)	14.3±2.9	13.5±2.9	14.9±2.8	<0.0001
MVE (L)	7.2±1.6	7.4±2	7±1.2	0.001
Tidal volume/ideal weight	7±1.3	7.4±1.5	6.7±1.1	<0.0001
RI+	9.6 (4.6)	13.2 (10)	9.2 (2.9)	<0.0001*
P_{peak} (mm H_2O)	24.1±4.5	23.2±4.7	24.8±4.3	<0.0001
$P_{plateau}$ (mm H_2O)	23.9±4.1	23.6±3.7	24±4.2	0.711
WOB (j/L)	1.2±0.2	1.1±0.2	1.2±0.2	<0.0001
Flow	0.4±0.1	0.4±0.1	0.4±0.1	0.158
I/E	0.6±0.2	0.6±0.2	0.7±0.2	<0.0001
DP (mm H_2O)	15.3±3.4	15±3.3	15.6±3.4	0.018

*Comparisons made using the Mann-Whitney U test. Values presented as median (interquartile range). SD: Standard deviation, PaO_2: partial arterial oxygen pressure, SO_2: oxygen saturation, $ETCO_2$: end-tidal carbon dioxide, FiO_2: fraction of inspired oxygen, RR_{set}: set respiratory rate, PEEP: positive end-expiratory pressure, P_{mean}: mean airway pressure, MVE: minute ventilation, RI: respiratory index, P_{peak}: peak airway pressure, $P_{plateau}$: plateau airway pressure, WOB: work of breathing, I/E: inspiratory/expiratory ratio, DP: driving pressure

Table 8. SOFA and SOFA component scores evaluated at ICU admission and on the seventh day				
Parameters (mean ± SD)	**Total n=717**	**Non-COVID-19 sepsis n=303 (42.3%)**	**COVID-19 sepsis n=414 (57.5%)**	**p-value**
SOFA, admission	7.8±3.3	7.2±3.7	8.2±2.9	<0.0001
Respiratory (Horowitz)	2.7±0.9	2.7±0.9	2.7±1	0.995
Hepatic (bilirubin+)	0 (0)	0 (0)	0 (0)	0.509*
Hematologic (platelet+)	0 (0)	0 (1)	0 (0)	<0.0001*
Neurologic (GCS+)	2.6±1.5	2.2±1.4	2.8±1.5	<0.0001*
Renal	2 (3)	3 (3)	2 (3)	0.296
Cardiovascular+	0 (0)	0 (0)	0 (0)	<0.001*
SOFA, day 7	8.4±4.5	7.8±3.7	8.9±4.9	0.002
Respiratory (Horowitz)	2.5±1.1	2.5±1.1	2.5±1.1	0.525
Hepatic (bilirubin+)	0 (1)	0 (1)	0 (1)	0.024*
Hematologic (platelet+)	0 (1)	0 (1)	0 (1)	0.549*
Neurologic (GCS)	2.4±1.6	2.2±1.4	2.6±1.6	0.005
Renal+	1 (4)	1 (3)	1 (4)	0.014*
Cardiovascular+	0 (0)	0 (0)	0 (2)	<0.0001*

*Comparisons made using the Mann-Whitney U test. Values presented as median (interquartile range). GCS: Glasgow coma scale, SOFA: sequential organ failure assessment, SD: standard deviation, COVID-19: coronavirus disease-2019, ICU: intensive care unit

When compared to other sepsis agents, SARS-CoV-2 sepsis presents with milder hyperinflammation, T-lymphocyte suppression and insufficient adaptive immune response, extensive macrophage infiltration in the lungs, and early fibrosis, indicating the presence of different phenotypic sepsis specific to this infection. Inappropriate and high-dose immunosuppressive treatments impair the immune response in these patients, and thus increase the risk of secondary infections, further complicating treatment with a clinical picture including more than one sepsis (sepsis[2], sepsis[3], etc.).

In a retrospective study of patients that died due to bacterial sepsis and severe COVID-19, Yu et al. (12) reported that the activated partial thromboplastin time, prothrombin time, and INR values were lower and the fibrinogen and D-dimer levels were higher in the COVID-19 group (12). In another study, Leisman et al. (13) showed that many acute phase reactants, including D-dimer, CRP, and ferritin, were similar or higher in patients with COVID-19 compared to those with sepsis or ARDS. As a result of the activation of different inflammatory cascades in COVID-19 sepsis, endothelial damage, hypofibrinolysis, immunomicrothrombus, and hypercoagulopathy are seen more frequently than non-COVID-19 sepsis cases. In addition, patients with COVID-19 sepsis require anticoagulant treatment at a higher rate and may present with microcirculation disorder, organ damage, and different clinical symptoms. In our study, the ICU admission and mean follow-up values of CRP, which is an acute phase reactant that plays a key role in the complement system and opsonization, were found to be significantly higher in the COVID-19 sepsis group. In addition, this group had significantly higher fibrinogen associated with inflammation and coagulopathy and significantly lower INR compared to the non-COVID-19 sepsis group. Considering that it is related to steroid treatment and the high incidence of diabetes in COVID-19 patients, the admission and mean glucose levels of our COVID-19 group were determined to be significantly higher.

When the parameters evaluating hepatic and gastrointestinal function were compared between the two groups, it was determined that the AST, ALT, bilirubin, and lipase values, which initially did not significantly differ, showed a significant increase in the COVID-19 sepsis group during the follow-up period. AST and ALT play an important role in the prognosis of COVID-19 (14). Cai et al. (15) reported that 76.3% of 417 patients with COVID-19 had impaired liver function test results, and 21.5% had liver damage at the time of hospitalization, while the ALT, AST, total bilirubin, and gamma-glutamyl transferase levels increased more than three times than the normal ranges. In a prospective observational study, Rasch et al. (16) found increased lipase levels in 31% of patients with COVID-19-associated ARDS without evidence of pancreatitis. Similarly, during the one-week follow-up, we detected significantly elevated lipase values in the COVID-19 sepsis group. Lipasemia seen after SARS-CoV-2 infection can be explained by the direct damage of the virus to pancreatic cells and decreased organ perfusion due to microcirculation and endothelial damage (16). The significant increase in bilirubin levels in the COVID-19 sepsis group during the follow-up period also indicates effects on bile duct epithelial cells (cholangiocytes) with a higher angiotensin-converting enzyme (ACE)-2 expression than hepatocytes (17). Unlike inflammatory damage in sepsis, involvement and direct organ damage due to SARS-CoV-2 are more prominent in all cells and organs where ACE-2 receptors are common.

When the mechanical ventilation parameters were compared between the two groups, the number of days on mechanical ventilation was found to be significantly higher in the COVID-19 sepsis group. The higher PEEP and FiO_2 levels and the lower tidal volume detected in our COVID-19 cases are consistent with the results of the study and FiO_2 levels and are consistent with the review of 20 studies by Tsonas et al. (18) in which they compared the mechanical ventilator parameters of non-COVID-19 and COVID-19 ARDS groups in 2021. In the current study, hypercarbia, an indicator of a ventilation/perfusion mismatch, was found to be significantly higher in the COVID-19 sepsis group, although the minute respiratory frequency was adjusted higher. While primary pulmonary sepsis mostly causes ARDS as a result of alveolar epithelial damage, pulmonary endothelial and alveolar epithelial damage is seen together in ARDS associated with COVID-19. It has been argued that rather than using the term typical ARDS, it would be more appropriate to refer to COVID-19 lung involvement as acute vascular distress syndrome (AVDS), which is characterized by an intrapulmonary right-to-left shunt, increased pulmonary blood flow, and ventilation/perfusion mismatch (19,20). The invasion of endothelial cells by SARS-CoV-2 via ACE-2 receptors and endotheliitis suggest a specific pulmonary vascular disorder induced by this virus, indicating AVDS rather than typical ARDS (21).

In our study, organ dysfunction in both sepsis groups with the primary focus of infection being the lungs were evaluated with ICU admission and seven-day follow-up SOFA scores, and these scores were found to be significantly higher in the COVID-19 sepsis group. In studies comparing SARS-CoV-2-related and non-COVID-19 organ damage in the literature, it was found that the SOFA scores were higher in the non-COVID-19 sepsis at the time of ICU admission, and organ dysfunction was also more prominent in this group (9,11,12). However, in contrast to our study, previous research did not re-evaluate patients for organ dysfunction during the follow-up period. In a prospective cohort study by Remy et al. (22) evaluating patients with COVID-19 and sepsis, the mean SOFA scores were reported to be similar between the two groups. In another prospective observational study conducted by Grigorescu et al. (23) to compare bacterial sepsis and COVID-19 sepsis cases, organ dysfunction was evaluated over a five-day follow-up period, and although the SOFA scores were similar between the two groups at baseline, they significantly increased in the COVID-19 sepsis group after five days of follow-up compared to the bacterial sepsis group. The reason for the multi-organ failure seen in SARS-CoV-2 sepsis may be systemic endotheliitis, endovasculitis, and direct viral cytotoxic effect, as well as vascular dysfunction, which has a more chronic course of irregular inflammatory response compared to other sepsis agents through a mechanism that has not yet been elucidated (24).

In our study, organ dysfunction in the patients with sepsis was evaluated with ICU admission and seven-day follow-up SOFA scores. By evaluating each component of this scoring system, the effects of sepsis due to different pathogens on each organ system and their changes over time were determined. In the neurological evaluation using the GCS score as a component of SOFA, COVID-19 sepsis was found to have a significantly higher score. This can be explained by the requirement for stronger sedation and longer prone positioning times in COVID-19 cases.

The admission SOFA score, used to evaluate hematological and cardiac dysfunction, was found to be significantly higher in the non-COVID-19 sepsis group. However, in the COVID-19 sepsis group, hepatic, renal, and cardiac dysfunction was more pronounced according to the SOFA scores evaluated during the follow-up. Although the rate of chronic renal failure was higher in the non-COVID-19 group, CRRT requirement and renal dysfunction significantly increased in the COVID-19 sepsis group during the follow-up period. It remains unclear whether SARS-CoV-2 contributes to this damage by directly targeting organs with a high expression of alternative cell receptors, especially ACE-2 and L-SIGN, or through the expression of genes on the coagulation system and endothelial immunomicrothrombosis mechanisms (25-28).

The mortality rates reported by Karakike et al. (8) in patients with COVID-19 requiring mechanical ventilation are similarly high when compared to the sepsis-related mortality data published before 2019 (29). In our study, the mortality rates were statistically similar between the two sepsis groups. In our study, we found that although the patients with COVID-19 sepsis were younger and had fewer comorbidities, this group had a similar mortality rate to the non-COVID pneumosepsis group. This finding reveals the destruction caused by COVID-19 viral sepsis with multisystemic involvement in healthy adults.

Our study has certain limitations. First, it had a single-center and retrospective design despite the large sample size of 717 patients. Second, although the causes of pneumosepsis in the non-COVID-19 group were similar to the literature, these factors were not differentiated. Third, admission and one-week follow-up values were evaluated to minimize hospital-acquired infections, but it was not possible to exclude cases complicated with culture-negative secondary infections. However, since pulmonary involvement mainly determines clinical presentation in patients with COVID-19 cases, the inclusion of primary pulmonary sepsis cases in the non-COVID-19 sepsis group and the examination of their effects on the organ system separately based on the idea that they can better define each other can be regarded as the strong aspects of our study. Another strength of the study is that data were obtained from the electronic recording system verified by the researchers.

Conclusion

Despite the patient population with lower mean age and less comorbidities, it was observed that organ dysfunction was higher in COVID-19 sepsis patients during admission to the ICU and follow-up. Mortality rates were similar in the two sepsis groups. Although the definition of sepsis-3 is not pathogen-specific, SARS CoV-2-associated sepsis cases occur with different phenotypic features.

While the pathogen causing sepsis can be controlled with rapid diagnosis and appropriate antimicrobial treatment, these patients become more susceptible to secondary infections due to the lack of appropriate antiviral treatment in COVID-19 sepsis, immunomicrothrombosis, secondary organ damage, and widespread immunosuppression.

Ethics

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital (decision no: 2021-20-17, date: 18.10.2021).

Informed Consent: Due to the pandemic condition, verbal informed consent was obtained from the relatives of the patients included in the study.

Authorship Contributions

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

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ÖZGÜN ARAŞTIRMA / *ORIGINAL RESEARCH*

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COVİD-19 Hastalarında Yoğun Bakım Ünitesi Kabulündeki Antitrombin Seviyelerinin Prognostik Önemi

The Prognostic Value of Antithrombin Levels in COVID-19 Patients on Intensive Care Unit Admission

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Sunulan: Makalenin özeti 21-25 Ekim 2023 tarihinde İtalya/Milan'da yapılan ESICM kongresinde poster bildiri olarak sunulmuştur.

ÖZ *Amaç:* Aşırı enflamasyona bağlı hiperkoagülopati, koronavirüs hastalığı-2019 (COVİD-19) hastalarında mortalite ve organ yetmezliğinden sorumlu olabilir. Anormal pıhtılaşma profilleri, kötü sonlanımlarla ilişkilendirilmiştir. Bu çalışmada, yoğun bakım ünitesine (YBÜ) kabul edilen kritik COVİD-19 hastalarında antitrombin (AT) düzeylerinin prognostik değerini değerlendirmeyi amaçladık.
Gereç ve Yöntem: Dört yüz on kritik COVİD-19 hastası retrospektif olarak analiz edildi. YBÜ'ye yatışta enflamatuvar ve konvansiyonel pıhtılaşma parametreleri ile AT aktivite seviyeleri kaydedildi. Hastaların klinik sonuçları değerlendirildi.
Bulgular: YBÜ kabulündeki AT seviyeleri ölenlerde yaşayanlara göre anlamlı olarak daha düşüktü (%77,9 vs. %82,5; p=0,027). D-dimer değerleri ise ölenlerde yaşayanlara anlamlı olarak daha yüksekti (2775 vs. 1495 µg/L; p<0,001). AT ve D-dimer için kesme değerleri sırasıyla %70,5 ve 1585 µg/L olarak bulundu. AT ve D-dimer birlikte analiz edildiğinde, mortalite tahmini sadece D-dimer veya AT'den daha iyi olarak bulundu.
Sonuç: Düşük AT seviyeleri, COVİD-19 hastalarında yüksek D-dimer seviyeleri ile birlikte ciddi hastalık ve mortalitenin göstergesi olabilir. COVİD-19 hastalarında AT eksikliğini teşhis etmek ve yönetmek hayatta kalmak için faydalı olabilir. Bu nedenle, AT seviyesi ölçümleri rutin laboratuvar araştırması paneline dahil edilmelidir.
Anahtar Kelimeler: Antitrombin, COVİD-19, D-dimer, hiperkoagülopati, mortalite

ABSTRACT *Objective:* Hypercoagulopathy related to hyperinflammation may be responsible for mortality and organ failure in coronavirus disease-2019 (COVID-19) patients. Abnormal coagulation profiles were associated with poor outcomes. In this study, we aimed to evaluate the prognostic value of antithrombin (AT) levels in critically ill COVID-19 patients on the intensive care unit (ICU) admission.
Materials and Methods: Four hundred ten critically ill COVID-19 patients were retrospectively analyzed. Inflammatory and conventional coagulation parameters as well as AT activity levels were recorded on the ICU admission. The clinical outcomes of patients were analyzed.
Results: AT levels on the ICU admission were significantly lower in non-survivors than survivors (77.9% vs. 82.5%; p=0.027). Besides AT, D-dimer values of non-survivors were significantly higher than survivors (2775 vs. 1495 µg/L; p<0.001). The cut-off levels for AT and D-dimer were 70.5% and 1585 µg/L, respectively. When AT and D-dimer were analyzed together, mortality estimation was better than only D-dimer or AT.
Conclusion: Low AT levels may be indicative of severe disease and mortality together with high D-dimer levels in COVID-19 patients. Diagnosing and managing AT deficiency in COVID-19 patients could be beneficial for survival. So AT level measurements should be included in the routine panel of laboratory investigation.
Keywords: Antithrombin, COVID-19, D-dimer, hypercoagulopathy, mortality

Giriş

Haziran 2023 itibariyle, Dünya Sağlık Örgütü'ne bildirilen 6 milyondan fazla ölüm dahil olmak üzere 767 milyon doğrulanmış koronavirüs hastalığı-2019 (COVİD-19) olgusu olmuştur (1). COVİD-19'a bağlı aşırı enflamasyon durumu, hastalarda endotel hücre aktivasyonuna ve hiperkoagülopatiye katkıda bulunmaktadır (2). COVİD-19'un neden olduğu hiperkoagülopati de organ yetmezliklerine ve ölüme yol açabilmektedir. Bu nedenle klinisyenlerin etkin bir antikoagülan tedavi stratejisi uygulamaları ve tedavi yeterliliğini monitorize etmeleri sağkalım açısından önemlidir. Bu konuda yapılan çalışmalarda özellikle D-dimer ve fibrinojen düzeylerinin COVİD-19 hastalarında prognostik öneme sahip olduğu bulunmuştur (3). Ancak antitrombin (AT) düzeylerinin sonuca etkisine ilişkin veriler azdır.

AT, doğal antikoagülan olup trombin ve faktör Xa'nın ana inhibitörüdür. Trombozun önlenmesi ve kanın akışkanlığı için gereklidir. Bunun yanı sıra AT'nin anti-enflamatuvar özelliklere sahip olduğu ve düşük AT düzeylerinin sepsis hastalarında kötü prognozla ilişkili olduğu bildirilmiştir (4,5). COVİD-19 hastalarında yapılan çalışmalarda da azalmış AT seviyeleri kaydedilmiştir (6,7). Yüz dört COVİD-19 hastasıyla yaptığımız önceki çalışmamız, düşük AT düzeylerinin mortalite ve tromboembolik olaylarla ilişkili olduğunu göstermiştir (8).

Biz bu retrospektif çalışmada, COVİD-19 hastalarının yoğun bakım ünitesine (YBÜ) kabulü sırasındaki AT seviyelerinin, hastalık prognozuyla ilişkisini incelemeyi amaçladık.

Gereç ve Yöntem

İstanbul Üniversitesi, İstanbul Tıp Fakültesi'nde Mart 2020 ile Haziran 2021 tarihleri arasında YBÜ'de takip edilmiş olan ve laboratuvar ile onaylanmış 18 yaş ve üzeri COVİD-19 hastasının verileri retrospektif olarak incelendi. Verilerine ulaşılamayan, tekrarlanan yatışı olan ve 18 yaş altı hastalar çalışma dışı bırakıldı. COVİD-19 tanısı, hastaların nazofarengeal sürüntü örneğinin revers transkriptaz-polimeraz zincir reaksiyonu ile değerlendirmesi ile konuldu. Dünya Sağlık Örgütü'ne göre şiddetli akut solunum sendromu koronavirüs-2 pnömonisi teşhisi konuldu (9). Veriler mevcut elektronik tıbbi kayıtlardan ve hasta dosyalarından araştırmacılar tarafından toplandı. İstanbul Üniversitesi, İstanbul Tıp Fakültesi Klinik Araştırmalar Etik Kurulu çalışmayı onayladı (karar no: 12, tarih: 29.05.2020). Retrospektif çalışma olması nedeniyle hastalardan yazılı bilgilendirilmiş onam alınmadı.

Hastalar YBÜ'de kalış süresince klinik sonlanımlarına göre yaşayanlar ve ölenler olmak üzere 2 gruba ayrıldı. Hastaların YBÜ kabulü sırasındaki demografik, klinik ve laboratuvar verileri kaydedildi. Hastalara ait yaş, cinsiyet, vücut kitle indeksi, başvuru sırasındaki hastalık şiddeti [akut fizyoloji ve kronik sağlık değerlendirmesi-II (APACHE-II) ve girişte sıralı organ yetmezliği değerlendirmesi (SOFA) skorları], komorbiditeleri (kronik kalp hastalığı, hipertansiyon, kronik pulmoner hastalık, diabetes mellitus, kronik böbrek yetmezliği, maligniteler, kronik serebrovasküler hastalık) ve laboratuvar değerleri [trombosit sayısı, protrombin zamanı (PZ), aktive parsiyel tromboplastin zamanı, ferritin, D-dimer, AT aktivitesi, fibrinojen, C-reaktif protein (CRP), lökosit, lenfosit], PaO_2/FiO_2 oranları, klinik sonlanım, YBÜ yatış süreleri (gün), renal replasman tedavisi, mekanik ventilatör tedavisi ihtiyaçları ile vazopressör tedavi ihtiyaçları kaydedildi ve gruplar arasında karşılaştırıldı.

Laboratuvarımızda AT aktivitesinin normal aralığı %75-125 olması nedeniyle <%75 olan AT seviyeleri taze donmuş plazma (TDP) (10 mL/kg) ile tedavi edildi. Türkiye Cumhuriyeti Sağlık Bakanlığı'nın önerilerine göre YBÜ'ye kabul edilen tüm hastalara kontrendikasyon yoksa trombofilaksi amacıyla günde iki kez 40 mg düşük moleküler ağırlıklı heparin (enoksaparin), asetilsalisilik asit ve dipiridamol verildi.

Çalışmamızda, birincil sonlanım noktası COVİD-19 hastalarının YBÜ'ye kabulü sırasındaki AT seviyeleri ile sağkalım arasındaki ilişki, ikincil sonlanım noktası ise diğer hematolojik ve enflamatuvar belirteçlerin COVİD-19'un prognozu üzerine etkisidir.

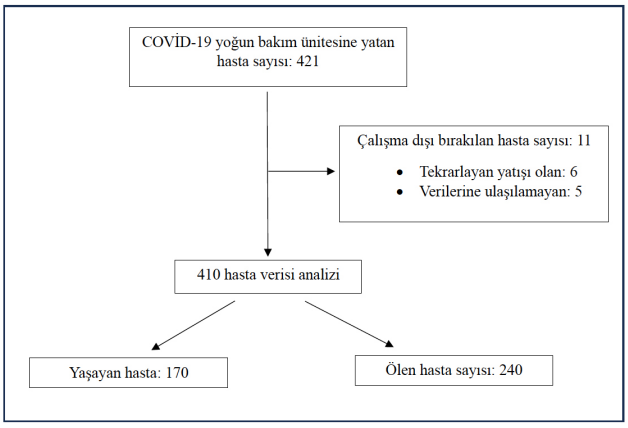
İstatistiksel Analiz

Tanımlayıcı analizler uygulandı ve Kolmogorov-Smirnov testi ile normallik kontrol edildi. Sürekli değişkenler ortalama ± standart sapma, kategorik değişkenler frekans (yüzde; %) olarak verildi. Grup karşılaştırmaları ki-kare analizi kullanılarak yapıldı. Normal dağılım gösteren sürekli değişkenlerin analizi için Student t-testi kullanıldı. Normal dağılım göstermeyen sürekli değişkenler için Mann-Whitney U testi kullanıldı ve değişkenler medyan olarak sunuldu. Korelasyonlar, Spearman korelasyon katsayısı kullanılarak yapıldı. Kesme değerlerini belirlemek için bir alıcı işletim karakteristiği (ROC) eğrisi analizi kullanıldı. Hastaların sağkalım analizleri Kaplan-Meier eğrisi kullanılarak yapıldı. İstatistiksel analiz SPSS 25.0 istatistik paketi (Chicago, Illinois, ABD) ile yapıldı ve p-değerinin <0,05 olması istatistiksel olarak anlamlı kabul edildi.

Bulgular

Dört yüz yirmi bir COVİD-19 hastasının verileri incelendi. Altı hastanın tekrarlayan yatışı olması ve 5 hastanın da AT seviyeleri bakılmaması nedeniyle 11 hasta çalışma dışı bırakıldı (Şekil 1). Çalışmaya dahil edilme kriterlerini karşılayan 410 kritik COVİD-19 hastasının demografik verileri Tablo 1'de özetlenmiştir. Yüz yetmiş hasta YBÜ'den servise taburcu edilirken 240 hasta YBÜ yatışı esnasında kaybedilmiştir (%41 vs. %59). Ölen hastaların yaş ortalaması, YBÜ kabulündeki SOFA ve APACHE-II skorları yaşayanlara göre daha yüksekti (p=0,005, p<0,001, p<0,001, sırasıyla).

Hastaların klinik özellikleri incelendiğinde ölen hastalarda yaşayanlara göre mekanik ventilasyon, renal replasman tedavisi ve vazopressör tedavi gereksiniminin anlamlı olarak daha fazla olduğu görüldü (p<0,001) (Tablo 2). Uygulanan antikoagülan tedaviler açısından ise her iki grup arasında anlamlı farklılık görülmedi.



Şekil 1. Çalışma akış şeması
COVİD-19: Koronavirüs hastalığı-2019

Tablo 1. Hastaların demografik ve klinik özellikleri

Parametreler	Yaşayanlar (n=170)	Ölenler (n=240)	p-değeri
Cinsiyet (erkek) (n, %)	113 (%66)	149 (%62)	0,36
Yaş (yıl)	63,5 (54-73)	68 (58-77)	**0,005**
Vücut kitle indeksi (kg/m²)	26 (25-26,3)	26 (25-28)	**0,034**
APACHE-II	15,5 (10,8-21)	19 (14-26)	**<0,001**
YBÜ kabulündeki SOFA	4 (3-6)	6 (4-8)	**<0,001**
Komorbiditeler			
Hipertansiyon (n, %)	89 (%52)	122 (%50)	0,76
Diabetes mellitus (n, %)	58 (%34)	84 (%35)	0,85
Kronik kardiyak hastalık (n, %)	56 (%32)	95 (%39)	0,17
Kronik pulmoner hastalık (n, %)	33 (%19)	42 (%17)	0,62
Kronik serebrovasküler hastalık (n, %)	14 (%8)	36 (%15)	**0,04**
Kronik renal hastalık (n, %)	20 (%11)	37 (%15)	0,30
Malignite (n, %)	26 (%14)	59 (%24)	**0,02**

YBÜ: Yoğun bakım ünitesi, APACHE-II: Akut fizyolojik ve kronik sağlık değerlendirmesi-II, SOFA: sıralı organ yetmezliği değerlendirmesi

Tablo 2. Hastaların klinik özellikleri ve uygulanan antikoagülan tedaviler

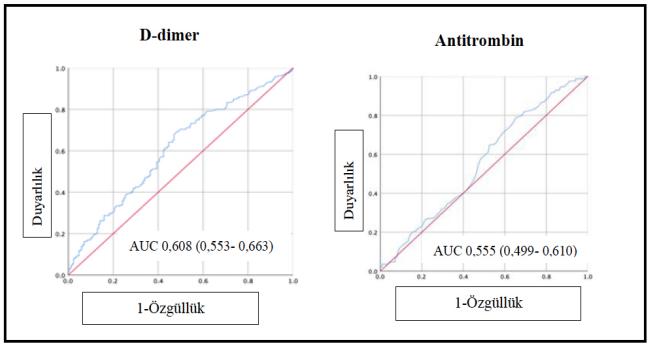
Parametreler	Yaşayan (n=170)	Ölen (n=240)	p-değeri
Mekanik ventilasyon ihtiyacı (n, %)	78 (%45)	220 (%91)	**<0,001**
Vazopressör tedavi ihtiyacı (n, %)	80 (%47)	213 (%89)	**<0,001**
Renal replasman tedavi ihtiyacı (n, %)	24 (%14)	76 (%31)	**<0,001**
YBÜ kalış (gün)	8 (5-14)	7,5 (3-13)	**0,038**
Asetilsalisilik asit (n, %)	162 (%95)	232 (%97)	0,48
Düşük moleküler ağırlıklı heparin (n, %)	170 (%100)	239 (%99,6)	0,39
Dipiridamol (n, %)	164 (%96,5)	232 (%97)	0,91

YBÜ: Yoğun bakım ünitesi

Hastaların laboratuvar parametreleri Tablo 3'te gösterilmiştir. Ölen hastalarda yaşayanlara göre istatistiksel olarak anlamlı daha düşük AT seviyeleri kaydedildi (%77,9 vs. %82,5; p=0,027). D-dimer ve ferritin değerleri ise ölenlerde yaşayanlara göre anlamlı derecede daha yüksekti (2275 vs. 1495 µg/L, p<0,001; 1060 vs.741 ng/mL, p=0,001, sırasıyla).

YBÜ kabulündeki AT aktivitesi ve D-dimer seviyeleri, APACHE-II skoru (r=-0,274, p<0,001; r=0,163; p=0,001, sırasıyla) ve SOFA skoru (r=-0,33, p<0,001; r=0,212, p<0,001, sırasıyla) ile negatif korelasyon gösterdi. Ayrıca AT, D-dimer ve CRP ile anlamlı olarak negatif korele bulundu (r=-0,109, p=0,028; r=-0,182, p<0,001, sırasıyla).

Mortalite tahmini için AT ve D-dimer seviyelerine göre ROC eğrileri tasarlandı (Şekil 2). AT aktivitesi için kesme değer %70,5 idi (duyarlılık: %78, özgüllük: %34). D-dimer için ise kesme değer 1585 µg/L bulundu (duyarlılık: %69 ve özgüllük: %52).

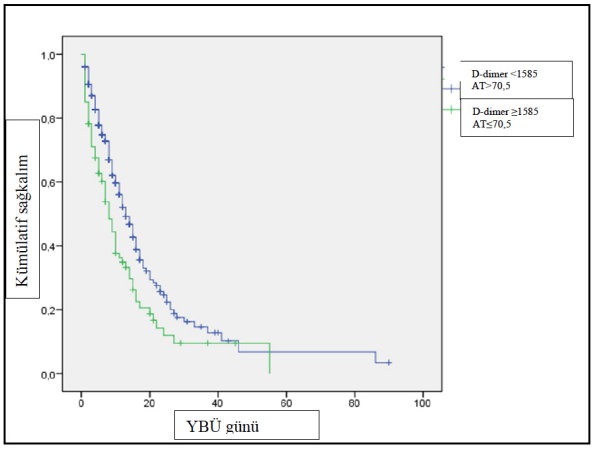


Şekil 2. D-dimer ve antitrombin seviyelerine göre mortalite tahmini için ROC eğrileri
ROC: Alıcı işletim karakteristiği, AUC: eğri altındaki alan

Şekil 3'te AT ve D-dimer için Kaplan-Meier sağkalım analizi yapılmıştır. Eş zamanlı AT seviyesi ≤%70,5 ve D-dimer seviyeleri ≥1585 µg/L olan hastalarda kümülatif sağkalım daha düşüktü (log-rank ki-kare değeri =10,44; p=0,001).

Tartışma

Bu retrospektif çalışmanın ana bulgusu, COVİD-19 hastalarında YBÜ kabulünde diğer koagülasyon parametreleri ile birlikte düşük AT düzeylerinin mortalite ile ilişkili olmasıdır. Çalışmamızda incelediğimiz 410 COVİD-19 hastasında, ölenlerde yaşayanlara göre anlamlı derecede daha düşük AT



Şekil 3. COVİD-19 hastalarında Kaplan-Meier sağkalım analizi. Antitrombin (AT) seviyesi ≤%70,5 ve D-dimer ≥1585 µg/L (n=87) olan hastalar yeşil çizgiyle, olmayanlar (n=323) ise mavi çizgiyle gösterilmiş olup AT aktivitesi ≤%70,5 ve D-dimer ≥1585 µg/L olan hastalarda daha kısa yaşam süresi gözlenmekte (p=0,001)
COVİD-19: Koronavirüs hastalığı-2019, YBÜ: yoğun bakım ünitesi

Tablo 3. Hastaların yoğun bakım ünitesi kabulündeki laboratuvar parametreleri

Değişkenler	Yaşayanlar	Ölenler	p-değeri
Antitrombin aktivitesi (%)	82,5±19	77,9±21,1	**0,027**
PaO_2/FiO_2	126,5 (89,8-213,3)	98,5 (70-162,3)	**<0,001**
CRP (mg/L)	98 (39,3-180,7)	119,8 (49-184,5)	0,196
Lökosit (10^8/µL)	9,6 (5,9-13,7)	10,1 (7,2-13,5)	0,302
Ferritin (ng/mL)	741,5 (316,3-1475,8)	1060,5 (482,3-2195)	**0,001**
D-dimer (µg/L)	1495 (877,5-3280)	2275 (1250-4630)	**<0,001**
Lenfosit (10^8/µL)	0,6 (0,4-1,0)	0,59 (0,3-0,97)	0,169
Trombosit (10^8/µL)	247 (159,8-344,5)	218,5 (160-316,5)	0,231
Fibrinojen (mg/dL)	594,5 (473,8-693,1)	555 (425,1-684,9)	0,218
PZ (sn)	14,1 (13,2-16)	14,3 (13,1-16,4)	0,639
aPTZ (sn)	30 (26,5-35,4)	30,5 (26,2-36,6)	0,502

PaO_2: Parsiyel oksijen basıncı, FiO_2: inspire edilen oksijen fraksiyonu, CRP: C-reaktif protein, PZ: protrombin zamanı, aPTZ: aktive protrombin zamanı

ve daha yüksek D-dimer seviyeleri bulunmuştur. Ayrıca AT ile D-dimerin birlikte incelenmesiyle sağkalım tahmininin daha iyi olabileceği gösterilmiştir.

Sepsis hastalarında yapılan çeşitli çalışmalarda düşük AT seviyelerinin mortaliteyle ilişkili olduğu belirtilmesine rağmen COVİD-19 hastalarındaki çalışmalar sınırlıdır. Bazı çalışmalarda düşük AT değerleri, COVİD-19 hastalarında tromboembolik olaylar ve mortalite için bir risk faktörü olarak değerlendirilmiştir (6,8). Önceki bir çalışmada, AT seviyeleri ölenlerde yaşayanlara göre daha düşük olmasına rağmen bu fark istatistiksel olarak anlamlı bulunmamıştır (%84 vs. %91) (10). Yine başka bir çalışmaya göre, fark istatistiksel olarak anlamlı olmasa da terminal dönemdeki hastalarda AT seviyeleri daha düşüktü (11). Chen-Goodspeed ve ark.'nın (12) yaptığı prospektif çalışmada AT seviyesinin 100'ün altında olması mortalitede 8 kat artışla ilişkilendirilmiştir. Ancak örneklem sayısının küçük olması ve kısa izlem süresi bu çalışmanın sonuçlarına sınırlılık getirmiştir. Bizim çalışmamızda da literatüre benzer şekilde ölen hastalarda AT seviyelerinin daha düşük olduğu gözlendi. Ancak çalışmamızın büyük örneklem büyüklüğü, uzun zaman çerçevesi ve hasta çeşitliliğinden kaynaklı AT seviyelerindeki farklılık istatistiksel olarak anlamlı bulunmuştur.

COVİD-19 hastalarının prognozunu değerlendirmek için çeşitli biyobelirteçlerin kullanımı önceki çalışmalarda belirtilmiştir. Uluslararası Tromboz ve Hemostaz Derneği, COVİD-19 hastalarında pıhtılaşma parametrelerinden, D-dimer, PZ ve fibrinojenin izlenmesini önermiştir (13). Özellikle son araştırmalar, yüksek D-dimer düzeylerinin yüksek mortalite riski taşıyan hastaları tanımlayabileceğini ve böylelikle kritik bakım, erken yönetim ihtiyacı hakkında bilgilendirici olabileceğini bildirmiştir (2,10). Retrospektif bir çalışmada YBÜ kabulündeki D-dimer seviyesi için kesme değeri 2140 µg/L bulunmuş ve %88,2 duyarlılık, %71,3 özgüllük ile hastane mortalitesini tahmin edebileceği gösterilmiştir (14). Literatüre benzer şekilde bizim çalışmamızda da ölenlerde D-dimer düzeyleri anlamlı olarak daha yüksekti ancak D-dimer için kesme değeri daha düşük bulunmuştur.

COVİD-19 hastalarında D-dimerin diğer parametrelerle ilişkisi değerlendirilmiştir. D-dimer ve CRP'nin birlikte değerlendirilmesinin tromboemboli gelişimi açısından yüksek pozitif öngörüye sahip olduğu belirtilmiştir. Bu sonuçlar, D-dimer >9000 µg/L ve CRP >280 mg/mL olduğunda tromboemboli olasılığının %92 olduğunu göstermektedir. (15). Başka bir çalışmada, D-dimer ve CRP değerleri birlikte analiz edildiğinde bu kombinasyon, COVİD-19 ciddiyetinin tahmininde, yalnızca CRP veya D-dimere göre daha iyi bulunmuştur (16). Çalışmamızda AT ve D-dimer birlikte analiz edilmiştir. Sadece D-dimer veya sadece AT değeri değil bu iki parametrenin birlikte değerlendirilmesiyle mortalite tahmininin daha iyi yapılabileceği gösterilmiştir.

AT değerleri ile diğer belirteçler arasındaki ilişki henüz netlik kazanmamıştır. Son yıllarda yapılan bir çalışmada AT ile D-dimer ile arasında anlamlı negatif korelasyon gözlenmesine rağmen faktör Xa, uluslararası normalizasyon oranı ya da fibrinojen ile AT arasında bir korelasyon gösterilememiştir (12). Aynı çalışmada CRP ile AT arasında negatif korelasyon gözlenmesine rağmen bu durum istatistiksel olarak anlamlı değildir. Yaptığımız çalışmada AT, D-dimer ve CRP ile anlamlı olarak negatif korelasyon göstermiş olup aşırı enflamasyonla ilgili bize yol göstermesi açısından AT'nin önemli olabileceğini göstermektedir.

AT, anti-enflamatuvar özellikleri de olan bir antikoagülandır. COVİD-19'da aşırı enflamasyon ve koagülopatiye bağlı olarak düzeyinin azalmasıyla organ yetersizliklerinin artabileceği belirtilmiştir (17). Yakın zamandaki bir çalışmada COVİD-19 hastalarındaki düşük AT seviyesinin artmış mekanik ventilasyon ve ekstrakorporeal membran oksijenasyon desteği ile ilişkili olduğu bildirilmiştir (18). Ancak düşük AT düzeyleri ile böbrek hasarı ya da diğer organ yetersizlikleri arasındaki ilişkiyi inceleyen çalışma sayısı sınırlıdır. Çalışmamızda yaşayan ve ölen hastalar arasında organ yetersizlikleri karşılaştırılmış olup AT değerine göre değerlendirme yapan çalışmalara ihtiyaç vardır.

AT eksikliği, etkin antikoagülan tedavi için AT konsantreleri veya TDP ile tedavi edilebilir. Düşük doz AT tedavisinin (3 gün boyunca 1.500 IU/gün) sepsis kaynaklı dissemine intravasküler koagülasyon (DİK) olan hastalarda sonuçları iyileştirdiği bildirilmiştir (19). Japonya'da, AT seviyeleri <%70 olan sepsise bağlı DİK hastalarında AT takviyesi kullanılmıştır (20). Protokolümüze göre AT seviyeleri <%75 olan hastalara ülkemizde AT konsantresi bulunmadığı için TDP uygulanmıştır. Çünkü laboratuvarımızın AT için normal referans aralığı %75-125 arasındaydı. Ancak çalışmamızda AT'nin mortalite açısından kesme değeri %70,5 olarak bulunmuştur. AT tedavisi için net bir kesme değer olmayıp daha fazla çalışma yapılmasına ihtiyaç bulunmaktadır.

Bu çalışmanın belirli sınırlılıkları vardır. İlk olarak, çalışma retrospektif olarak gözlemsel bir şekilde tasarlanmıştır. İkincisi, ikincil enfeksiyon verileri bu çalışmaya dahil edilmemiştir. Sepsis kaynaklı koagülopatiler, bu hastalarda pıhtılaşma profili üzerinde ek bir etkiye sahip olabilir.

Sonuç

COVİD-19 hastalarında D-dimer seviyesinin klinik sonlanımla ilişkisi çok sayıda çalışmada gösterilmiştir. Ancak AT düzeylerinin sonuca etkisine ilişkin veriler azdır. Çalışmamız, yüksek D-dimer ile birlikte düşük AT seviyelerinin COVİD-19 hastalarında kötü sonlanımla ile ilişkili olduğunu göstermektedir. COVİD-19 hastalarında AT eksikliğini teşhis etmek ve yönetmek sağkalım için faydalı olabilir. Bu nedenle, AT seviyesi ölçümlerinin rutin laboratuvar araştırması paneline dahil edilmesi gerektiği sonucu varmış bulunmaktayız.

Etik

Etik Kurul Onayı: Çalışma için İstanbul Üniversitesi, İstanbul Tıp Fakültesi Klinik Araştırmalar Etik Kurulu tarafından onay verildi (karar no: 12, tarih: 29.05.2020).

Hasta Onamı: Retrospektif çalışma olması nedeniyle hastalardan yazılı bilgilendirilmiş onam alınmadı.

Yazarlık Katkıları

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OLGU SUNUMU / *CASE REPORT*

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Fournier Gangrenili Hastada Somatik Oksimetri Takibi

Somatic Oximetry Monitoring in a Patient with Fournier Gangrene

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ÖZ Fournier gangreni, perine ve genital bölgede, fasyal planlar arasında hızlı yayılan ve yumuşak doku nekrozu ile seyreden mortal bir cerrahi acil durumdur. Nekrotik dokuların erken debridmanı ile dokuların oksijenizasyonunu artırmak tedavinin amacıdır. Bu olgunun tedavisinde sıvılar, antibiyotikler ve yapılan debridmanların etkinliğini daha yakın değerlendirebilmek için hemodinamik takip yanında non-invaziv bir yöntem olan somatik oksimetri monitörizasyonu uygulandı. Tedavinin etkinliğinde, rSO_2 değerleri ile diğer laboratuvar ve takip parametrelerinin korele olarak yükseldiği gözlemlendi.
Anahtar Kelimeler: Fournier gangreni, nekrotik doku, doku oksijenasyonu, somatik oksimetri, rSO_2

ABSTRACT Fournier's gangrene is a mortal surgical emergency characterized by rapidly spreading soft tissue necrosis between fascial planes in the perineum and genital area. The goal of treatment is early debridement of necrotic tissues to improve tissue oxygenation. In the treatment of this case, somatic oximetry monitoring, which is a non-invasive method, was applied in addition to hemodynamic monitoring to evaluate the effectiveness of fluids, antibiotics and debridements more closely. In the efficacy of the treatment, it was observed that rSO_2 values correlated with other laboratory and follow-up parameters.
Keywords: Fournier's gangrene, necrotic tissue, tissue oxygenation, somatic oximetry, rSO_2

Giriş

Fournier gangreni, perine ve genital bölgede, fasyal planlar arasında hızlı yayılan ve yumuşak doku nekrozu ile seyreden önemli cerrahi acillerdendir. Mortalitesi günümüzde teşhis ve tedavi yöntemlerindeki gelişmelere rağmen %16-40 arasında değişmektedir (1). Tedavideki amaç nekrotik dokuların erken debridmanıyla dokuların oksijenizasyonunu artırmaktır. Standart monitorizasyonda kullanılan kalp hızı (Nb), periferik oksijen saturasyonu (SpO_2), hemoglobin ve hematokrit (Htc) düzeyi, laktat, pH, baz açığı gibi parametreler doku oksijenasyonunu göstermede her zaman yeterli olmayabilir. Bu nedenle doku oksijenasyonunun (rejyonel oksijen saturasyonu, rSO_2), non-invaziv değerlendirilmesi için near-infrared spektroskopi (NIRS) tekniği kullanılmaktadır.

NIRS tekniği ile değerlendirilen somatik/serebral oksimetre, bölgesel oksijen doygunluğunu izlemede gerçek zamanlı bilgi vermekte ve sensör altında kalan dokudaki perfüzyonun yeterliliği hakkında klinik veri sunmaktadır. Ayrıca bölgesel oksijen dağıtımı ve oksijen tüketimi arasındaki kritik dengede oluşan değişimin de hızlı göstergesidir (2). Bu teknikle periferal oksijenasyon ve sistemik hemodinamik takip ölçütleri gibi değişkenlerin öngöremediği verileri elde etmek mümkündür.

Olgumuzda, Fournier gangreninde nekrotik dokuların en yakın yerine uygulanan somatik oksimetriyle hastanın hemodinamik takibinin ve yara iyileşmesinin, doku oksijenizasyonu ile olan korelasyonunu vurgulamayı amaçladık.

Olgu Sunumu

Olgumuz ateş, halsizlik, terleme, ishal, sırt ağrısı, skrotumda ağrı ve renk değişikliği sebebiyle ambulansla acil servise getirildi. Kırk altı yaşındaki erkek hastanın özgeçmişinde, sadece diabetes mellitus vardı. İki gün önce ishal, sırt ağrısı nedeniyle başka bir merkeze başvuran hastaya adını bilmediği intramusküler tedavi uygulanmış, ertesi gün uyluk iç yüzünde ağrı ve hassasiyeti olmuştu.

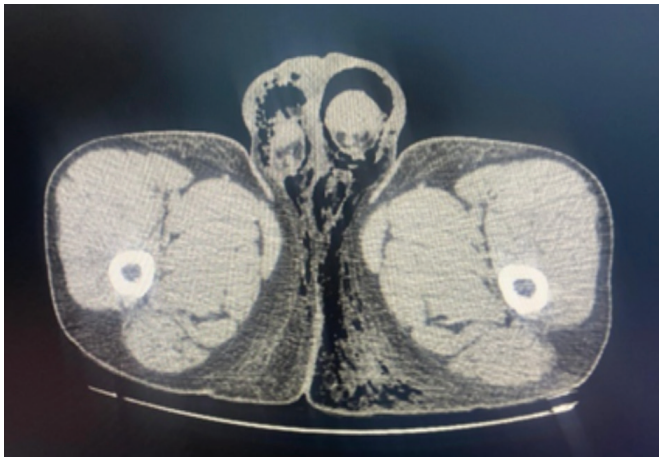
Hastanın genel durumu kötü, takipneik, taşikardik, konfüze, toksik görünümde, ateş: 38,1 °C, kan basıncı: 90/60 mmHg, Nb: 105/dk, solunum sayısı: 32/dk,

SpO_2: %97 ölçüldü. Fizik muayenesinde, skrotumda yaygın ödem, hiperemik nekrotize alanlar, perianal bölgeye uzanan gangrenöz alanlar izlendi (Şekil 1). Her iki testis hassastı.

Laboratuvar sonuçlarına göre [glukoz: 420, kan üre nitrojeni: 40, kreatinin: 1,43, glomerül filtrasyon hızı: 57, Na: 121, K: 3,3, C-reaktif protein (CRP): 350, prokalsitonin: 78, platelet: 71.000, arter kan gazı; pH: 7,4, HCO_3:16, laktat: 5,8, uluslararası normalleştirilmiş oran: 1,3] sepsis tablosu mevcuttu (Tablo 1,2). Hasta septisemi, metabolik asidoz, pansitopeni nedeniyle genel cerrahi, üroloji, nefroloji, enfeksiyon hastalıkları ve hematoloji klinikleri ile konsülte edildi (Tablo 1,2). Fournier gangreni tanısı doğrulanan hastaya elektrolit ve HCO_3 replasmanı yapıldıktan sonra acilen ameliyata alındı. Genel cerrahi ve üroloji klinikleri tarafından beş saat süren operasyonda, perine ve skrotuma agresif debritman ve fasyotomi yapılan hasta postoperatif yoğun bakım ünitesine (YBÜ) yatırıldı.

İntravenöz sıvı yüklemesi, kristalize insülin ve bikarbonat infüzyonu, metranidazol 3x1 g, imipenem 4x500 mg, vankomisin 2x1 g ve flukonazol 1x400 mg tedavileri başlandı. Eritrosit süspansiyonu, taze donmuş plazma replasmanı yapıldı ve hasta parenteral beslenmeye başlandı.

Hastanın sırt bölgesinde yara alanının sınırına en yakın yere [bilateral T8 seviyesinde, scapula inferiorunda, posterior axiller hat, (Şekil 2,3)] NIRS probları yapıştırılarak somatik monitörizasyon (rSO_2) ile doku oksijenizasyon takibi yapıldı. Başlangıçta bilateral rSO_2 değerleri sağ/sol: 64/50 olarak ölçüldü fakat yaklaşık altı saat sonra bu değerin sağ/sol: 50/33 olarak gerilediği görüldü (Şekil 4, Tablo 1). Yara kültürlerinde *Escherichia coli* ve *Streptococcus mitis*, kan kültüründe koagülaz negatif stafilokok üredi.



Şekil 1. Fournier gangreni gelişen alanların (scrotum, perine) görüntüleme bulguları

Üçüncü günde prokalsitonin ve CRP geriledi. rSO_2 sağ/sol: 60/40 ölçüldü (Tablo 1). Hastaya yatışının beşinci gününde kolostomi açıldı. Günlük yara yeri pansumanı ve günaşırı olarak ameliyathanede sedasyon altında yara debridmanı yapıldı. Bu uygulamalardan sonra rSO_2 değerlerinde sağ/sol: 60/44, 64/63 ve 69/71 olarak yükselmeler gözlemlendi. On beşinci günde intraoperatif alınan yara yeri kültüründe *E. coli* ve *Acinetobacter baumannii* üredi. Eritrosit ve trombosit süspansiyonu ve albumin replasmanına devam edildi. Tedaviye kolistin 2x150 mg eklendi. Hastanın YBÜ'de on sekiz günlük yatışı süresince vazopressör ajan ihtiyacı olmadı. CRP ve prokalsitonin değerleri geriledi, sepsis tablosu düzeldi. Perine ve skrotumdaki yaraları da önemli ölçüde düzelen hasta, rSO_2 değerleri sağ/sol: 71/72 olarak genel cerrahi servisine devredildi (Tablo 1).

Serviste aralıklı olarak pansuman yapılmaya devam edildi, kolostomisi kapatıldı. Flukonozal ve vankomisin 29 gün, kolistin 53 gün, imipenem 67 gün verildi. Plastik cerrahi tarafından iki kez deri grefti konulan ve flep yapılan hasta iki aylık yatıştan sonra şifa ile taburcu edildi. Bu olgu sunumu için hastadan bilgilendirilmiş onam alınmıştır.

Tartışma

Fournier gangreninde, perianal ve genital bölgedeki fasyal planlar boyunca agresif seyirli doku nekrozu sepsise ilerleyerek yüksek mortaliteye sahip klinik bir tablo oluşabilir. Gangrenöz dokuya en yakın ve uygun alandan somatik oksimetri monitörizasyonu uygulanması hastanın tedavi sürecinin yakın takibinde faydalı olmuştur.

Yoğun bakımda sık karşılaşılan durumlarda doku oksijenasyonunun yakın takibi gerekli olup ve NIRS doku oksijenasyon parametreleri arasında güçlü bir yere sahiptir. Serebral ve doku oksimetresi, bölgesel oksijenasyonu ölçmenin basit yoludur. NIRS'nin gösterdiği doku O_2 değeri %55-85 arasında değişir. NIRS tekniği ile beyin, böbrek, mezenter gibi dokularda oksijenasyonun yeterliliği ve dokularda tüketilen oksijen miktarı değerlendirilebilir (2,3). Hastanın hemodinamik parametrelerinin yanında takip ederken enfeksiyon ve gangrenöz hasar nedeniyle yıkıma uğramış dokunun beslenmesini de takip ederek iyileşme süreci yönetilmeye çalışılmıştır. Özellikle ilk gün somatik oksimetri monitörizasyonunda sol tarafta oluşan düşük rSO_2 değerlerinin, yara debridmanı, pansumanlar ve yapılan tedaviler sonucunda beşinci günden sonra yükselmeye başlayarak bazal ölçüm değerlerine ve üzerine çıktığı görülmüştür.

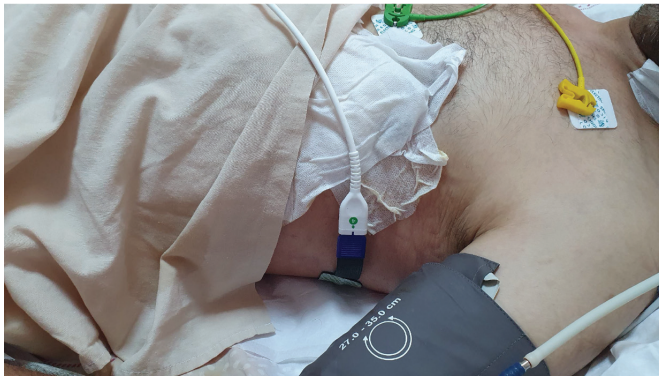
Tablo 1. rSO_2 değerleri ile diğer kan parametrelerinin günlük takip değerleri

Günler	1	2	3	5	9	12	15	18
rSO_2 (sağ/sol) Bazal değer (64/50)	50/33	58/42	60/40	60/44	64/63	69/71	66/60	71/72
Hb (gr/dL)	14,8	10,5	10,1	7,7	8	7,4	7,9	7,2
WBC ($x10^3$/µL)	3	1,6	1,8	5,8	-	-	-	-
Htc	40,7	28,2	21,3	22,5	-	-	-	-
Plt ($x10^3$/µL)	71	54	40	64	146	256	276	304
CRP (mg/dL)	>350	308	345	297	196	172	158	115
Prokalsitonin	-	89	86	25	2	2	1	0,68
Kreatinin (mg/dL)	1,43	1,35	0,91	0,8	0,52	0,54	0,59	0,54
BUN (mg/dL)	40	35	37	34	12	9	7	12
GFR	57	62	100	106	127	125	120	125
ALT (IU/L)	23	23	60	52	15	14	14	12
AST (IU/L)	42	77	163	68	25	15	21	13
Potasyum (mmol/L)	3,3	3,6	2.6	2,7	2,7	4,1	3,8	3,5
INR	1,36	1,49	1,36	1,46	1,46	1,84	1,63	-
Laktat (mmol/L)	5,8	5,7	4,1	2,2	1,7	1,4	1,4	1,3

CRP: C-reaktif protein, Hb: hemoglobin, WBC: beyaz kan hücresi, Htc: hematokrit, Plt: platelet, BUN: kan üre nitrojeni, GFR: glomerül filtrasyon hızı, ALT: alanin aminotransferaz, AST: aspartat aminotransferaz, INR: uluslararası normalleştirilmiş oran

Tablo 2. Kan gazı takip değerleri

	İlk geliş	1. gün	2. gün	3. gün
pH	7,41	7,28	7,48	7,54
PO_2	124	86,1	93,8	97,6
PCO_2 (mmHg)	17,8	28	28	34
HCO_3 (mmol/L)	16	14,6	20,8	29,4
Baz fazlalığı (BE)	-13	-13,3	-5	3,9
Laktat (mmol/L)	5,8	4,9	3,4	2,1

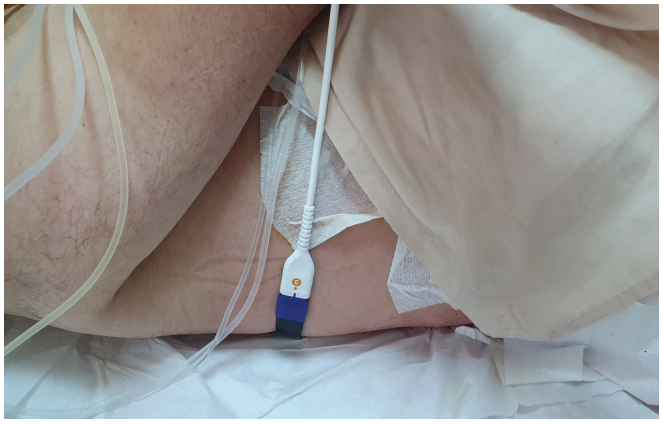


Şekil 2. Sol somatik oksimetri probunun yerleşimi

NIRS'nin sadece serebral değil farklı dokuların (iskemik ekstremite, böbrek vb.) monitorizasyonunda da kullanılabileceğine dair yayınlar mevcuttur (4,5). Bu konudaki çalışmalar, hastanın hemodinamik verilerinin her zaman yeterli olmadığı doku oksijenasyonunu tespit etmede NIRS'nin yararlı olduğunu göstermiştir (6,7). Olgumuzda hemodinamik ve yara iyileşmesini takip ederken, gangrenöz dokunun beslenmesi, sepsise neden olan odağın kontrol edilmesi ve doku oksijenasyonu gibi sorunları da daha yakın gözlemlemek için somatik oksimetri monitörizasyonunu kullanmayı uygun gördük.

Olgumuz, non-spesifik şikayetlerinden dolayı Fournier gangreni tanısı koymak ve tedaviye başlanması açısından hastaneye geç müracaat eden bir olguydu. Sepsis nedeniyle bir süre YBÜ'de takip edilen olgumuz, sıvı resusitasyonu, uzun süreli geniş spektrumlu antibiyoterapi, kan şekeri regülasyonu, nutrisyonel destek, sistemik hastalıkların tedavisi, günlük yapılan geniş debridman ve pansumanlar ile 2,5 ay sonunda iyileşerek taburcu edildi. Tedavisi esnasında NIRS ile yapılan somatik oksimetri monitörizasyonundaki değerler hastanın hemodinamisi, hemoglobin, laktat, trombosit düzeyi, akut faz reaktanları, karaciğer fonksiyon testleri, böbrek fonksiyon testleri ile korele olduğu görüldü.

Bu gelişmelerin sonucu olarak NIRS günümüzde kan ve vücut sıvılarının analizi için iyi bir araç olmakla birlikte aktif ve sürekli gelişen bir araştırma alanı olmaya devam etmektedir. NIRS, hemoglobine özgünlüğü ve duyarlılığı, invaziv olmayan



Şekil 3. Sağ somatik oksimetri probunun yerleşimi

Şekil 4. Sağ/sol somatik oksimetri monitörizasyonunda bazal değerler

tanı amaçlı fırsatlar oluşturmaktadır (8). Fournier gangreni, mortal seyreden bir hastalık olması nedeniyle sadece hastanın hemodinamik verileri ve yara iyileşmesinin takibiyle yetinmenin yetersiz kalacağını düşündük. Tedavide verilen sıvılar, antibiyotikler, yapılan debridmanlar ve pansumanların etkinliğini daha yakın değerlendirebilmek için non-invaziv bir yöntem olan rSO_2 monitörizasyonu da uygulamayı düşündük. Tedavinin etkinliğinde, rSO_2 değerleri ile diğer laboratuvar ve takip parametrelerinin korele olarak yükseldiğini gözlemledik.

Somatik oksimetri uyguladığımız Fournier gangreni olgusundaki gibi yoğun bakım hastalarında uygun endikasyonların varlığında somatik oksimetri ile yapılacak takiplerin hastanın kliniği ve tedavi süreci için yararlı olacağı kanaatindeyiz.

Etik

Hasta Onamı: Bu olgu sunumu için hastadan bilgilendirilmiş onam alınmıştır.

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