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REVIEW / *DERLEME*

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Sepsisin Erken Teşhisi ve Prognoz Tahmininde Hangi Kalp Atım Hızı Analiz Ölçümleri ve Parametreleri Kullanışlı Olabilir? Bir Sistematik Derleme

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ABSTRACT

Sepsis causes a series of pathological changes, such as cardiovascular, respiratory, and thermoregulation. These changes alter heart rate variability (HRV). Even without any changes in the vital signs or clinical presentation of the disease, HRV may still be altered due to sympathetic nervous system activation caused by infection. Our aim in this review was to present sepsis-related HRV measures and parameters by examining the literature and their possible role in predicting the severity and mortality of sepsis. Databases were searched for original research articles reporting on human HRV-related sepsis published in the English language between April 1996 and May 2023. After completion of the article search, a total of 79 articles were selected for further evaluation where the full text of the articles was reviewed and 13 of the articles met the criteria for inclusion. The mean values of each HRV parameter were corrected to the sample size of each study, and the overall means were calculated accordingly. Statistical comparisons were performed after correcting for sample size using the Willcoxon signed-rank test. After the final evaluation, with a total of 1453 patients, 9 studies on sepsis in humans were included. The weighted mean age was 64.24 years, and 53.9% were male. Of the studies included, all underwent frequency domain analysis, and four underwent non-linear analysis. Seven of the nine studies were conducted in the emergency departments, and two were conducted in the intensive care units. 6 studies compared parameters between survivors and non-survivors, and 3 studies compared parameters between different severity levels of sepsis. SDNN, RMSSD, SDNN, HTI, LFnu, HFnu, LF/HF ratio, SD1, SD2, detrended fluctuation analysis (DFA)α_1, and DFAα_2 appear to be related to mortality in patients with sepsis outcome. Therefore, monitoring these parameters for the early detection of sepsis may be beneficial.

Keywords: Sepsis, variability in heart rate, time domain parameters, frequency domain parameters, non-linear analysis

ÖZ

Sepsis, kardiyovasküler, solunum ve termoregülasyon gibi sistemlerde patolojik değişikliklere neden olur. Bu değişiklikler de kalp hızı değişkenliğinde (HRV) alterasyonlara neden olur. Vital bulgularda veya hastalığın klinik sunumunda herhangi bir değişiklik olmasa bile, enfeksiyona bağlı olarak sempatik sinir sistemi aktivasyonu nedeniyle HRV parametreleri değişebilir. Bu sistematik derlemedeki amacımız, literatürü inceleyerek sepsise ilişkin HRV ölçümlerini ve parametrelerini sunmak ve bunların sepsisin şiddetini ve ölüm riskini tahmin etmedeki olası rolünü araştırmaktır. Veritabanları, Nisan 1996 - Mayıs 2023 tarihleri arasında İngilizce dilinde yayınlanmış sepsis üzerine HRV analizlerini insan çalışmalarını bildiren orijinal araştırma makaleleri için tarandı. Makale araması tamamlandıktan sonra, 79 makale daha ayrıntılı bir değerlendirmeye tabi tutulmak üzere seçildi ve bu makalelerin tam metinleri incelendikten sonra 13 makale kriterlere uygun olarak sınıflandırıldı. Her HRV parametrelerinin ortalama değerleri her çalışmanın örnek büyüklüğüne göre düzeltildi ve genel ortalamalar hesaplandı. İstatistiksel karşılaştırmalar Wilcoxon eşleştirilmiş diziler testi ile yapıldı. Toplam 1453 hastanın yer aldığı dokuz çalışma dahil edildi, ortalama yaş 64,24 yıl ve tüm katılımcıların %53,9'u erkekti. Dahil edilen çalışmaların hepsi zaman, frekans domain analizi gerçekleştirdi ve dört tanesi bu analizlere ek olarak doğrusal olmayan analizler gerçekleştirdi. Dokuz çalışmanın yedisini acil serviste ve ikisini hastanelerin yoğun bakım ünitelerinde gerçekleştirildi. Altı çalışma sağ kalanlar ile hayatını kaybedenler arasındaki parametreleri, üç çalışma ise sepsisin farklı şiddet seviyeleri arasındaki parametreleri karşılaştırdı. SDNN, RMSSD, SDNN, HTI, LFnu, HFnu, LF/HF oranı, SD1, SD2, eğilimsiz dalgalanma analizi (DFA)α_1 ve DFAα_2, sepsis sonucuyla ilişkili gibi görünmektedir. Bu nedenle, sepsisin erken teşhisi için bu parametrelerin izlenmesinin faydalı olabilir.

Anahtar Kelimeler: Sepsis, kalp atım hızı değişkenliği, zaman tabanlı parametreler, frekans tabanlı parametreler, doğrusal olmayan analizler

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Introduction

Sepsis is a disorder characterized by the presence of infectious organisms in regions of the body that should ordinarily be devoid of bacteria or viruses, such as blood or tissues, due to a bacterial or viral infection. Sepsis can cause a heightened inflammatory response throughout the body. And, as a result of the body's overreaction, some organs may receive less oxygen and/or blood perfusion, a condition known as septic shock (1). The sympathetic nervous system (SNS) is integral to the development and progression of septic shock. Research has shown that dysfunction within the sympathetic branch of the autonomic nervous system (ANS) disrupts heart and vascular regulation, contributing to circulatory collapse in septic shock (2). This condition involves an inadequate response to low blood pressure and inflammatory stress, leading to compromised SNS function (3). In the early stages of septic shock, elevated levels of catecholamines are present; however, the sympathetic regulation of the heart and blood vessels remains impaired, suggesting that central autonomic dysregulation plays a significant role in the resulting circulatory failure (2). Therefore, monitoring the activity of the ANS in patients with sepsis or septicemia is important. Various methods are available for assessing ANS function, but heart rate variability (HRV) analysis has gained popularity in recent years due to its ease of use, non-invasive nature, and low cost. Both electrocardiography (ECG) and photoplethysmography (PPG) can be used to assess HRV, namely autonomic nervous function. The RR interval time series, which consists of the time intervals between consecutive R waves of the QRS complexes in ECG or PPG signals, is used to assess HRV (3).

HRV analysis includes several methods, with the most common being the time-domain analysis. The proposed method involves extracting numerical data through a basic mathematical examination of the time intervals between successive heartbeats. These figures quantify the extent of HRV across different time scales, whether extensive recordings spanning 24 hours or brief recordings lasting only a few minutes (3). The most commonly examined parameters were the standard deviation of normal heartbeats (SDNN), the root mean square of successive heartbeat intervals (RMSSD), and the number of normal heartbeats occurring within intervals less than 50 milliseconds (NN50) (4). The second most common method is frequency domain analysis. Frequency domain analysis is an intricate analytical method that reveals the distribution of signals across specific frequency bands. High-frequency power (HF) denotes activity within the 0.15-0.40 Hz range, while low-frequency power (LF) represents activity within the 0.04 - 0.15 Hz range (5). The LF/HF ratio, a comparison of low-frequency to high-frequency frequencies, is sometimes interpreted as indicative of sympathovagal balance, although this interpretation is subject to controversy (6,7). On the other hand, non-linear methods differ from the above mentioned "classical" HRV analysis methods because they do not assess the variability of the heart rate but rather the quality, scaling, and correlation characteristics of the signal (8).

Although rare, sepsis patients who require admission to an intensive care unit (ICU) may experience a turbulent course because of a pathological inflammatory reaction called "Cytokine Storm". Increases in inflammatory markers, such as C-reactive protein (CRP), follow the initiation of a cytokine storm. Because it is crucial to start early pharmacological therapies to achieve better results, these factors help clinicians determine when to implement them (9). However, one disadvantage of these laboratory tests is that they may not sufficiently alert clinicians to start treatment promptly enough (10).

Sepsis triggers a range of pathological changes across various systems, including cardiovascular, respiratory, and thermoregulatory systems. These changes can lead to fluctuations in HRV. HRV may be affected even in the absence of noticeable changes in vital signs or clinical symptoms because infection-induced activation of the SNS can still influence HRV (11). This may enable us to begin pharmacological interventions at very early phases even 12-24 hours before clinical changes (such as fever, tachycardia or positive culture results) (11). As a new and promising tool, continuous monitoring of HRV and even complexity in ICU settings may also provide useful information regarding the overall health of patients. A predictive model for sepsis severity that combines HRV with laboratory values has shown superior performance compared with models based on single domains (such as clinical data, laboratory values, or HRV alone). This combined model achieves better discrimination and provides a more balanced sensitivity and specificity than individual domain-based models (12).

To date, apart from sepsis, which is a pathological condition caused by a positive feedback mechanism triggered by infection, changes in HRV parameters have been associated with cardiomyopathies (13), arterial hypertension (14), myocardial infarction (15), and kidney failure (16). However, HRV analysis involves several components that represent different dynamics of the ANS. There are more than 25 different parameters of HRV analysis, and these parameters belong to different HRV measures, such as time and frequency domain analysis and non-linear methods (4). Regarding the

mechanism of pathology, HRV parameters may be affected differently (3). Thus, it is crucial to select the most sensitive HRV measures and parameters corresponding to the underlying pathology and physiopathological mechanism to interpret the HRV analysis results as accurately as possible. In this review, we aimed to explore HRV measures and parameters related to sepsis by analyzing the existing literature and evaluating their potential role in predicting the severity and mortality of sepsis. We hypothesized which specific HRV parameters may serve as valuable indicators for identifying sepsis patients and forecasting disease progression and outcomes.

Methods

The EBSCO, PubMed, and Web of Science databases were searched for original research articles published in the English language between April 1996 and May 2023, focusing on research examining the relationship between sepsis and HRV in humans. This period was selected because "Task Force of The European Society of Cardiology" published the "Guidelines for HRV Measurement, Interpretation, and Clinical Use" in 1996 (5).

Both authors independently screened the titles, abstracts, and methods of the articles to assess their relevance according to the inclusion criteria. The articles deemed relevant by both authors were further reviewed. Other article types, such as reviews, meta-analyses, letters to the editor, and conference abstracts, were excluded. If no consensus on relevance was not initially reached, the full text of the article was reviewed. Any disagreements were resolved through discussion until consensus was reached in all cases.

Search Terminology

The search approach for this systematic review incorporated keywords such as "autonomic nervous system", "ANS", "heart rate variability", "HRV", "heart rate dynamics", "heart rate characteristics", "heart rate complexity", "heart rate fluctuations", and "spectral analysis". These terms were combined with terms related to sepsis, such as "sepsis", "septic shock", "septicemia", "infection", "endotoxemia", and "inflammation". The filters included studies focused on "human" subjects and settings like "ICU", "intensive care", "emergency department", "ER", and "hospital".

Selection Criteria and Data Extraction

Studies that met the following criteria were selected after the final review: (i) were published between April 1996 and May 2023; (ii) examined the ANS activity of human subjects in hospital settings (iii) analyzed ANS activity via time domain and/or frequency domain and/or non-linear analysis. We followed the guidelines for precise and reliable HRV measurement as outlined by "Task Force of the European Society of Cardiology". These guidelines ensure consistency and precision in data collection, facilitating valid assessments of HRV in clinical and research settings and provide frequency domain analysis results in normalized units because interstudy comparisons are not recommended with absolute powers (5).

All selected papers were imported into Mendeley (version 1.19.4, London, UK), from which all duplicates were removed. After completion of the article search, a total of 79 articles were selected for further evaluation where full text of the articles was reviewed and 13 of the articles met the criteria for inclusion.

Risk of Bias Assessment

The Cochrane Collaboration's Risk of Bias tool was used to evaluate the bias in randomized controlled trials (RCTs), while the ROBINS-I tool was applied for observational studies. Each study was independently reviewed by two assessors, and any differing opinions were resolved through discussion.

Statistical Analysis

Due to limited data in the studies, a meta-analysis could not be conducted; thus, a descriptive analysis was performed instead. In cases of significant clinical or statistical heterogeneity, descriptive analysis was performed, whereas subgroup analysis was performed to separate studies based on quality or the interventions used. The mean values of HRV parameters, including LFnu, HFnu, LF/HF, RMSSD, SDNN, HRV triangular index (HTI), SD1, SD2, detrended fluctuation analysis (DFA)α_1, and DFAα_2, were adjusted according to the sample size of each study, and overall means were calculated accordingly. The combined results are presented as means standard deviations (SDs). Statistical comparisons, adjusted for sample size, were conducted using the Wilcoxon signed-rank test.

HRV Measures Used in Included Studies with Sepsis

HRV analysis can be conducted using various measures, each providing distinct insights. The most commonly used methods for HRV analysis are time-domain, frequency-domain, and non-linear techniques. This section will outline the basic concepts behind these methods, followed by a discussion of their potential roles in the early detection, severity assessment, and prognosis of sepsis.

Time-domain Analysis

HRV, which is measured over monitoring periods ranging from 1 minute to more than 24 hours, is quantified using time-domain indices that evaluate the degree of HRV during these intervals (6). Common time-domain indices include the standard deviation of normal-to-normal intervals (SDNN), the root mean square of successive differences (RMSSD), the number of pairs of successive normal-to-normal intervals that differ by more than 50 milliseconds (NN50), the percentage of pairs of successive normal-to-normal intervals that differ by more than 50 milliseconds (pNN50), the HTI, and the triangular interpolation of the NN interval (TINN) (5,6).

SDNN, which refers to the standard deviation of the intervals between consecutive normal sinus beats, is typically measured in milliseconds. Although 5 min is the standard duration for short-term HRV recordings, some studies have proposed using shorter periods, ranging from 1 to 4 min. In these short-term recordings, respiratory sinus arrhythmia (RSA), driven by parasympathetic activity, is the dominant factor contributing to HRV, particularly during slow, regulated breathing. When measured over a full 24-hour period, SDNN is widely regarded as the "gold standard" for assessing cardiac risk because it has strong predictive value for both morbidity and mortality (6).

The parasympathetic nervous system's (PNS) activity is intimately linked to the percentage of successive NN intervals that differ by more than 50 ms, which is known as pNN50. However, for RSA assessment, RMSSD is frequently chosen over pNN50, particularly in older individuals. Finding the time difference between each pulse in milliseconds, squaring each difference, averaging them, and taking the square root yields the root mean square of consecutive differences between normal beats or RMSSD. The key time-domain metric for evaluating vagal tone is RMSSD, which represents beat-to-beat HRV and is strongly associated with the non-linear metric SD1. RMSSD also exhibits a strong correlation with pNN50 and HF power over a 24-hour period. HTI is a geometric measure that estimates the integral of the RR interval histogram density divided by its height, while TINN represents the base width of the NN interval histogram (6).

Frequency Domain Analysis

The frequency-domain analysis of HRV evaluates the proportion of a signal falling within the frequency bands. Researchers have identified several frequency bands that correlate with different physiological phenomena. The most studied bands in human HRV analysis are ultra-low frequency (ULF), very-low frequency (VLF), LF, HF, and the LF/HF ratio. The ULF band requires at least 24 hours of recording, which is often difficult to obtain (17). Although there is no consensus on the exact mechanisms generating ULF power, experimental evidence suggests that slow-acting biological mechanisms, such as circadian rhythms, may primarily drive ULF activity (18). The VLF band is thought to be generated by the activation of afferent sensory neurons in the heart and may be influenced by stress responses (19,20). This activation triggers feedback and feed-forward reflex mechanisms within the heart's intrinsic nervous system, as well as extrinsic cardiac ganglia in the thoracic cavity and spinal cord (21). The LF band, previously referred to as the baroreceptor range due to its strong correlation with baroreceptor activity, is influenced by both the parasympathetic (PNS) and SNS, along with baroreceptor function (5,6,22-24). In contrast, the HF band is primarily linked to parasympathetic or vagal activity, earning the label "respiratory band" due to its association with heart rate fluctuations during respiration (6). The LF/HF ratio is commonly used as an indicator of sympathetic and parasympathetic balance, as the LF component reflects both sympathetic and parasympathetic influences, whereas the HF component predominantly represents parasympathetic control (24).

Normalized HRV parameters, like LFnu and HFnu, are determined by dividing the raw values of LF or HF by the total spectral power, which is generally the sum of LF and HF. These values are expressed as percentages (5). Normalized HRV parameters are particularly helpful for comparing studies because they enhance the consistency and clarity of the results. By normalizing, the proportional changes in the frequency bands can be represented in a similar way, regardless of the spectral method used (5). However, this approach has certain limitations. A significant issue is the inherent relationship between LFnu and HFnu, where LFnu = 1 HFnu. The two values are mathematically interchangeable and do not provide distinct information. Including both LFnu and HFnu does not yield extra insights, as variations in one directly correspond to those in the other (25).

Non-linear Analysis Methods

The cardiovascular system, like all biological systems, exhibits complex dynamics. Goldberger proposed that reductions in variability and complexity could indicate the presence of pathological conditions (27). The heart rate, one of the most significant dynamic parameters, is influenced by neural, hormonal, and hemodynamic changes originating from various systems and organs.

Non-linearity refers to relationships between variables that do not follow a direct, proportional pattern and cannot be represented with a straight line. Non-linear metrics are valuable for capturing the underlying variability within a time series, highlighting the complex processes involved in heart rate regulation.

Some pathologies like myocardial infarction (MI), diabetes, and mood disorders, may decrease complexity (17,27,28). In this section, we review the most investigated non-linear measurements; Poincaré Plot parameters SD1, SD2, SD2/SD1, and DFA exponents DFAα_1 and DFAα_2.

Poincaré Plot

To analyze the Poincaré plot, an ellipse is fitted to the plotted points. The ellipse's width is determined by the standard deviation (SD1) of each point's distance from the y = x axis, and its length is determined by the standard deviation of each point's distance from the line y = x + average R-R gap (SD2) (4). It is believed that SD1 correlates with variations in blood pressure, power in the LF and HF bands, and the overall power of brief recordings (e.g., 5 minutes) (29,30). SD2 reflects LF band power and baroreflex sensitivity. The ratio of SD2 to SD1 (SD2/SD1) is considered analogous to the LF/HF ratio from frequency domain HRV analysis (31).

Detrended Fluctuation Analysis

DFA was used to extract the self-similarity (correlations) between consecutive RR intervals. The DFA calculates the scaling exponents (short-term, DFAα_1 and long-term, DFAα_2) from the time series and reflects the fractal correlation characteristics of complex dynamic heart rate series (6). DFAα_1 is suggested to reflect baroreceptor reflex activity, while DFAα_2 is thought to represent regulatory mechanisms that stabilize fluctuations in the cardiac cycle (32,33).

Results

The analysis included nine studies with a total of 1,453 patients. The mean age of the participants was 64.24 years, and 53.9% were male (34-42). Table 1 presents the main characteristics of all studies, such as sample size, mean age, study settings, and significant HRV findings ($p \leq 0.05$).

The included studies assessed various HRV parameters across different domains. In the time domain, the following parameters were evaluated: RMSSD, SDNN, NN50, pNN50, and TINN. In the frequency domain, the parameters included the normalized low-frequency power (LFnu), normalized high-frequency power (HFnu), the ratio of LFnu to HFnu (LFnu/HFnu), and the total power (TP). The non-linear methods assessed included Poincare Plot standard deviation 1 (SD1), Poincare Plot standard deviation 2 (SD2), the ratio of SD1 to SD2 (SD1/SD2), and short-term (α_1) and long-term (α_2) fractal scaling coefficients derived from (DFA). The significant HRV findings are summarized in Table 1.

Of the studies included, all performed frequency domain analysis, and four also performed non-linear analysis (Table 1). Seven of the nine studies were conducted in the emergency departments, and two were conducted in the intensive care units. 6 studies compared parameters between survivors and non-survivors (34-39), and 3 studies compared parameters between different severity levels of sepsis (40-42).

Table 2 shows the combined results of LFnu, HFnu, LF/HF, RMSSD, SDNN, HTI, SD1, SD2, DFAα_1, and DFAα_2 parameters of the selected studies, comparing the parameters between survivors and non-survivors of the sepsis (36,38-40). LFnu, LF/HF, SD2, DFAα_1, and DFAα_2 were lower in the non-survivor group, whereas HFnu, RMSSD, SDNN, HTI, and SD1 were higher in the non-survivor group.

Discussion

In this review, we found that non-surviving patients with sepsis had lower LFnu, LF/HF ratio, SD2, DFAα_1, and DFAα_2, while survivors exhibited higher HFnu, RMSSD, SDNN, HTI, and SD1. This suggests that HRV parameter monitoring can help predict mortality in patients with sepsis. However, the relationship between HRV and sepsis severity remains unclear, likely due to the limited number of studies that examined HRV parameters in relation to sepsis severity.

The role of the ANS in the pathophysiology of sepsis has gained attention, with vagus nerve stimulation known to influence cortisol release. Acetylcholine, the main neurotransmitter of the vagus nerve, has anti-inflammatory effects, (43) including reducing cytokine release (TNF, IL-1beta, IL-6, and IL-18) and mitigating the cytokine storm seen in septic shock (44).

Our findings align with those of studies that suggest HRV analysis, a non-invasive method for assessing autonomic function, may be helpful for predicting outcomes in patients with septic arthritis. Combining HRV monitoring with widely used clinical scoring systems, such as SOFA, qSOFA, mSOFA, and APACHE II, can improve prognosis prediction. HRV analysis is convenient, with smartwatches offering accessible, non-invasive monitoring options. Therefore, HRV is an ideal tool for use in emergency departments, general wards, and ICU settings.

Table 1. Summary of studies investigating heart rate variability (HRV) in sepsis and critical care patients

First author (year)	Sample size (n)	Sex (% of male)	Mean age (overall)	Study setting	Study groups	Significant HRV findings
Arbo et al. (34)	72	61.1	60.4±20.3	Emergency department	1. Sepsis 2. Severe sepsis 3. Septic shock	Decreased LFnu, Increased HFnu, Decreased LF/HF ratio correlate with the severity of the sepsis.
Bonjorno et al. (35)	60	58.3	50.3±13.0	Intensive care unit	1. Survivor 2. Non-survivor	Higher HTI and SD1 in surviving group.
Chen et al. (36)	132	47.0	66.7±10.2	Emergency department	1. Survivor 2. Non-survivor	Lower SDNN, Total Power (nu), LFnu/HFnu in non-survivors and higher HFnu in survivors.
Kim et al. (37)	189	56.1	57.517.6±	Emergency department	1. Severe sepsis patients admitted to ICU 2. Sepsis patients admitted to general ward, 3. Sepsis patients discharged within 24 hours 4. Healthy volunteers.	Total Power and LFnu were decreased in all groups compared to healthy individuals. HFnu was decreased in severe sepsis and sepsis patients admitted to general ward groups compared to healthy individuals.
Papaioannou et al. (38)	45	57.8	57.8	Intensive care unit	1. Survivor 2. Non-survivor	CRP negatively correlates with SDNN, LFnu, LF/HF and positively with HFnu and SD1/SD2 ratio. SDNN and HF are independent predictors of severity of sepsis.
Pong et al. (39)	364	49.2	67.1±16.1	Emergency department	1. No 30 day in-hospital mortality 2. 30 day in-hospital mortality	Increased SDNN, RMSSD, NN50, pNN50, TINN, HFnu, SD1, and decreased LFnu in 30 day in-hospital mortality group.
Prabhakar et al. (40)	343	50.7	67.5±15.6	Emergency department	1. Survivor 2. Non-survivor	Increased SDNN, RMSSD, TINN, HFnu, SD1 and decreased LF/HF, DFAα_1, DFAα_2, LF nu in non-survivors group.
Samsudin et al. (41)	214	50.5	66.9±15.6	Emergency department	1. Survivor 2. Non-survivor	Increased SDNN, RMSSD, TINN HFnu, SD1 and decreased DFAα_1, DFAα_2 and LF (nu) in non-survivors.
Tang et al. (42)	34	Not provided	52.9	Emergency department	1. Systemic inflammatory response syndrome 2. Severe sepsis 3. Healthy volunteers.	LFnu was decreased in severe sepsis patients.

HF: high-frequency, LF: low-frequency, RMSSD: root mean square of successive heartbeat intervals, SDNN: standard deviation of normal heartbeats, HTI: HRV triangular index, DFA: detrended fluctuation analysis

Table 2. Comparison of heart rate variability (HRV) parameters between survivors and non-survivors in sepsis and critical care patients

	Survivors			Non-survivors			
	Mean	**SD**	**n**	**Mean**	**SD**	**n**	**p-value**
LFnu	43.2864	24.63906	847	33.09029	24.7233	206	**0.02443**
HFnu	45.20782	24.23509	847	63.38981	24.4311	206	**0.02402**
LF/HF	2.762645	3.785706	673	1.521084	4.33735	166	**0.01041**
RMSSD	24.3383	33.82116	847	43.07961	49.0573	206	**0.02492**
SDNN	21.38553	22.22373	847	32.16214	32.9631	206	**0.02048**
HTI	4.8	2.7	21	6.5	3.15714	39	**0.01142**
SD1	19.34021	27.3337	746	27.45447	30.9277	235	**0.02506**
SD2	25.7	26.7	174	9.287356	37.1	40	**0.00154**
DFAα_1	0.683993	0.389328	551	0.517949	0.28654	156	**0.00561**
DFAα_2	0.955724	0.40811	725	0.683163	0.40357	196	**0.03295**

SD: standard deviation, HF: high-frequency, LF: low-frequency, RMSSD: root mean square of successive heartbeat intervals, SDNN: standard deviation of normal heartbeats, HTI: HRV triangular index, DFA: detrended fluctuation analysis

In this review, we found that non-survivors had significantly lower LFnu, LF/HF ratio, SD2, DFAα_1, and higher DFAα_2 and HFnu, RMSSD, SDNN, HTI, and SD1. Several studies support this, including a study by Chao et al. (10) that determined whether decreases in SDNN predict elevations in CRP in COVID-19 patients. With a 90.9% positive predictive value, significant declines in SDNN predicted increases in CRP levels in the following 72 hours. Natarajan et al. (45) found that RMSSD was significantly decreased before the onset of COVID-19 symptoms. Aragón-Benedí et al. (46) found that lower SDNN and HFnu are associated with a poor prognosis, higher mortality, and higher IL-6 levels in COVID-19 patients. Similarly, Krishnan et al. (47) found that SDNN, RMSSD, LF, HF, and DFA parameters were associated with Sepsis-related acute respiratory failure patients. Kenig and Ilan (48) proposed a predictive model for severe sepsis that included the mean RR interval and DFAα_2 alongside other clinical parameters. This model aimed to enhance the efficacy of sepsis treatment by incorporating DFA analysis as a predictive component. Furthermore, a case report monitoring HRV in a patient with late-stage sepsis observed a reduction in LF and HF prior to death, indicating HRV alterations in the progression of sepsis (49). Although studies involving experimental animals are not included in this review, trends of decreasing SDNN and RMSSD are consistent with findings observed in a peritonitis-induced sepsis model in pigs (50).

HRV is a promising indicator of sepsis development. According to Brown et al. (51), changes in HRV, such as loss of complexity or changes in sympathovagal balance, can anticipate the development of shock and organ dysfunction and signal the onset of sepsis. Additionally, continuous monitoring of HRV in adult patients has been associated with reduced HRV, which coincides with the onset of sepsis (52).

Several HRV parameters have been found to be lower in non-surviving septic patients compared to survivors, among all the HRV measures studied for predicting mortality risk of sepsis. However, further research is necessary to identify which specific HRV parameters are most effective in predicting sepsis mortality, as well as to establish appropriate cutoff values for each parameter. In some studies investigating the predictive value of HRV analysis in sepsis, SDNN, RMSSD, and HFnu were particularly notable.

Sepsis can be predicted using longitudinal HRV data collected from regularly used commercial wearable devices, such as Apple Watch, FitBit, and Polar. Significant changes in HRV parameters, especially RMSSD, SDNN, HTI, LFnu, HFnu, LF/HF ratio, SD1, SD2, DFAα_1, and DFAα_2 are candidate parameters for the identification of sepsis. More studies are needed to evaluate the predictive power of these parameters by confirming the cases with laboratory tests.

Study Limitations

The low quantity and quality of the included papers are the primary limitations of this systematic review. Thus, although it may be concluded that monitoring the reduction of HRV and that these stood out parameters may be linked to sepsis detection and severity, more studies are needed to determine the best methodology and cutoff points that can be used.

Conclusion

In the studies included in this review, several HRV values were altered in non-surviving septic patients. SDNN, RMSSD, SDNN, HTI, LFnu, HFnu, LF/HF ratio, SD1, SD2, $DFA\alpha_1$, and $DFA\alpha_2$ appear to be related to mortality in patients with sepsis outcome. Therefore, monitoring these parameters for the early detection of sepsis may be beneficial. Larger and better-designed research is needed to support these conclusions.

Ethics

Authorship Contributions

Concept: H.K., Data Collection and Process: H.K., Analysis or Interpretation: H.K., H.FÖ., Literature Search: H.K., H.FÖ., Writing: H.K., H.FÖ.

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REVIEW / *DERLEME*

Status Epilepticus: A Practical Guide for Intensivists

Status Epileptikus: Yoğun Bakım Uzmanları İçin Pratik Bir Kılavuz

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ABSTRACT

This review explores the pathophysiology of status epilepticus in adults, along with its incidence and key clinical considerations. We present a comprehensive treatment approach, emphasizing both emergent and urgent therapies. Additionally, we examine the role of newer agents such as clobazam and brivaracetam. This review also includes dosing strategies and potential drug-drug interactions of commonly used antiseizure medications in critically ill patients. Treatment strategies for refractory and super-refractory status epilepticus are also discussed. Finally, we provide a practical algorithm for a structured management approach, along with dosing and titration guidelines for sedatives following seizure cessation.

Keywords: Status epilepticus, pharmacotherapy, antiseizure medications

ÖZ

Bu derleme, erişkinlerde status epileptikusun patofizyolojisini, insidansı ve temel klinik hususları ile birlikte araştırmaktadır. Acil tedavileri vurgulayan kapsamlı bir tedavi yaklaşımı sunulmuştur. Bu derlemede ayrıca klobazam ve brivaracetam gibi yeni ajanların rolü incelenmiş, kritik hastalarda sık kullanılan nöbet önleyici ilaçların doz stratejileri ve potansiyel ilaç-ilaç etkileşimleri de araştırılmıştır. Refrakter ve süper refrakter status epileptikus için tedavi stratejileri de tartışılmıştır. Son olarak, nöbetin kesilmesini takiben uygulanan sedatifler için dozlama ve titrasyon kılavuzlarının yanı sıra yapılandırılmış bir yönetim yaklaşımı için pratik bir algoritma sunulmuştur.

Anahtar Kelimeler: Status epileptikus, farmakoterapi, nöbet önleyici ilaçlar

Introduction

Definition and Clinical Considerations

Status epilepticus (SE) is a medical emergency requiring immediate intervention to prevent long-term consequences arising from sustained seizure activity. Historically, SE was defined as seizure activity or the occurrence of two or more seizures without recovery of consciousness, lasting beyond five minutes. However, in 2015, the International League Against Epilepsy (ILAE) and the Commission on Epidemiology introduced a precise operational definition, incorporating two critical time points: T1 and T2 (1).

•**T1 (Seizure Onset):** For bilateral tonic-clonic (convulsive) SE, treatment should commence at 5 minutes, as seizures are unlikely to resolve spontaneously. In focal SE, with or without impaired consciousness, this threshold extends to 10 minutes.

•**T2 (Risk of Neuronal Damage):** This marks the maximum time window for effective seizure control to prevent long-term complications. For convulsive SE, the threshold is 30 minutes, while for focal SE, it is 60 minutes.

This definition underscores the necessity of prompt treatment to mitigate the risks associated with SE. Status epilepticus arises from either the failure of mechanisms responsible for seizure termination or the activation of mechanisms leading to abnormally prolonged seizures. After T1, seizure activity generally requires medical intervention to halt progression. Beyond T2, the risk of significant neuronal damage increases, necessitating aggressive management to prevent irreversible harm.

The ILAE's operational framework for SE emphasizes the importance of timely recognition and intervention to reduce the risk of lasting neurological consequences (1).

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Incidence

The global incidence of SE varies significantly across different regions and populations. According to a meta-analysis, the pooled crude annual incidence rate of SE is approximately 12.6 per 100,000 persons (2). The incidence of all types of SE in the USA ranges from 18.3 to 41 per 100,000 people per year. The incidence of convulsive SE (CSE), specifically, has increased from 3.5 per 100,000 in 1979 to 12.5 per 100,000 in 2010 (3). The goal of therapy is the rapid termination of both clinical and electrical seizure activity, since appropriate and timely therapy of status epilepticus reduces the associated mortality and morbidity. Delayed treatment can lead to neuronal injury, irreversible damage to vulnerable regions in the hippocampus, thalamus, and neocortex, and in some cases, brain tissue hypoxia, and increased intracranial pressure.

Risk Factors

Common causes for status epilepticus have been listed in Table 1 below. In children, the most common causes for status epilepticus are remote structural disease, acute symptomatic disease, and febrile seizures. In adults, the most common causes for status epilepticus are acute symptomatic disease such as stroke and metabolic derangements (4,5).

Pathophysiology

During SE, typical seizure termination mechanisms fail, or abnormal excitatory mechanisms are activated, resulting in prolonged seizure activity. As seizures persist, changes in neurotransmitter receptor dynamics progressively reduce the efficacy of termination strategies. A retrospective study in adults found that 80% of patients treated within the first 30 minutes of seizure activity experienced successful seizure termination, whereas this response rate dropped to less than 40% after 2 hours of seizure activity (6). Animal studies further demonstrate that prolonged seizures induce changes in neuronal membrane receptors, making seizure activity increasingly resistant to termination over time.

Table 1. various causes leading to status epilepticus
Acute symptomatic disease
- Traumatic brain injury (TBI) - Acute ischemic stroke - Intraparenchymal hemorrhage - Metabolic derangements (hypoglycemia, hyponatremia)
Remote structural disease
- Encephalomalacia - Cerebral dysgenesis - Mesial temporal sclerosis
Antiseizure drug withdrawal/non-compliance
Febrile seizures
Central nervous system (CNS) infections
Autoimmune encephalitis
Idiopathic/cryptogenic

At the molecular level, benzo-diazepam sensitive synaptic gamma-aminobutyric acid, γ-aminobutyric acid (GABA, gamma sub-unit), is internalized during prolonged seizures, leading to a reduction in membrane receptor density. This poses a challenge for treatment particularly with benzodiazepines, which are the first-line therapy for seizure termination. Conversely, prolonged seizure activity promotes the translocation of N-methyl-D-aspartate (NMDA) receptors to the synaptic membrane, increasing excitatory signaling. These receptor changes can occur within as little as 5 minutes of seizure onset. Figure 1 explains additional factors that exacerbate ongoing seizure activity, including the release of peptides, neuroinflammation, and the breakdown of the blood-brain barrier, all contributing to the increasing difficulty of terminating seizures over time (7).

During convulsive SE, significant physiological changes occur, including alterations in heart rate, blood pressure, respiratory rate, blood glucose levels, body temperature, and electrolyte balance. The repetitive muscle contractions associated with convulsions impose extreme metabolic demands on the body. As convulsions persist, a shift to anaerobic metabolism occurs, resulting in increased lactic acid levels. Animal studies suggest that compensatory mechanisms begin to fail after 20 to 40 minutes of continuous seizure activity. Inadequate ventilation leads to hypoxia, which, coupled with pulmonary edema, contributes to respiratory acidosis. Simultaneously, metabolic acidosis develops due to lactic acid accumulation. Prolonged convulsions can also result in hyperthermia and rhabdomyolysis (7).

Prolonged SE can cause neuronal injury through mechanisms such as hypoxia, hyperthermia, acidosis, and hypoglycemia. This damage may lead to hippocampal sclerosis, characterized by the loss of neurons in the dentate nucleus and pyramidal layer of the hippocampus. Hippocampal sclerosis can serve as a focal point for seizures and epilepsy, perpetuating a vicious cycle of recurrent seizures and further neuronal injury (8).

Treatment

First-line (emergent) therapy: Effective initial therapy, also known as emergent therapy, according to the

Neurocritical Care Society (NCS), depends on multiple factors, including drug choice, dosage, and timing. Benzodiazepines are considered a first-line treatment, with lorazepam being the preferred option in hospitals due to its proven efficacy in clinical trials (9). Clinical trials have shown that IV lorazepam is more effective than IV phenytoin and at least as effective as phenobarbital or diazepam plus phenytoin. In an out-of-hospital setting, IV lorazepam has a slightly better response than IV diazepam and is comparable to intramuscular (IM) midazolam (10). IM midazolam enters the systemic circulation quickly, providing a seizure cessation action like IV lorazepam. This is a viable alternative when IV access is delayed (Table 2).

Timely and appropriate dosing is crucial for effective benzodiazepine therapy in status epilepticus. A lorazepam dose of 0.1 mg/kg (maximum 4 mg) is effective, while 10 mg of IM midazolam is appropriate for patients over 40 kg,

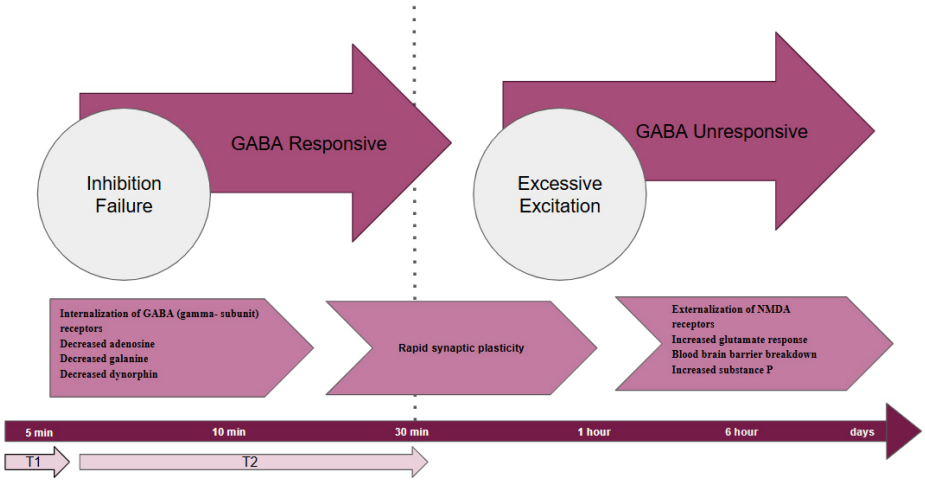

Figure 1. Changes at the neuronal level in status epilepticus (7)
GABA: gamma-aminobutyric acid, NMDA: N-methyl-D-aspartate

Table 2. First line (emergent) therapy (14,16)

Drug	Mechanism of action	Route/dose	Maximum dose per treatment	Pharmacokinetic pearls	Adverse reaction
Lorazepam	GABA-A receptor agonist	0.1 mg/kg up to 4 mg IV push over 2 minutes, if still seizing after 5 min, repeat x 1	4 mg IV per dose	Hepatic (conjugation metabolism) to inactive metabolite	Contains propylene glycol (caution with continuous infusion)
Midazolam	GABA-A receptor agonist	0.2 mg/kg up to 10 mg IM, IN, buccal or IV	10 IV/IM/IN mg per dose	Extensive hepatic (CYP 3A4) metabolism to an active metabolite Drug-drug interaction with CYP 3A4 inducer and inhibitor	Caution in renal impairment with continuous infusion only Active metabolite will accumulate in renal failure
Diazepam	GABA-A receptor agonist	0.15 mg/kg up to 10 mg IV push may repeat x 1 0.20 mg/kg up to 20 mg PR	10 mg IV per dose 20 mg PR per dose	Rapid onset; hepatic metabolism by CYP 3A4 and CYP2C19 to an active metabolite	PR dose needs to be rounded to nearest 2.5 mg IV formulation contains propylene glycol (caution with continuous infusion)

GABA: gamma-aminobutyric acid, IV: intravenous, IM: intramuscular, IN: intranasal, PR: rectal

when IV access is unavailable. Concerns about respiratory compromise and airway management with benzodiazepines are countered by evidence suggesting a lower intubation rate in treated patients compared to those left untreated.

Second line (urgent) therapy: Although various antiseizure medications are available for urgent therapy in status epilepticus, no clinical trials definitively support one agent over another in terms of efficacy. Studies reveal suboptimal response rates, with less than 50% seizure cessation for phenytoin or phenobarbital, and variable responses for valproate (70-88%) and phenytoin (25-84%) (11,12). More recently the ESETT trial showed no difference in efficacy when levetiracetam, valproate, or phenytoin were utilized as second line agent for the management of status epilepticus (13). In this study, status epilepticus was stopped in approximately 50% of patients in each treatment group. It is, therefore, important to consider individual medication and patient-specific factors when choosing the second-line agent. Traditional agents such as phenobarbital and (fos)phenytoin have limitations, including prolonged infusion times and risks such as hypotension, respiratory depression, and arrhythmias, often necessitating airway protection and cautious infusion rates to mitigate adverse effects. Propylene glycol in these drugs can cause toxicity, including severe metabolic acidosis. Fosphenytoin allows faster administration but is still constrained by cardiovascular risks and in vivo conversion time. In contrast, newer agents such as levetiracetam and lacosamide can be infused more quickly, offering practical benefits such as reduced monitoring time and faster therapeutic concentrations. They also have fewer drug-drug interactions. Finally, valproate with a broad mechanism of action may be helpful in controlling seizures as a second-line agent. Valproate should be avoided in those with thrombocytopenia, severe liver disease, or pregnancy or of childbearing age. Additionally, the combination of valproate and carbapenem should be avoided, as it results in subtherapeutic valproate concentrations (Table 3). Therapeutic drug monitoring should be performed when available to help guide therapeutic decision making (Table 4).

In recent years, novel antiseizure medications such as clobazam and brivaracetam have gained popularity. The exact mechanism by which brivaracetam exerts its antiseizure effects remains unknown, though it is a high-affinity ligand of synaptic vesicle protein 2A (SV2A).

Compared to levetiracetam, brivaracetam binds to SV2A with 10- to 30-fold greater affinity. Its rapid onset of action and availability in an intravenous (IV) formulation make it an appealing option for the treatment of SE, refractory SE (RSE), and super-refractory SE (SRSE). While animal studies suggest potential benefits of this agent in SE, clinical evidence remains limited. Phase III trials in epilepsy have shown that adding brivaracetam to ongoing levetiracetam therapy does not provide additional therapeutic benefit. Notably, patients who had not been exposed to levetiracetam responded better to brivaracetam. Among those previously treated with levetiracetam, efficacy was greater in patients who discontinued it due to adverse effects rather than due to insufficient response. Future randomized trials are needed to clarify the role of brivaracetam when co-administered with levetiracetam in SE (14).

Clobazam, a 1,5-benzodiazepine, enhances GABA-A receptor activity with greater selectivity for subunits involved in anxiolytic and anticonvulsant effects than for those mediating sedation. Its ease of administration, rapid onset, and favorable safety profile make it a viable option for SE treatment in patients with enteral access (14). However, given the limited clinical evidence, the potential role of this agent as an early add-on oral therapy for SE should be further explored through prospective randomized trials. Table 3 summarizes dosing and clinical pearls regarding these novel antiseizure medications.

Finally, the pathophysiology of status epilepticus highlights the importance of rapid seizure cessation to prevent neurological and metabolic complications. Prolonged status epilepticus can reduce the effectiveness of traditional treatments and increase the risk of refractory status epilepticus. Animal models indicate that benzodiazepine receptors undergo endocytosis after about 30 minutes, resulting in benzodiazepine refractoriness, while increased NMDA-glutamate receptor expression sustains an excitatory brain state and thereby elevates metabolic demands. This highlights the interest in starting anti-NMDA agents such as perampanel (enteral) or ketamine (intravenous) earlier in the course of status epilepticus therapy (15). Figure 2 demonstrates a practical approach to choosing antiseizure medications in status epilepticus. Individual patient factors such as organ function and drug-drug interactions should be prioritized when choosing the antiseizure medication(s). Table 5 summarizes important landmark clinical trials in urgent and emergent management of status epilepticus.

Table 3. Second line (urgent) therapy

Drug	Dosing LD MD	Clinically relevant PK interactions with other ASM	Approximate half Life (hr) in non-critically ill patients	Dose adjustment in renal impairment (Maintenance doses) HD CRRT	Dose adjustment in hepatic impairment (Maintenance doses)	Comment
Levetiracetam	LD: 60 mg/kg over 10-15 min (max 4500 mg). MD: 1500-4000 mg/day divided in 2 doses	NA	6	HD: 50% removed; 500 mg-1000 mg daily with 250-500 mg in the evening dose post HD CRRT: depending on the dialysate flow rate and critical illness dose adjustment may not be necessary	Not indicated	New evidence for IV push dosing in doses as high as 4500 mg Avoid in patients with severe psychiatric medical history
Lacosamide	LD: 10 mg/kg IV over 5-10 min (max 400 mg). MD: 200-600 mg/day in 2 divided doses	NA	13	Reduce dose in severe renal impairment (CrCl < 30 mL/min); max 300 mg/day. HD: Administer up to 75% of the indication-specific maximum dose; administer a supplemental dose (up to 50%) after each hemodialysis session CRRT: depending on the dialysate flow rate and critical illness dose adjustment may not be necessary	Consider dose reduction	Monitor PR interval prior to initiation and while on therapy if on other PR prolonging agents such as dexmedetomidine
Fosphenytoin/ phenytoin	LD: 20 mg PE/kg IV (max 1500 mg) MD: 100 mg IV every 8 hours	Induces CYP 1A2, 2B6, 2C, 3A3/4. Generally avoid use with most CYP3A4 substrates. Coadministration with valproate displaces phenytoin from protein binding sites Induces metabolism of valproate.	15	Not indicated	Consider dose reduction	May cause rash, fever, hypotension, or arrhythmias (more common with IV phenytoin than IV fosphenytoin). IV phenytoin formulation contains 40% propylene glycol; may cause metabolic acidosis. Only compatible in saline (unlike fosphenytoin) Severe tissue injury may occur with extravasation of IV phenytoin, including rare purple glove syndrome.
Clobazam	LD: 1 mg/kg (most case reports utilized 60-70 mg) MD:20-40 mg in 2 divided doses	Clearances of valproic acid and primidone are significantly reduced in the presence of clobazam. Phenobarbital, phenytoin, and carbamazepine are associated with increased clobazam concentrations.	40 hours (parent drug) 80 hours (active metabolite: N-desmethylclobazam)	NA IHD has shown not to affect clobazam concentration based on a case report.	Given extensive hepatic metabolism dose adjustment should be considered. Maximum daily dose in mild-moderate hepatic impairment is 40 mg/day. **not studies in severe hepatic impairment**	Concentrations of the active metabolite N-desmethylclobazam are 3 to 5 times higher in patients who are known CYP2C19 poor metabolizers compared to CYP2C19 extensive metabolizers. Dose adjustment is needed in patients who are poor CYP2C19 metabolizers.

Table 3. Continued

Perampanel	LD: 12-32 mg MD: 4-12 mg nightly	Phenytoin, carbamazepine, oxcarbazepine can reduce perampanel's concentration.	109	Not indicated although use is not studied in CrCl <30 mls/min or HD.	Dose reduction should be considered; in mild liver impairment maximum daily doe is 6 mg/day In moderate liver impairment maximum daily dose is 4 mg/day *Use is not recommended in severe (child-pugh class C).	Perampanel is a selective non-competitive inhibitor of the ionotropic α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor Life-threatening psychiatric behavior such as suicidal thoughts are reported with this agent.
Valproate	LD: 40 mg/kg IV; max 3000 mg. If still seizing, give additional 20 mg/kg IV (max 2000 mg) MD: 2000-4500 mg divided in 2-4 doses	Phenytoin and valproate may displace each other from protein binding sites Valproate markedly inhibits lamotrigine metabolism leading to ↑↑ lamotrigine levels and risk of side effects including rash.	12	Not indicated	Caution in hepatic impairment.	Highly plasma protein bound (up to 90%). May cause hyperammonemia encephalopathy (treated with L-carnitine supplementation), hepatotoxicity, thrombocytopenia, and platelet dysfunction Concurrent use with carbapenems (meropenem,doripenem, imipenem, ertapenem) may result in markedly decreased valproic acid plasma concentrations.
Phenobarbital	LD: 15-20 mg/kg IV x once, may repeat 5 mg/kg to 10 mg/kg Seizure MD: 2 mg/kg/day in divided doses	Phenobarbital reduces serum concentration of carbamazepine Phenobarbital may decrease the serum concentration of phenytoin Valproate increases the serum concentration of phenobarbital and phenobarbital reduces the serum concentration of valproate.	80 hours	Not indicated unless Crcl <10 msl/min In patients with Crcl <10 mls/min, administer 50% of total daily dose **in HD, a supplemental dose of 50% of usual dose should be given after HD** frequent therapeutic drug monitoring may be necessary.	No specific dose adjustment-higher accumulation is expected.	Some dosage forms may contain propylene glycol Common adverse effects include hypotension, bradycardia, CNS depression, and dose related respiratory depression.
Topiramate	LD: 200-400 mg MD: 100-400 mg/day in 2-4 divided doses (reports up to 1600 mg/day)	Use with zonisamide and other carbonic anhydrase inhibitors may worsen metabolic acidosis Use with caution with valproic acid may worsen high ammonia levels CYP 3A4 inducers can reduce topiramate concentration significantly.	21	Reduce dose by ~50% HD: supplemental dose may be necessary	Consider dose reduction.	May cause metabolic acidosis; caution with propofol, acetazolamide, zonisamide and metformin May cause renal stones.
Brivaracetam	LD: 50-200mg MD: 100-300mg/day in two divided doses	Patients who are poor CYP 2C19 metabolizers or those also on CYP 2C19 inhibitors may need dose reduction.	9	Contraindicated in patients undergoing dialysis, but can be used in patients with AKI.	Consider dose reduction min 50 mg/day and max 150 mg/day.	high-affinity synaptic vesicle glycoprotein 2A ligand that is structurally related to levetiracetam.

ASM: anti-seizure medication, LD: loading dose, MD: maintenance dose, HD: hemodialysis, CRRT: continuous renal replacement therapy

Table 4. List of urgent ASM and its drug monitoring including adverse drug reactions		
ASM	Therapeutic drug monitoring (mcg/mL)	Adverse drug reaction (ADR) monitoring
Phenytoin	Total: 10-20 *Corrected for albumin* Free: 1-2	Nystagmus, lethargy, coma, thrombocytopenia, gingival hyperplasia, rash,Steven Johnson syndrom and Liver Function Tests. Narrow therapeutic index; close drug monitoring is required.
Phenobarbital	20-40 Adults: Trough levels up to 80 mcg/mL are used in SE	Drowsiness, hepatoxicity, rash - Steven Johnson syndrom, thrombocytopenia
Valproic acid	50-100 Adults: trough levels up to 175 mcg/mL are used in SE	Drowsiness, thrombocytopenia, hyperammonemia, polycystic ovarian syndrome, teratogenic, hepatotoxicity
Lacosamide	2.8-18 (Test of compliance)	PR interval prolongation - risk of atrioventricular block, bradycardia, balance & coordination difficulties
Levetiracetam	12-46 (Test of compliance)	Aggression, psychosis, asthenia
ASM: anti-seizure medication, SE: status epilepticus		

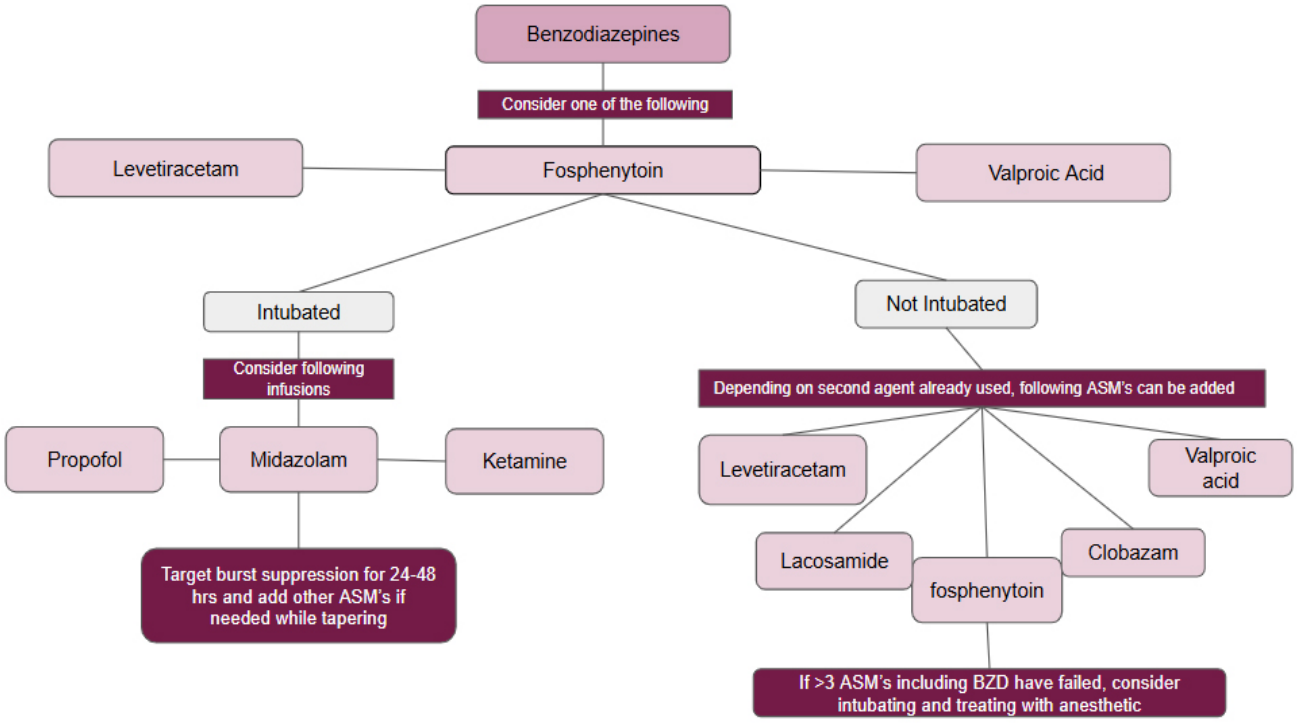

Figure 2: Practical approach to antiseizure medication selection in status epilepticus
ASM: anti-seizure medication, BZD: benzodiazepines

Refractory Status Epilepticus and Super Refractory Status Epilepticus

RSE is defined as SE that persists despite at least two appropriately dosed parenteral ASMs, while SRSE is SE that persists either for at least 24 hours after the onset of continuous anesthetic medications (i.e., midazolam, propofol, pentobarbital, and ketamine) or during the weaning of these medications. However, it is important to note that, prolonged requirement for anesthetic coma was strongly associated with poor functional outcomes and functional decline. Mechanical

ventilation was required in more than 90% of cases, one-third of which ultimately required tracheostomy. Longer duration of mechanical ventilation was associated with mortality. Additionally, cardiac arrhythmias requiring intervention, and pneumonia predicted poor functional outcome (17).

Recent case reports (18,19) have shown that ketamine represents a safe and effective treatment option for refractory seizures without intubation, and thus has the potential to reduce morbidity associated with intubation in a carefully selected patient population. Early initiation may increase the likelihood of success. Table 6 summarizes appropriate dosing of anesthetics in this context.

Discontinuation of Anesthetics

Once under the anesthetic, patients are monitored on continuous EEG and targeted for burst suppression. This is aimed to last for at least 24-28 hours. Once achieved, the anesthetic can be weaned every 3 hours by 20-50% (Table 6) (20). If brief seizures progress to SE, anesthetic tapering should be stopped, and the dose should be increased to the prior, effective level. In addition, another anti-seizure medication can be added to aid in weaning anesthetic. Another 24-48 hours period of electrographic stability should be achieved before attempting an anesthetic withdrawal.

While deep sedation and burst suppression are well-described interventions for refractory status epilepticus, the specifics on weaning sedation are based on expert opinion, small observational studies, and standard critical care principles rather than large, dedicated randomized controlled trials. For now, clinicians rely on continuous EEG monitoring, gradual tapering, and strong maintenance antiseizure drug coverage to prevent rebound seizures and optimize outcomes.

Table 5. Selected landmark trials in status epilepticus

Trial	n	Intervention	Primary outcome	Secondary outcome	Results	Comments
VA study (9)	348	Diazepam (0.15 mg/kg) followed by phenytoin (18 mg/kg), lorazepam (0.1 mg/kg), phenobarbital (15 mg/kg), and phenytoin (18 mg/kg)	Cessation of all motor seizure activity within 20 minutes of the start of the assigned medication.	Adverse effects, Mortality and need for additional ASM*	Lorazepam alone had the highest initial success rate of controlling status epilepticus (around 65%) Diazepam + phenytoin and phenobarbital alone followed in success rates (~55-58%). Phenytoin alone had a lower success rate (~44%)	Diazepam was given in combination with phenytoin, whereas lorazepam was given alone. Phenobarbital was also a stand-alone agent. This creates slight differences in how the regimens were compared.
RAMPART (10)	893	10 mg IM versed vs 4 mg IV lorazepam	Cessation of Seizures before arrival to the ED* without the need for additional ASM	Intubation, occurrence of recurrent seizures and complication	Midazolam was non inferior to lorazepam in preventing prehospital status.	Study conducted in the US with trained paramedics, hence not generalizable for rural areas.
ESETT (13)	384	Second line agents in BZD* refractory status Levetiracetam(60 mg/kg) vs Fosphenytoin (20 mg/kg) vs valproic acid (40 mg/kg)	Cessation of status epilepticus without the need for additional ASM within 60 min	Safety, clinical improvement functional outcomes, mortality and morbidity	No difference in primary and secondary outcomes between medications	The study was under powered and the time frame of 60 minutes may not capture long term effectiveness of drugs and seizure recurrences

VA: veterens affair, RAMPART: rapid anticonvulsant medication prior to arrival trial, ESETT: established status epilepticus trial, ASM: antiseizure medication, ED: emergency department, BZD: benzodiazepines

Table 6. List of anesthetics that can be used in refractory and super refractory status

Drug	Dosing: Loading dose Maintenance dose	Side effects	Tapering dose when seizure control or burst suppression is achieved for at least 24 hours	Comments
Propofol	LD: 1-2 mg/kg MD: 30-200 mcg/kg/min	Hypotension; Propofol-related infusion syndrome (PRIS) (80/kg/min > 48 hrs) respiratory depression	20% reduction in every 3 hours	Adjust calorie intake 1.1 kcal/mL. Monitor creatine kinase (CK), triglyceride, lactate, amylase, and lipase
Midazolam	LD: 0.2 mg/kg MD: 0.05-2.9 mg/kg/h	Hypotension Respiratory depression	50% decrease every 3 hours	Tachyphylaxis with prolonged use Accumulation of active metabolite in renal impairment
Ketamine	LD: 0.5-1.5 mg/kg MD: 1-10 mg/kg/h	Cardiac arrhythmias Emergence phenomenon Hyper/hypotension Metabolic acidosis	20% reduction every 3 hours	Cautious use in patients with history of severe cardiovascular disease Monitor LFTs
Pentobarbital	LD: 5-15 mg/kg MD: 0.5-5 mg/kg/h	Cardiac depression Hypotension Metabolic acidosis Paralytic ileus Respiratory depression	20% reduction every 3 hours	Contains propylene glycol Monitor for hemodynamic adverse effects such as hypotension, bradycardia Potent CYP enzyme inducer

Conclusion

SE presents a significant clinical challenge due to its potential for rapid progression to irreversible neuronal damage. The ILAE's operational framework underscores the importance of early recognition and time-sensitive treatment. Delayed intervention increases the risk of mortality and long-term morbidity, evidenced by the steep decline in treatment efficacy beyond 30 minutes of seizure activity.

Recent insights into the pathophysiological mechanisms of SE provide a basis for targeted interventions. The role of receptor dynamics (e.g., GABA-A receptor internalization and NMDA receptor externalization) has informed the use of benzodiazepines and highlighted the need for alternative therapies in benzodiazepine-resistant cases.

Advances in ASM pharmacokinetics, newer agents like brivaracetam, clobazam, and perampanel, and adjunctive therapies like ketamine offer hope for better outcomes in refractory cases. However, the management of SRSE remains complex, requiring careful balancing of sedation, ventilation, and systemic support to minimize complications. Further research is needed to refine treatment algorithms for RSE and SRSE, identify biomarkers predicting treatment response, and develop neuroprotective agents to mitigate long-term neuronal damage.

In conclusion, managing SE requires a multidisciplinary approach, combining prompt intervention with an understanding of its complex pathophysiology. Standardized protocols and emerging therapies promise to improve patient outcomes, especially in refractory and super-refractory cases.

Footnotes

Authorship Contributions

Concept: S.F., Design: S.F., I.J., Data Collection and Process: S.F., I.J., Analysis or Interpretation: S.F., I.J., Literature Search: S.F., I.J., Writing: S.F., I.J.

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

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ORIGINAL RESEARCH / *ÖZGÜN ARAŞTIRMA*

Sleep Disturbances Associated with Delirium in Conscious Patients in the Intensive Care Unit

Yoğun Bakım Ünitesinde Yatan Bilinci Açık Hastalarda Deliryuma Bağlı Uyku Bozuklukları

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ABSTRACT

Objective: The primary aim of the study was to analyse the relationship between subjective sleep quality assessed with the numeric rating scale (NRS) and the presence of delirium identified with both the confusion assessment method for the intensive care unit (CAM-ICU) and intensive care delirium screening checklist (ICDSC). The secondary objective was to analyse the effect of other selected predictors on delirium.

Materials and Methods: The prospective observational study included 126 non-intubated patients staying in the intensive care unit for more than 24 hours. Delirium was assessed simultaneously with both instruments (CAM-ICU and ICDSC) twice daily, and perceived sleep quality (NRS) was evaluated once a day. From 126 patients, 1299 paired questionnaires and 278 NRS records were obtained.

Results: There were 37 (29.4%) and 40 (31.7%) patients identified as CAM-ICU positive or having an ICDSC score ≥4, respectively. An NRS ≤5 was found in 93 patients (73.8%). A statistically significant relationship between the incidence of delirium (assessed by two instruments) and sleep quality (NRS ≤5) was confirmed. The CAM-ICU positivity was 0.391 [95% confidence interval (CI), 0.36 to 0.421 ($p<0.001$)], and the ICDSC positivity was 0.463 [95% CI, 0.435 to 0.491 ($p<0.001$)]. This relationship strength (assessed using Kendall's Tau) was rated as moderate.

Conclusion: The study suggests a relationship between delirium and subjectively assessed sleep quality. In this respect, sleep disturbances are likely to contribute to the development of delirium, even without valid objective data confirming them as a definite risk factor.

Keywords: Intensive care unit, delirium, sleep disturbances, delirium screening tool

ÖZ

Amaç: Çalışmanın temel amacı, sayısal derecelendirme ölçeği (NRS) ile değerlendirilen öznel uyku kalitesi ile hem yoğun bakım ünitesi için konfüzyon değerlendirme yöntemi (CAM-ICU) hem de yoğun bakım deliryum tarama kontrol listesi (ICDSC) ile tanımlanan deliryum varlığı arasındaki ilişkiyi analiz etmektir. İkincil amaç ise seçilen diğer belirleyicilerin deliryum üzerindeki etkisini analiz etmekti.

Gereç ve Yöntem: Prospektif gözlemsel çalışmaya yoğun bakım ünitesinde 24 saatten fazla kalan entübe olmayan 126 hasta dahil edildi. Deliryum her iki cihazla (CAM-ICU ve ICDSC) eş zamanlı olarak günde iki kez, algılanan uyku kalitesi (NRS) ise günde bir kez değerlendirildi. Yüz yirmi altı hastadan 1299 eşleştirilmiş anket ve 278 NRS kaydı elde edildi.

Bulgular: CAM-ICU pozitif veya ICDSC skoru ≥4 olan sırasıyla 37 (%29,4) ve 40 (%31,7) hasta vardı. Doksan üç hastada (%73,8) NRS ≤5 bulundu. Deliryum insidansı (iki araçla değerlendirilen) ile uyku kalitesi (NRS ≤5) arasında istatistiksel olarak anlamlı bir ilişki doğrulandı. CAM-ICU pozitifliği 0,391 [%95 güven aralığı (GA), 0,36 ila 0,421 ($p<0,001$)] ve ICDSC pozitifliği 0,463 [%95 GA, 0,435 ila 0,491 ($p<0,001$)]. Bu ilişkinin gücü (Kendall's Tau kullanılarak değerlendirildi) orta düzeyde olarak derecelendirildi.

Sonuç: Çalışma deliryum ile subjektif olarak değerlendirilen uyku kalitesi arasında bir ilişki olduğunu düşündürmektedir. Bu bakımdan, uyku bozukluklarının, kesin bir risk faktörü olduğunu doğrulayan geçerli objektif veriler olmasa bile, deliryum gelişimine katkıda bulunması muhtemeldir.

Anahtar Kelimeler: Yoğun bakım ünitesi, deliryum, uyku bozuklukları, deliryum tarama aracı

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Introduction

Sleep is vital for physical and mental health. Nowadays, more attention is paid to sleep disturbances in intensive care unit (ICU) patients, as they may contribute to the development of delirium. Studies have shown numerous similarities in the clinical and physiological profiles of patients with delirium and sleep disturbances (1). A study of 29 ICU patients found an association between delirium and severe sleep reduction (2). There is an electrophysiological relationship between sleep architecture changes and delirium, with delirium occurring in patients with rapid eye movement sleep loss and those with clinically confirmed atypical sleep, characterised by electroencephalography findings suggesting wakefulness (2-4). A meta-analysis confirmed that preexisting sleep disturbances are likely associated with higher rates of postoperative delirium [odds ratio (OR): 5.24; 95% confidence interval (CI): 3.61-7.60; $p<0.001$] (5). Even though the link between sleep disturbances and delirium was studied and analysed by many authors (1,6,7), the available literature suggests that there may be a close relationship between delirium, sleep, circadian rhythm, and critical illness. However, no causal pathway has yet been clearly described, and the directionality of the relationship is not understood. The attempts to reduce the incidence of delirium are based on identifying and modifying risk factors. Sleep disturbances are thus one of the potentially modifiable risk factors. Professionals' increasing interest in the recent Society of Critical Care Medicine (SCCM) guidelines on sedation and delirium is reflected in the recognition that professionals' increasing interest in the recent SCCM guidelines on sedation and delirium, therefore, the sleep promotion strategy is a fundamental and integral part of delirium prevention and management (8).

Therefore, the present study aimed to investigate the relationship between subjective sleep quality assessed with the numeric rating score (NRS) and the presence of delirium identified with both the confusion assessment method for the intensive care unit (CAM-ICU) and the intensive care delirium screening checklist (ICDSC). The second endpoint was to analyse the effect of other selected predictors on the occurrence of delirium.

Materials and Methods

Design

A Prospective Observational Study

Patients: Data for the study were collected in the Department of Anaesthesiology and Intensive Care Medicine ICU (5 beds) and multidisciplinary ICU (10 beds) of AGEL Hospital between February 2020 and August 2020. Adult conscious patients who consented to participate and were staying in the ICU for more than 24 hours were included in the study. The following demographic data were collected: Age, sex, smoking status, and alcohol consumption. The following were recorded from the clinical data: operation, length of stay in ICU, overall mortality, type of admission, pain visual analogue scale (VAS), sedation richmond agitation-sedation scale (RASS), therapeutic intervention scoring system (TISS) score, history of mechanical ventilation, restraints, and medication (opioids, benzodiazepines, antipsychotics). The exclusion criteria were a terminal illness; a diagnosis of dementia; and an altered consciousness: Glasgow coma scale (GCS) score ≤12 or deep sedation (RASS score ≤ -4).

Assessment instruments: Two instruments for diagnosing delirium were used in the study. The ICDSC includes the following eight items: Altered level of consciousness, inattention, disorientation, hallucination-delusion, agitation or retardation, inappropriate speech or mood, sleep-wake cycle disturbance and symptom fluctuation. Each positive item scores one point. If the total score is ≥4, delirium is diagnosed. Scores of 1-3 indicate subsyndromal delirium (9).

When using the CAM-ICU to diagnose delirium, the first step is to assess the level of sedation with the RASS (in deeply sedated patients, not responding to stimulation, RASS score ≤-4, the presence of delirium cannot be established). The second step is an assessment of four key features of delirium: Acute change or fluctuating course of mental status (Feature 1), inattention (Feature 2), altered level of consciousness (Feature 3), and disorganised thinking (Feature 4). Delirium is considered positive when Feature 1 and Feature 2, and either Feature 3 or Feature 4 are present. If not, delirium is excluded (CAM-ICU negative). RASS scores ranging from 0 to -3 are associated with hypoactive delirium. A RASS score of +1 to +4 suggests hyperactive delirium. Mixed delirium occurs when a patient fluctuates between the two forms of delirium (10).

Sleep quality was assessed with the NRS. Patients used this 10-point analogue scale to rate their subjective quality of sleep. All assessments were performed in the morning, between 8.00 AM and noon. Nurses asked patients the following question: Could you rank your sleep of last night on a scale between 0 (a worst night's sleep) and 10 (a best night's sleep)?

Good vs. bad sleep definition: In the study, patients' sleep was classified as either good (NRS >5) or bad (NRS

≤5), and the sample was divided accordingly. The cut-off was arbitrarily determined based on literature data (16) showing good statistical results, namely a sensitivity of 83%, a specificity of 79%, an area under the receiver operating characteristic curve of 0.81 (95% CI: 0.74-0.87).

Process of translation: The instrument was translated and linguistically validated according to the guidelines and standards, for the translation and cultural adaptation of patient-reported outcome measures (11).

Data Collection

Two assessment instruments (CAM-ICU and ICDSC) were used to detect delirium. Sleep quality was subjectively evaluated with the NRS. Nurses performed delirium screening twice a day, and sleep quality was assessed once a day. On average, the forms took approximately 5 minutes to complete. In total (126 patients), 1299 paired questionnaires and 278 NRS records were obtained.

Ethical Aspects

The study, conducted in accordance with the Declaration of Helsinki, was approved by the Ethics Committee of Vzdělávací a výzkumný institut AGEL (no: INT 2019003, date: 08.12.2019). Respondents' participation was voluntary and anonymous. The author approved using the Czech version of the CAM-ICU. The ICDSC was translated with the author's permission. The NRS was used as published by Rood et al. (12).

Statistical Analysis

Relationships between pairs of metrics, ordinal or binary variables, were tested using Kendall's τ coefficient. The relationships between a set of explanatory variables-differentiators and predictors-on one side, and the predicted (explained, dependent) binary or metric variables on the other, were evaluated by multivariate regression with a reduction of dimensionality known as optimized potentials for liquid simulations (OPLS). This test can cope with the problem of severe multicollinearity (high intercorrelations) in the matrix of explanatory variables, while ordinary multiple regression fails to evaluate such data correctly. The multicollinearity in OPLS is favourable, as it enhances the predictive power of the model. In the OPLS models with binary predicted variables, the logarithm of the ratio of the probability of positive outcome to the probability of adverse outcome (logarithm of the likelihood ratio) was chosen as a single dependent variable, ensuring that the predicted probability ranged between 0 and 1. The statistical software SIMCA-P v.12.0 from Umetrics AB (Umeå, Sweden), which was used for OPLS analysis, enabled the identification of the number of relevant components, the detection of multivariate non-homogeneities, and the testing of multivariate normal distribution and homoscedasticity (constant variance).

Results

The study comprised 126 consecutively admitted patients (76 males/50 females; 60.3/39.7%) with a median age of 71 (60,77). Twenty-seven patients (21.4%) had a positive history of mechanical ventilation, and 38 respondents (30.2%) underwent surgery. Acute admissions prevailed (81%). The admission diagnoses varied, with the most frequent being the following international classification of diseases (ICD) categories (in descending order): Diseases of the respiratory system (ICD J) 17.5%, diseases of the circulatory (ICD I) and digestive (ICD K) systems 16.7% each. 18.3% of admissions were classified as abnormal clinical findings (ICD R), including frequent ICU syndromes (shock, hypovolemia, sepsis, etc.) without further specification. The most frequently administered drugs related to analgesia, sedation and delirium treatment were opioids (53 patients; 42.1%), antipsychotics (38 patients, 30.2%) and benzodiazepines (27 patients, 21.4%). The median length of stay in the ICU and hospital was six days (from 4 to 9) and 15.5 days (from 9 to 20), respectively. During their stay in the ICU, ten patients (7.9%) died. The number of deaths throughout the entire hospital stay until discharge (including ICU deaths) was 18 (14.3%). The median TISS score measuring nursing workload was 557, suggesting that the sample primarily included conscious patients who were not critically ill.

From the 126 patients, 1299 paired records assessing delirium and 278 records evaluating subjective sleep quality were obtained. According to CAM-ICU assessment, 37 patients were classified as delirium-positive (326 records; 29.4%) and 89 delirium-negative (973 records; 70.6%). Combining delirium-positivity with RASS, 18 patients showed hyperactive delirium (total of 152 records, 14.3%), 12 hypoactive delirium (94 records; 9.5%) and seven mixed forms (80 records, 5.6%). According to ICDSC, delirium (a score of 4-8) was diagnosed in 40 patients (total of 346 records; 31.7%), subsyndromal delirium (a score of 1-3) in 32 patients (381 records; 25.4%) and 54 patients (572 records; 42.9%) were delirium-negative. Thirty-three patients (total of 75 records; 26.2%) reported good sleep (NRS >5), and 93 patients (203 records; 73.8%) had lousy sleep (NRS ≤5). Based on this rating, the studied population was divided into two subgroups. (Table 1).

Table 1. Demographic and clinical data (n=126) and paired observation (1299)

Variables	n (%)	Median (quartiles)	Paired observation
Men	76 (60.3)		
Mechanical ventilation	27 (21.4)		
Operation	38 (30.2)		
Acute admission	102 (81)		
ICD: A, C, D, E, F	19 (15.1)		
ICD: I	21 (16.7)		
ICD: J	22 (17.5)		
ICD: K	21 (16.7)		
ICD: R	23 (18.3)		
ICD: M, N, S	20 (15.9)		
Opioids	53 (42.1)		
Benzodiazepines	27 (21.4)		
Antipsychotic drugs	38 (30.2)		
CAM-ICU +	37 (29.4)		326
Hyperactive form (RASS +1/+4)	18 (14.3)		152
Hypoactive form (RASS 0/-3)	12 (9.5)		94
Mix	7 (5.6)		80
CAM-ICU -	89 (70.6)		973
ICDSC negative (0)	54 (44.4)		572
Subsyndromal delirium (ICDSC 1-3)	32 (25.4)		381
Delirium (ICDSC 4-8)	40 (31.7)		346
NRS >5*	33 (26.1)		75
NRS ≤5*	93 (73.8)		203
Age		71 (60, 77)	
Length of hospitalization on ICU		6 (4.25, 9)	
Length of hospitalization on hospital		15.5 (9, 20)	
ICU mortality	10 (7.9)		
Hospital mortality (overall include ICU mortality)	18 (14.3)		
TISS		557(555, 557)	

*: 278 overall observation numeric rating score, CAM-ICU: Confusion assesment method for the intensive care unit, RASS: Richmond agitation sedation scale, ICDSC: Intensive care delirium screening checklist, ICU: Intensive care unit, TISS: Therapeutic intervention scoring systém, NRS: Numeric rating score, ICD: International classification of diseases

Kendall's τ values (using 95% CI), which were used to express the power of the relationships, were interpreted as follows: higher values indicated stronger relationships. In contrast, positive or negative values indicated direct or indirect causality (13). Almost all the following parameters were shown to be statistically significant regarding sleep disturbance ($p<0.001$), excluding alcohol, age, RASS, gender, operation, type of admission, some diagnoses, and hospital mortality. The results obtained (ranked by the absolute strength of the first three in the relationship and given with CI) were GCS -0.383 (-0.413 - -0.352), physical restraints 0.243 (0.209-0.276), VAS 0.196 (0.161-0.23) (Tables 2,3).

The association between poor sleep quality (bad sleep, NRS ≤5) and delirium assessment (CAM-ICU, ICDSC) scores was studied. The results showed a significant relationship ($p<0.001$) between sleep disturbances and delirium assessment methods. Kendall's τ was 0.391 (CI: 0.36-0.421) for CAM-ICU positivity and 0.463 (0.435-0.491) for ICDSC positivity, respectively. An important point was that these positive associations (delirium positivity and bad sleep) were rated moderate (Table 4) (13).

Advanced statistics were used to select a set of predictors (risk factors) evaluated in the OPLS model to assess variances in the presence of delirium (for each diagnostic tool). In the OPLS model for multivariate regression, the risk factor with the highest statistical confidence for the CAM-ICU positivity and ICDSC positivity was the first three predictors (according to component loading): (1) GCS followed by (2) physical restraints and (3) VAS. The association of these three predictors were assessed as moderate to strong (14), and prediction is recommended. The rest of the variables and the degree of influence of the monitored variables were evaluated as weak, and thus, they are not suitable for predicting disorders (Tables 5,6).

Discussion

In this study, we have identified critical findings. Firstly, although screening questionnaires can help diagnose delirium quickly (within 2 to 5 minutes), different questionnaires may detect delirium in varying ways. Unfortunately, the patient's ability to answer the questionnaire is limited in the ICU environment. Secondly, we found that patients who reported poor sleep quality had a higher incidence of delirium: 93 (73.8%) compared to 33 (26.1%). While several validated methods exist for screening, monitoring, and diagnosing sleep in the ICU, each technique has limitations and cannot be used for all patients. This is also one of the reasons why the effects

Table 2. Relationships between sleep disturbances and metric indices (n=278)

Variable	n total	n	NRS >5 good sleep median (quartiles)	n	NRS ≤5 bad sleep median (quartiles)	Kendall's τ (95% CI)	p-value
Alcohol	278	75	1 (1, 1)	203	1 (1, 1)	0.049 (0.0131, 0.0849)	0.066
Age	278	75	71 (60, 78)	203	71 (60.3, 78)	0.0156 (-0.0204, 0.0515)	0.499
Length of ICU stay	278	75	7 (5, 13)	203	9 (6, 15)	0.136 (0.1, 0.171)	<0.001
Length of hospital stay	278	75	17 (10, 29)	203	20 (14, 31)	0.106 (0.0704, 0.142)	<0.001
GCS	278	75	15 (15, 15)	203	15 (14, 15)	-0.383 (-0.413, -0.352)	<0.001
VAS	278	75	0 (0, 2)	203	1 (0, 3)	0.196 (0.161, 0.23)	<0.001
TISS	278	75	557 (555, 558)	203	557 (555, 557)	-0.13 (-0.165, -0.0944)	<0.001
RASS	278	75	0 (0, 0)	203	0 (0, 1)	0.0561 (0.0202, 0.0919)	0.033

GCS: Glasgow coma scale, VAS: visual analog scale, TISS: therapeutic intervention scoring System, RASS: Richmond agitation sedation scale, NRS: numeric rating score, CI: confidence interval

Table 3. Relationships between sleep disturbances and binary indices (n=278)

Variable	n	NRS >5 good sleep		NRS ≤5 bad sleep		Kendall's τ (95% CI)	p-value
		n	%	n	%		
Mechanical ventilation	278	30	10.7%	55	19.8%	0.234 (0.2, 0.268)	<0.001
Smoking	278	44	15.8%	54	19.4%	0.116 (0.0806, 0.152)	<0.001
Men	278	91	32.8%	81	29.2%	-0.0048 (-0.0407, 0.0312)	0.864
Benzodiazepines	278	11	4.1%	18	6.6%	0.101 (0.0655, 0.137)	<0.001
Opioids	278	28	9.9%	42	15.0%	0.151 (0.116, 0.186)	<0.001
Antipsychotics	278	36	12.8%	44	15.9%	0.103 (0.0672, 0.138)	<0.001
Operation	278	31	11.1%	27	9.7%	0.0213 (-0.0147, 0.0572)	0.444
Type of admission	278	120	43.3%	111	40.1%	0.0377 (0.0017, 0.0736)	0.175
Restraints	278	5	1.9%	25	8.9%	0.243 (0.209, 0.276)	<0.001
ICU mortality	278	10	3.6%	22	7.8%	0.151 (0.115, 0.186)	<0.001
ICD: A	278	5	1.8%	6	2.3%	0.0344 (-0.0016, 0.0704)	0.215
ICD: C	278	10	3.6%	2	0.7%	-0.133 (-0.168, -0.0973)	<0.001
ICD: D	278	3	1.2%	1	0.3%	-0.0684 (-0.104, -0.0325)	0.014
ICD: E	278	2	0.8%	2	0.7%	0.0002 (-0.0358, 0.0362)	0.996
ICD: F	278	3	1.1%	8	2.9%	0.106 (0.0697, 0.141)	<0.001
ICD: I	278	20	7.2%	15	5.3%	-0.0377 (-0.0736, -0.0017)	0.174
ICD: J	278	27	9.7%	35	12.7%	0.101 (0.0654, 0.137)	<0.001
ICD: K	278	25	9.1%	26	9.5%	0.0357 (-0.0003, 0.0716)	0.199
ICD: M	278	0	0.1%	1	0.5%	0.0567 (0.0207, 0.0925)	0.041
ICD: N	278	7	2.5%	6	2.1%	-0.0102 (-0.0461, 0.0259)	0.715
ICD: R	278	28	10.1%	20	7.2%	-0.0529 (-0.0888, -0.017)	0.057
ICD: S	278	15	5.4%	9	3.2%	-0.0635 (-0.0993, -0.0276)	0.022
Hospital mortality	278	23	8.2%	25	9.1%	0.0475 (0.0115, 0.0833)	0.087

NRS: Numeric rating score, ICD: International classification of diseases, CI: confidence interval

Table 4. Relationships between sleep disturbances and delirium parameters (CAM-ICU/ICDSC) (n=278)

Tool	Parameters	n	NRS >5 good sleep		NRS ≤5 bad sleep		Kendall's τ (95% CI)	p-value
CAM-ICU	Feature 1	278	25	9.0%	82	29.8%	0.471 (0.442, 0.498)	<0.001
	Feature 2	278	15	5.3%	52	18.7%	0.345 (0.313, 0.376)	<0.001
	Feature 3	278	14	5.0%	61	22.1%	0.419 (0.388, 0.448)	<0.001
	Feature 4	278	13	4.8%	53	18.9%	0.36 (0.329, 0.391)	<0.001
	CAM-ICU +	278	13	4.8%	56	20.3%	0.391 (0.36, 0.421)	<0.001
	HYPER	278	5	1.8%	28	9.9%	0.271 (0.238, 0.304)	<0.001
	HYPO	278	4	1.3%	16	5.9%	0.194 (0.159, 0.228)	<0.001
	MIX	278	4	1.5%	13	4.6%	0.142 (0.107, 0.177)	<0.001
ICDSC	Altered level of consciousness	278	13	4.8%	63	22.7%	0.434 (0.404, 0.463)	<0.001
	Inattention	278	14	5.2%	49	17.8%	0.329 (0.296, 0.36)	<0.001
	Disorientation	278	10	3.5%	42	15.2%	0.326 (0.294, 0.358)	<0.001
	Hallucination, delusion	278	4	1.5%	15	5.5%	0.171 (0.136, 0.206)	<0.001
	agitation or retardation	278	13	4.7%	51	18.3%	0.354 (0.322, 0.385)	<0.001
	Inappropriate speech or mood	278	5	1.8%	31	11.0%	0.295 (0.262, 0.328)	<0.001
	Sleep-wake cycle disturbance	278	0	0.0%	132	47.3%	0.528 (0.501, 0.553)	<0.001
	Symptom Fluctuation	278	20	7.1%	85	30.6%	0.663 (0.643, 0.683)	<0.001
	ICDSC 0 (normal)	278	119	42.9%	15	1.2%	-0.793 (-0.806, -0.78)	<0.001
	ICDSC 1-3 (subsyndrome delirium)	278	17	6.1%	64	23.2%	0.413 (0.383, 0.442)	<0.001
	ICDSC 4-8 delirium	278	11	3.8%	63	22.9%	0.463 (0.435, 0.491)	<0.001

CAM-ICU: Confusion assessment method for the intensive care unit, ICDSC: Intensive care delirium screening checklist, NRS: Numeric rating score, HYPER: hyperactive, HYPO: hypoactive, MIX: both form

of poor sleep quality and delirium development on patient outcomes are not immediately apparent. Finally, to prevent the growth of delirium, predicting its occurrence based on various indicators is trending; however, many of these indicators are not modifiable (e.g., age, TISS, gender).

The incidence of delirium varies considerably depending on the population of patients examined and diagnostic methods. Delirium has been reported in 16-89% of ICU patients, and its incidence appears to be highest (up to 80%) in mechanically ventilated patients (14,15). Our reported incidence (29.4% when assessed with the CAM-ICU and 31.7% with ICDSC, respectively) lies within the lower part of the range, which could be explained by patients' characteristics (the majority were not very sick and were not mechanically ventilated). Delirium includes three motor subtypes-hyperactive, hypoactive, and mixed-which may be associated with different prognoses. In the present study, 14.3% of cases were hyperactive, 9.5% hypoactive, and 5.6% mixed. A meta-analysis of 18 studies showed different incidences: Hypoactive (11%), followed by mixed (7%) and hyperactive (4%) (16). Another methodological pitfall of assessing delirium with certain diagnostic instruments is influenced by sedative drugs, which may affect the results, potentially leading to overrated positivity in cases where the RASS is not 0. A possible solution is to assess consciousness only after pharmacological sedation wears off. Therefore, to assess the persistence of delirium, many ICUs use routine daily sedation disruptions, (spontaneous awakening trials) as a part of standardised protocols for the need for further sedation (8). The ICDSC diagnosed subsyndromal delirium (10) in 25.4% of cases. Subsyndromal delirium could be viewed as a pre-delirium-a transition between delirium and normal mental status. It is common in ICU patients, but its true incidence and effect on the outcomes of critically ill patients remain unclear. In a meta-analysis of 6 studies, subsyndromal delirium was found in one-third of critically ill patients, with a limited impact on their outcomes (17). One of the study's primary goals was to assess the impact of sleep disturbances (for our purposes, classified subjectively as bad sleep, NRS ≤5) and their association with studied parameters. The study presumes that sleep disturbances may be a risk factor for delirium and prolonged mechanical ventilation, independently associated with other parameters (ICU deaths, ICU length of stay, and

Table 5. Relationships between CAM-ICU and predictors for the predictive component as evaluated by OPLS model (n=1299)						
		OPLS model Predictive component			Ordinary multiple regression	
	Variable	Component loading	t-statistics	R[a]	Regression coefficient	t-statistics
Relevant predictors (matrix X)	Day	-0.134	-10.87	-0.193**	0.056	5.43**
	Supervision	0.058	2.78	0.083*	0.004	0.25
	Mechanical Ventilation	0.108	8.76	0.155**	-0.010	-1.08
	Smoking	0.109	10.85	0.156**	-0.003	-0.30
	Men	0.026	1.56	0.038	-0.060	-4.08**
	Alcohol	0.159	24.38	0.228**	0.061	11.31**
	Benzodiazepines	0.192	6.68	0.276**	0.015	0.53
	Opioids	0.102	4.25	0.147**	-0.008	-0.42
	Antipsychotics	0.171	12.91	0.245**	0.012	1.06
	Operation	-0.135	-6.78	-0.194**	-0.143	-10.44**
	Age	0.051	4.10	0.073**	0.070	4.51**
	Restraints	0.458	24.78	0.656**	0.233	16.86**
	ICU mortality	0.147	10.02	0.211**	0.064	3.05**
	ICD: A	-0.060	-2.33	-0.086*	-0.006	-0.25
	ICD: C	-0.104	-7.99	-0.149**	-0.029	-3.01**
	ICD: F	0.182	14.53	0.260**	0.012	0.72
	ICD: I	0.058	4.84	0.083**	0.017	2.04*
	ICD: N	0.025	1.63	0.036	-0.004	-0.39
	ICD: R	-0.062	-4.02	-0.089**	0.012	0.53
	ICD: S	-0.062	-6.28	-0.088**	-0.008	-1.23
	Hospital mortality	0.142	9.07	0.204**	0.016	1.01
	GCS	-0.648	-36.65	-0.929**	-0.580	-19.05**
	VAS	0,280	16.80	0.401**	0.152	13.18**
	TISS	-0.036	-2.66	-0.052*	0.054	2.61*
	RASS	0.168	10.18	0.241**	-0.018	-1.74
(matrix Y)	CAM-ICU	1.000	71.65	0.809**		
Explained variability		65.5% (64.4% after cross-validation)				

R[a]:Component loadings expressed as a correlation coefficients with predictive component, *: p<0.05, **: p<0.01, OPLS: Optimized potentials for liquid simulations, GCS: Glasgow coma scale, VAS: visual analog scale, TISS: therapeutic intervention scoring system, RASS: Richmond agitation sedation scale, ICD: International classification of diseases, CAM-ICU: confusion assessment method for the intensive care unit

hospital length of stay). Our findings are consistent with these hypotheses and are similar to data reported by other authors (18,19). Even though our results are based on subjective assessments, which is a substantial limitation, the relationship between delirium and sleep disorders has been confirmed. On the other hand, contrary data exist. The study by Kamdar et al. (20) has shown no difference between subjectively perceived sleep quality assessed with the Richards-Campbell sleep questionnaire (RCSQ) in patients with and without delirium (mean RCSQ 57 vs 58) and there is no relation between perceived sleep quality and transition to delirium (adjusted OR: 1; 95% CI: 0.99-1.00). Interventional studies, however, suggest the opposite. According to Patel et al. (21), the sleep efficiency index has the potential to predict the development of delirium, with patients reporting high sleep efficiency index scores demonstrating a reduced risk of delirium (OR: 0.9; 95% CI: 0.84-0.97). Similarly, Van Rompey et al. (22) revealed, using Cox regression, that earplugs lowered the risk of delirium or

Table 6. Relationships between ICDSC and predictors for the predictive component as evaluated by OPLS model (n=1299)

		OPLS model Predictive component			Ordinary multiple regression	
	Variable	**Component loading**	**t-statistics**	**R[a]**	**Regression coefficient**	**t-statistics**
Relevant predictors (matrix X)	Day	-0.092	-7.11	-0.136**	0.039	2.77*
	Supervision	0.066	2.80	0.098*	0.027	1.07
	Mechanical ventilation	0.179	17.49	0.264**	0.032	2.24*
	Smoking	0.086	6.88	0.126**	0.042	2.38*
	Men	0.067	4.70	0.100**	-0.020	-2.63*
	Alcohol	0.187	15.94	0.276**	-0.068	-6.51**
	Benzodiazepines	0.183	5.88	0.270**	-0.016	-0.66
	Opioids	0.123	8.22	0.182**	0.018	1.32
	Antipsychotics	0.192	15.35	0.284**	0.024	2.65*
	Operation	-0.081	-3.61	-0.120**	-0.115	-9.82**
	Type of admission	0.046	2.36	0.068*	0.022	1.72
	Restraints	0.425	25.43	0.628**	0.219	16.99**
	Length of ICU stay	0.072	4.29	0.106**	0.037	3.98**
	ICU mortality	0.183	11.53	0.271**	0.104	5.38**
	ICD: A	-0.081	-5.00	-0.119**	-0.020	-1.11
	ICD: C	-0.103	-7.61	-0.151**	-0.018	-2.59*
	ICD: F	0.195	9.28	0.287**	0.061	2.91*
	ICD: K	0.073	3.21	0.108**	0.065	6.43**
	ICD: S	-0.080	-3.75	-0.118**	-0.045	-3.44**
	Hospital mortality	0.164	16.84	0.242**	0.023	1.53
	GCS	-0.632	-70.86	-0.934**	-0.560	-40.14**
	VAS	0.273	25.68	0.403**	0.129	11.03**
	TISS	-0.095	-28.18	-0.140**	0.028	2.20*
	RASS	0.148	10.05	0.218**	-0.020	-1.54
(matrix Y)	ICDSC	1.000	59.96	0.805**		
Explained variability		64.8% (63.9% after cross-validation)				

R[a]:Component loadings expressed as a correlation coefficients with predictive component, *: $p<0.05$, **: $p<0.01$, OPLS: optimized potentials for liquid simulations, GCS: Glasgow coma scale, VAS: visual analog scale, TISS: therapeutic intervention scoring system, RASS: Richmond agitation sedation scale, ICDSC: intensive care delirium screening checklist

mild confusion in the ICU by 53% (hazard ratio: 0.47; 95% CI: 0.27-0.82), with more patients reporting better subjectively assessed sleep quality. Previous studies that have addressed the problem are far from providing unambiguous results.

Another issue regarding the sleep-delirium study is the selection of adequate assessment instruments. Many authors have mentioned problems finding suitable techniques for assessing delirium and detecting sleep disorders simultaneously. It seems reasonable to combine an objective instrument with a subjective assessment (23). A possible approach (suitable mainly for non-ICU patients) is an objective assessment of sleep by actigraphy in combination with another subjective method, a monitoring technique based on alterations in motor activity (23). In ICU patients with altered consciousness, such as those with lower GCS or under sedation, polysomnography, together with a validated subjective questionnaire filled out by nurses, is considered the gold standard (24).

According to reported results, patients with perceived poor sleep quality more often received a sedative medications (benzodiazepines, opioids, and antipsychotics). Thus, the optimal approach to analgesia and sedation in ICU patients seems to be an important consideration. Good clinical practice is well-established, involving using drugs with short half-lives, implementing nurse-driven sedation protocols, including daily awakening trials, limiting deep sedation, minimising the use of muscle relaxants, and monitoring the depth of sedation if necessary (12). Maintenance of normal circadian rhythm, promotion of physiological (good quality) sleep, and prevention of sleep deprivation and disorders are crucial parts of ICU nursing care and are closely related to sedation strategy, affecting numerous clinical outcome parameters, including delirium incidence. Recently, the main principle of delirium management has been shifting from treatment to prevention, requiring knowledge of the associated risk factors. According to Ely et al. (25), patients staying in the ICU have ten or more risk factors for delirium onset. A meta-analysis by Zaal et al. (26) identified 11 risk factors for delirium supported by solid or moderate levels of evidence. Similarly, Van Rompaey et al. (27) grouped the most important risk factors into four domains, with 13 risk factors being identified as significant. Our findings agree with the previously mentioned studies, and add more statistical significance to relationships between delirium and its predictors by applying an OPLS model with consistent results. All the findings above related to sleep and delirium are generalisable and applicable to everyday clinical practice in the form of the ABCDE bundle of proper analgesia, sedation, and delirium management. It has been shown that such a bundle of care, including appropriate pain management, light sedation, avoidance of benzodiazepines, early awakening and weaning from mechanical ventilation, routine delirium monitoring and early mobilisation, improves patient outcomes and decreases delirium incidence by one-third (14).

Study Limitations

The study's primary limitations are the size of the sample, the number of patients, including its unicentric design and the selection of subjective sleep quality instruments. For a complex and comprehensive evaluation, valid, consistent, and objective methods for sleep measurement, such as actigraphy and polysomnography must be combined with subjective assessment instruments that are completed by patients or nurses. The high-quality multicenter randomised trial could overcome these limitations and increase knowledge of the relationship between sleep disturbances and delirium in ICU patients.

Conclusion

Even though the relationship between sleep disturbances and delirium has not been fully elucidated, many authors assume a bidirectional causal relationship, suggesting that sleep disorders are a risk factor for the development of delirium. The results of the presented study are consistent with this hypothesis. Early detection of delirium is fundamental, and choosing appropriate diagnostic tools remains a concern. Modern trends in intensive care reflect this two-way relation between sleep and delirium by respecting sleep-promoting (primarily non-pharmacological) strategies, delirium prevention, and early therapy as the standard of nursing care. More detailed analysis of this sleep-delirium association is needed for better and more personalised care in the future, minimising the incidence of delirium and need for sedation while maximising ICU patients' sleep quality.

Ethics

Ethics Committee Approval: The study, conducted in accordance with the Declaration of Helsinki, was approved by the Ethics Committee of Vzdělávací a výzkumný institut AGEL (no: INT 2019003, date: 08.12.2019).

Informed Consent: Adult conscious patients who consented to participate and were staying in the ICU for more than 24 hours were included in the study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: H.L., Concept: H.L., P.M., Design: H.L., P.M., K.A., Data Collection or Processing: H.L., P.M., Analysis or Interpretation: H.L., K.A., Literature Search: H.L., P.M., Writing: H.L., P.M., K.A.

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ORIGINAL RESEARCH / *ÖZGÜN ARAŞTIRMA*

Anemia Development and Retrospective Evaluation of Blood Transfusions in Patients in Anesthesia Intensive Care Unit

Anestezi Yoğun Bakım Ünitesinde Yatan Hastalarda Anemi Gelişimi ve Kan Transfüzyonlarının Retrospektif Değerlendirilmesi

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ABSTRACT

Objective: Anemia is a common problem of critically ill patients in intensive care units (ICU). This retrospective single-center study. We aimed to investigate the incidence of anemia and transfusions, transfusion-related risks, and clinical outcomes. We also investigated the contribution of the amount of blood taken for diagnosis and follow-up purposes to anemia.

Materials and Methods: In this retrospective single-center study (01.01.2015-31.12.2015), patients aged 18 years and older who were hospitalized for more than 24 hours were divided into two groups male (Group E) and female (Group K) and compared. The first 30-day hemoglobin (Hb) values, Hb values before and after transfusion, daily blood losses, and fluid balance, indications for transfusion, and related complications, and the number of erythrocyte suspensions used were recorded.

Results: Anemia was present in 60.7% and 83.9% of the patients on day 1 and day 3. Anaemia developed on the 3rd day in 55.6% of non-anemic patients. The mean Hb before transfusion was 7.5±1.3 g/dL and the mean Hb after transfusion was 6.9±1.1 g/dL. We found that the acute physiology and chronic health evaluation II score was higher in patients who received transfusion, and mortality was higher in female patients. On the 1st day of hospitalization, a mean of 37.0±15.7 mL/person blood sample was taken; due to repeated blood samples (mean 147.2±117.1 mL), we found that Hb values decreased significantly to require blood transfusion.

Conclusion: It was found that the majority of the patients admitted to the ICU were anaemic. Hb values continued to decrease over time. Repeated blood sampling contributed to the development of anaemia. Febrile reaction was the most common transfusion-related complication. It was concluded that practices in accordance with the current universal transfusion guidelines were performed.

Keywords: Anemia, blood transfusıon, intensive care unit

ÖZ

Amaç: Yoğun bakım hastalarında anemi gelişimi sık karşılaşılan bir problemdir. Yoğun bakım kritik hastalarında anemi ve transfüzyon insidansını, transfüzyon ilişkili risklerileri ve klinik sonuçları, tanı ve takip amaçlı alınan kan miktarının anemiye gelişimine katkısını retrospektif olarak araştırmayı amaçladık.

Gereç ve Yöntem: Retrospektif tek merkezli çalışmaya (01.01.2015-31.12.2015) 24 saatten uzun süreli yatan, 18 yaş ve üstü hastalar erkek (Grup E) ve kadın (Grup K) olarak iki gruba ayrılarak karşılaştırıldı. Transfüzyon yapılan ve yapılmayan hastaların ilk 30 günlük hemoglobin (Hb) değerleri, transfüzyon öncesi ve sonrası Hb değerleri, günlük kan kayıpları ve sıvı dengesi, transfüzyon endikasyonları ve ilişkili komplikasyonlar, kullanılan eritrosit süspansiyonu sayıları kaydedildi.

Bulgular: Hastaların yatışın 1. günü %60,7, 3. gününde %83,9'u anemikti. Anemik olmayanların %55,6'sında 3. günde anemi geliştiği saptandı. Hastaların transfüzyon öncesi Hb ortalaması 7,5±1,3 g/dL, transfüzyon sonrası Hb ortalaması 6,9±1,1 g/dL idi. Transfüzyon yapılanlarda akut fizyoloji ve kronik sağlık değerlendirmesi II skorunun daha yüksek olduğu ve bunlardan kadın hastaların mortalitelerinin daha yüksek olduğunu tespit ettik. Yatışın 1. günü ortalama 37,0±15,7 mL/kişi kan örneğinin alındığını; tekrarlayan kan örnekler (ortalama 147,2±117,1 mL) nedeniyle, Hb değerlerinin kan transfüzyonu gerektirecek şekilde anlamlı derecede düştüğünü tespit ettik.

Sonuç: Yoğun bakıma kabul edilen hastaların çoğunluğunun anemik olduğu, zaman içinde Hb değerlerinde düşüş devam ettiği; tekrarlayan kan örneklemlerinin anemi gelişimine katkısı olduğu; transfüzyon ilişkili komplikasyon olarak en sık febril reaksiyon görüldüğü tespit edildi ve mevcut evrensel transfüzyon rehberlerine uygun uygulamalar yapıldığı görüşüne varıldı.

Anahtar Kelimeler: Anemi, kan transfüzyonu, yoğun bakım ünitesi

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Introduction

Anemia, which is one of the most common hematological problems in society, can be defined as a decrease in the erythrocyte mass, which causes insufficient oxygen delivery to the tissues.

The development of anemia in critically ill patients during intensive care unit (ICU) follow-up and treatment is a common problem (1). Surgical procedures, coagulopathies, gastrointestinal system loss, intravascular hemolysis, nutritional deficiencies, and recurrent blood loss are among the most common causes of anemia in the ICU (2). Taking blood from ICU patients for diagnosis and follow-up, diagnostic blood loss (DBL) (coronary artery calcium) and phlebotomy are among the most important causes of anemia that are mostly neglected (3). In studies, because of the multiple causes of anemia, approximately one-third of ICU patients underwent transfusion without clinical indication, and the mortality rate in emergency department patients increased due to this high rate of transfusion (1,4,5). Transfusion of blood and blood products can be beneficial only when morbidity or mortality cannot be prevented by all other treatment methods. However, blood transfusion can reduce morbidity and mortality when used correctly despite the risks (6,7).

This study aimed to define the incidence of anemia and transfusion in patients undergoing follow-up and treatment, to determine the threshold hemoglobin (Hb) value used for transfusion, to identify the risks associated with transfusion, to evaluate the relationship between transfusion and clinical outcomes, and to investigate retrospectively the contribution of the amount of blood taken for diagnostic and follow-up to anemia. This investigation was conducted in the ICU of the Department of Anesthesiology and Reanimation Fırat University Hospital.

Materials and Methods

In our study, after obtaining approval from the Fırat University Hospital administration for reviewing patient records and the approval of the Fırat University Non-Interventional Research Ethics Committee, (decision no: 18, date: 05.10.2016) the hospital files of all patients who were followed up and treated in Fırat University Hospital Anesthesia ICU between 01.01.2015-12.31.2015 and the data recorded in Enlil Hospital Information Management System of Fırat University Hospital were analyzed retrospectively.

Patients with a hospitalization time of less than 24 hours, patients younger than 18 years, patients with a history of bleeding diathesis and/or hematologic disease, patients with acute renal failure (0.5 mg/dL/day increase in serum creatinine (Cr) basal value and/or 24-hour urine volume <400 mL) or chronic renal failure (Cr >1.3 mg/dL in women, Cr >1.5 mg/dL in men) and patients with sepsis having extreme values were excluded from the evaluation. Patients were divided into two groups, male (Group E) and female (Group K), and their data were compared.

Age, Glasgow coma scale (GCS) values, hospitalization diagnoses, and additional diagnoses during admission, presence of co-morbidities, acute physiology and chronic health evaluation II (APACHE II) scores calculated in the first 24 hours, and Hb values measured at admission to anesthesia ICU (AICU) were recorded. Daily Hb values, daily DBL, and daily fluid balance (FB) in the first 30 days of hospitalization, Hb values before and after transfusion, indications for transfusion, number of erythrocyte suspension (ES) units used, complications associated with transfusion, and length of stay in the ICU were recorded. Daily FB was calculated using the difference between the total amount of enterally and parenterally administered fluids and the total urine volume within 24 hours. TKC was calculated separately for each patient based on blood tests such as hemogram, biochemical analysis, arterial blood gas (ABG), etc., for each day in the ICU. The amount of blood taken was recorded as 2 mL for ABG, 5 mL for hemogram, 1 mL for erythrocyte sedimentation rate, 5 mL for biochemical analysis, 3 mL for coagulation tests, 30 mL for blood culture, 6 mL for human immunodeficiency virus and hepatitis testing, 5 mL for drug levels, and 2 mL for standard excretion.

Statistical Analysis

Statistical analysis of the data was performed using the SPSS version 22.0. Data obtained from the census were evaluated by the chi-square test and Fisher's exact test if the expected value was less than 5; the Wilcoxon rank sum test, t-test, and Mann-Whitney U test were used for the data obtained by measurement. $P<0.05$ was considered significant.

Results

A total of 413 patients were admitted to the AICU during the year between 01.01.2015 and 12.31.2015. Each admission of the patients who were admitted to the ICU more than once at different times in the same year, 3 patients in Group E, and 10 patients in Group K, was included in the evaluation separately. Data from 184 patients were excluded. The data of 229 patients-119 males and 110 females-, were evaluated.

Since 90% of these patients had less than 30 days of stay in the ICU, the data on the first 30 days of hospitalization were evaluated, because the data on hospitalization after 30 days could adversely affect the arithmetic mean as extreme values.

In general, the mean length of stay in the ICU was 12.2±16.6 days (min: 2 days, max: 87 days). The duration of stay in the AICU of 90% of the patients included in the study was less than 30 days. Of these, 69.4% (n=159) had less than 10 days of stay in the AICU.

The reasons for admission to the ICU were 31.4% postoperative follow-up, 10% trauma, and 58.6% medical diseases including respiratory system problems such as chronic obstructive pulmonary disease, and pneumonia; neurological problems such as cerebrovascular disease, intracranial mass; cardiovascular system problems such as ischemic heart disease, myocardial infarction, etc., Table 1.

The median of GCS values was found to be 9 (Table 1). There was no statistically significant difference between the two groups in terms of the reasons for admission to ICU, GCS values, length of stay in ICU, and exit from ICU ($p>0.05$, Table 1).

The mean APACHE II scores were found to be 21.20±6.9 (min: 6, max: 37), 20.93±6.68 in Group E and 21.50±7.33 in Group K. Patients who underwent blood transfusion, 22.00±4.51 in Group E, 23.90±6.21 in Group K, had significantly higher APACHE II scores than those who did not undergo blood transfusion, 20.59±7.72 in Group E, 20.64±7.54 in Group K. However, no statistically significant difference was detected between the groups (Table 2).

It was found that 60.7% of the patients, 62.2% in Group E and 59.1% in Group K, were anemic on the day of admission to the ICU. It was observed that this rate increased to 83.9%, 81.9% in Group E and 86.2% in Group K on the 3rd day of hospitalization, and decreases in mean Hb values continued over the following days. Anemia developed on the 3rd day of hospitalization in 55.6%, 50% in Group E, and 63.2% in Group K, of patients who were not anemic on the day of admission to the ICU. In terms of changes in Hb values, although women had lower Hb values in all periods, there was no statistically significant difference between the two groups except for the 3rd and 20th days of hospitalization ($p<0.05$).

An equal number of 58 (25.3%) patients from both groups were transfused with ES for indications such as anemia (41.4%), acute bleeding (24.1%), surgical intervention (12.1%) or hemodynamic instability (22.4%), (Table 3). Pre-transfusion Hb values were below 7 g/dL in 24 patients, between 7-10g/dL in 31 patients, and above 10 g/dL in 3 patients, who underwent transfusion due to acute hemorrhage.

In our study, the mean pre-transfusion Hb value was 7.5±1.3 g/dL (min: 4.7 g/dL, max: 10.5 g/dL); for transfusions with anemia indication, the mean pre-transfusion Hb values were 6.9±1.1 g/dL (min: 4.7 g/dL, max: 9.2 g/dL). There was no statistically significant difference between the groups in terms of the reasons for transfusion patients' admission to the ICU (Table 4).

18.9% of the transfused patients underwent transfusion within the first 24 hours of their stay in the ICU, and approximately half (46.5%) were transfused within the first three days (Figure 1).

Complications developed in 17.2% (n=10) of the transfused patients and were thought to be associated with transfusion (Table 5). The most common complication was febrile reaction (90%). An allergic reaction developed in one patient.

When we look at the exit status of patients from the ICU, 17.5% of the discharged patients and 38.4% of the patients who died were transfused. Among transfused patients, the number of patients who died was higher in Group K, and this difference was statistically significant ($p<0.05$, Table 6).

Although the amount of DBL per ICU day was higher in transfused patients than in non-transfused patients, it was significantly higher in patients who underwent transfusion per ICU day ($p<0.05$). There was no statistically significant difference between the groups in terms of total DBL and FB amounts, and mean values per intensive care day ($p>0.05$, Table 7).

Discussion

Anemia is either present or may develop in the early period in the majority of patients who are monitored in the the ICU. Anemia was reported in 95% of the patients 3 days after admission to the ICU (3,8). In our study, although the female patients had lower Hb values, similar changes were observed in the Hb values of both male and female patients undergoing intensive care in our AICU. According to the definition of World Health Organization (WHO); Hb values Hb <13 g/dL [Haemotocrit (Htc) <39%] in adult men and Hb <12 g / dL (Hct <36%) in non-pregnant women are accepted as anemia (9). According to this definition, it was observed that 60.7% of the patients were anemic on the day they were admitted to the ICU. This rate was 83.9% on the 3rd day of their hospitalization, and the decrease in mean Hb values continued over time. Anemia developed on the third day of hospitalization in 55.6% of the patients who were not anemic at the time of their admission to the ICU. These changes in Hb

Table 1. Characteristics of patients				
	Group E n (%)	**Group K n (%)**	**Total n (%)**	
Age groups (year)				
<50	41 (34.5)	37 (33.6)	78 (34.1)	X^2=0.40 p=0.980
51-69	33 (27.7)	30 (27.3)	63 (27.5)	
>70	45 (37.8)	43 (39.1)	88 (38.4)	
Surgical ıntervention				
Yes (postoperative acceptance)	43 (36.1)	49 (44.5)	92 (40.2)	X^2=1.734 p=0.420
During their stay	15(12.6)	13(11.8)	28 (12.2)	
No	61 (51.3)	48 (43.6)	109 (47.6)	
Admittance diagnosis				
Postoperative follow-up	35 (29.4)	37 (33.6)	72 (31.4)	X^2=7.514 p=0.185
Respiratory system problems	31 (26.1)	31 (28.2)	62 (27.1)	
Neurological problems	21 (17.6)	20 18.2)	41 (17.9)	
CVS system problems	5 (4.2)	5 (4.5)	10 (4.4)	
Trauma	18 (15.1)	5 (4.5)	23(10.0)	
Other	9 (7.6)	12(10.9)	21 (9.2)	
Associated disease				
Single system disease	47 (39.5)	43 (39.1)	90 (39.3)	X^2=8.510 **p=0.037**
Two system disease	24 (20.2)	32(29.1)	56 (24.5)	
More than two system disease	7 (5.9)	13(11.8)	20 (8.7)	
No	41 (34.5)*	22 (20.0)	63 (27.5)	
GKS				
Coma (3)	11 (9.2)	12(10.9)	23(10.0)	X^2=3.975 p=0.409
Precoma (4-7)	29 (24.4)	37 (33.6)	66 (28.8)	
Stupor (8-12)	55 (46.2)	38 (34.5)	93 (40.6)	
Confusion (13-14)	19(16.0)	17(15.5)	36 (15.7)	
Oriented (15)	5 (4.2)	6 (5.5)	11 (4.8)	
Admittance Hb (g/dL)				
S7	0 (0.0)	3 (2.7)	3(1.3)	X^2=3.851 p=0.146
7-10	33 (27.7)	25 (22.7)	58 (25.3)	
S10	86 (72.3)	82 (84.5)	168 (73.4)	
Transfusion status				
Yes	29 (24.4)	29 (26.4)	58 (25.3)	X^2=0.120 p=0.729
No	90 (75.6)	81 (73.6)	171 (74.7)	
Exit status from ICU				
Discharged	75 (63.0)	68 (61.8)	143 (62.4)	X^2=0.036 p=0.851
Death	44 (37.0)	42 (38.2)	86 (37.6)	

*: p<0.05, in Group E according to Group K, Hb: hemoglobin, ICU: intensive care unit, GCS: Glasgow coma scale, CVS: cardiovascular system

levels compared to the values at the time of admission were statistically significant.

Corwin et al. (4) showed that 50% of intensive care patients underwent blood transfusion during hospitalization, and this rate increased to 85% in patients with hospitalization longer than one week. Vincent et al. (3) reported, similar to Corwin et al. (4), that the majority of transfusions were performed in the first week of admission to ICUs and that 73% of the patients in

the ICU for more than one week were transfused. In the same study, they reported that 41% of patients underwent transfusion within 28 days. In our study, we observed that 25.3% of the patients underwent transfusion within 30 days, 39.8% of the patients hospitalized for more than one week underwent transfusion, and a statistically significant relationship was observed between the duration of ICU stay and transfusion rates. There was no statistically significant difference between the groups in terms of length of stay in the ICU.

Table 2. Evaluation of APACHE II scores of patients

	Number of patients	Mean ± SD	p-value
Male	119	20.93±6.67	0.541
Female	110	21,50±7.33	
Underwent T ransfusion	58	22.95±5.47*	**0.028**
No Transfusion	171	20.61 ±7.35	
Underwent Transfusion			
Male	29	22.00±4.51	0.189
Female	29	23.90±6.21	

*: p<0.05, people underwent transfusion compared to who did not, SD: standard deviation, APACHE: acute physiology and chronic health evaluation

Table 3. Distribution of transfusion indications by groups

First transfusion reason	Group E n (%)	Group K n (%)	Total n(%)
Anemia	11 (37.9)	13 (44.8)	24 (41.4)
Acute hemorrhage	8 (27.7)	6 (20.7)	14 (24.1)
Surgery during follow-up	3 (10.3)	4 (13.8)	7 (12.1)
Hemodynamic instability	7 (24.1)	6 (20.7)	13(22.4)
Total	29 (100)	29 (100)	58 (100)
X^2=0.672, p=0.880			

Table 4. Distribution of transfusion patients' reasons for admission to intensive care unit

Reasons for admission to intensive care	Group E n (%)	Group K n (%)	Total n (%)
Postoperative follow-up	8 (27.6)	8 (27.6)	16 (27.6)
Respiratory system problems	6 (20.7)	10 (34.5)	16 (27.6)
Neurological problems	4(13.8)	6 (20.7)	10 (17.3)
Cardiovascular system problems	0 (0.0)	2 (6.9)	2 (3.4)
Trauma	11 (37.9)	2 (6.9)	13 (22.4)
Other	0 (0.0)	1 (3.4)	1 (1-7)
X^2=10.631, p=0.059			

In blood transfusion practice, there may be different implementations depending on the hospital. Hébert et al. (10) observed many institutional changes in their study, including patients with similar age, arrival APACHE II scores, and similar conditions in four main categories; cardiovascular diseases, respiratory failure, major surgeries, and trauma. Vincent et al. (3) found significant differences in the transfusion rates of ICUs, with the highest rate (44.2%) observed in academic hospitals. The researchers attributed this difference between hospitals to the patient populations examined. Our hospital is a university hospital and tertiary health center that also serves the surrounding provinces. Therefore, patients with serious diseases can be treated in our hospital. Therefore, APACHE II scores of transfused patients are expected to be higher than those of non-transfused patients. More invasive procedures are applied to patients with serious disease, different laboratory tests are required, and therefore the blood volume taken is higher, and as a result, these patients are more prone to anemia (11). Similarly, the high APACHE II score in our AICU was associated with a higher number of blood samples for diagnostic purposes.

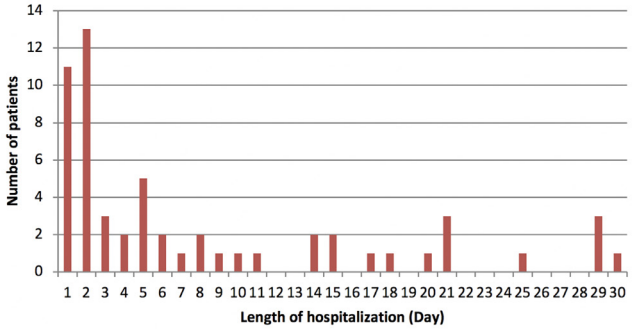

Figure 1. Distribution of transfused patients according to days in which transfusion implemented

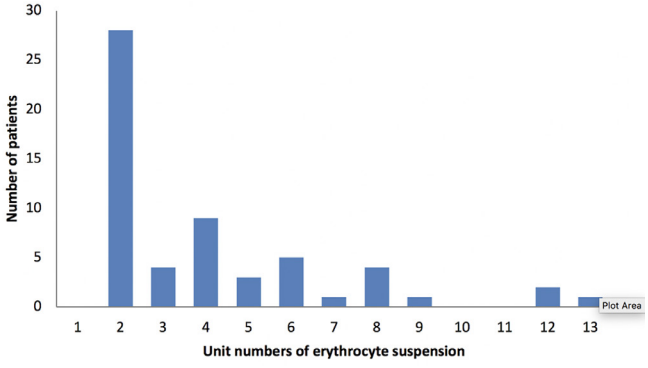

Figure 2. Unit numbers of transfused erythrocyte suspension

Threshold Hb level is one of the main determinants of transfusion decisions (12). The threshold Hb value for blood transfusion varies between hospitals from 7-12 g/dL (10,12-14). As a result of the multicenter ABC study involving 3534 patients, the transfusion threshold Hb value was found to be 8.4 g/dL (3). A similar threshold Hb value (8.6 g/dL) was found in the CRIT study (14). In the same study, many patients were able to tolerate Hb values of 7 g/dL and below. According to the Cochrane group (15), the threshold for transfusion should be 7-9 g/dL in patients without severe cardiac disease. In our study, the mean pre-transfusion Hb value was generally 7.5±1.3 g/dL (min: 4.7 g/dL, max: 10.5 g/dL), and in transfusions with anemia indication, it was 6.9±1.1 g/dL (min: 4.7 g/dL, max: 9.2 g/dL). Three patients with Hb values of 10 g/dL and over before transfusion were transfused for acute hemorrhage.

In a study by King et al. (16), a non-hemolytic febrile reaction was observed in 6.8% of patients who received ES transfusions without leukocyte reduction. Allergic reactions are common after transfusion of blood products, and the severity of these reactions varies clinically (17). During our study, complications developed after transfusion in 17.2% of the patients who underwent transfusion, with 9 febrile cases and 1 allergic reaction case.

In a meta-analysis (18), the daily blood intake for laboratory tests was 377 mL/day in the cardiothoracic ICU and 240 mL/day in the general surgery ICU. Corwin et al. (4) reported that approximately 60-70 mL of blood samples were obtained from 49% of the patients undergoing blood transfusion and there was no reason requiring transfusion in 29%, and that blood draw was one of the most common causes of transfusion in patients who were followed up in the ICU for a long time. Chant et al. (12) suggested that blood transfusion was correlated with the amount of blood transfused to critically ill patients

Table 5. Complications after transfusion

Complication after transfusion	Group E n (%)	Group K n (%)	Total n (%)
Febrile reaction	6 (10.3)	3 (5.2)	9 (15,5)
Allergic reaction	1 (1-7)	0 (0.0)	1 (1-7)
None	22 (37.9)	26 (44.8)	48 (82.7)
X^2=2.333, p=0.331			

Table 6. Exit status from intensive care unit by groups

Exit Status from ICU		Group E n (%)	Group K n (%)	Total n (%)
Discharged	Underwent	17 (%68.0)	8 (%32.0)	25 (%100)
Transfusion	No transfusion	58 (%49.2)	60 (%50.8)	118 (%100)
Death	Underwent	12 (%36.4)	21 (%63.6)	33 (%100)
Transfusion	No transfusion	32 (%60.4)	21 (%39.6)	53 (%100)
ICU: intensive care unit				

Table 7. Distribution of mean of diagnostic blood loss and fluid balance by groups

	Group E n [Mean+SS (mL)*]	Group K n [Mean±SS (mL)*]	p-value
DBL Total			
Underwent T ransfusion	29 (133.82±101.84)	29 (165.79±140.22)	p=0.323
No Transfusion	90 (134.80±124.06)	81 (137.86±127.32)	p=0.874
DBL, per ICU day			
Underwent Transfusion	29 (29.34±15.97)	29 (24.44±14.01)	p=0.220
No Transfusion	90 (21.84±8.86)	81 (22.85±11.28)	p=0.515
FB Total			
Underwent T ransfusion	29 (5019.31 ±7379.57)	29 (5286.38±7212.88)	p=0.890
No Transfusion	90 (5687.89±7281.94)	81 (5390.57±6583.11)	p=0.781
FB, per ICU day			
Underwent Transfusion	29 (531,96±472.92)	29 (694.82±991.64)	p=0.428
No Transfusion	90 (679.46±591.73)	81 (651.72±536.77)	p=0.750

*: The mean values of the transfused patients until the day of transfusion, DBL: Diagnostic blood loss, FB: Fluid balance, ICU: Intensive care unit, SD: standard deviation

with a hospitalization duration of approximately 50 days. In the studies performed, it was reported that most blood samples were taken in the ICU in the first 24 hours and that the number of samples decreased gradually in the following days (19,20). In the ABC study (3), the mean DBL was 41.1±39.7 mL/day in the ICU and there was a positive correlation between organ dysfunction and daily blood intake. A decrease in Hb concentration in ICU patients also contributes to increased blood loss and erythrocyte destruction during interventions such as central catheter placement, blood gas sampling, as well as DBL (21). In addition, erythrocyte production decreases due to the direct inhibitory effects of inflammatory cytokines on erythropoietin production in critical patients (22-24). In some studies, it was emphasized that in about one-third of transfusion events, no indication was identified; transfusions were usually performed due to daily DBL. It was concluded that blood transfusions should be conservative and transfusion guidelines should be followed (1,5,7). There are also studies reporting that factors, such as disease severity scores and mechanical ventilation therapy, have a positive correlation with high DBL (3,25). In our study, while the total DBL and per-intensive-care-day DBL patients who underwent transfusion (total DBL 149.76 mL; mean 26.89 mL/day) were found to be higher compared to non-transfused patients (total DBL 136.25 mL; mean 22.32 mL/day), a statistically significant difference was observed only in the per-ICU-day DBL for transfused patients. However, there was no statistically significant difference between the groups. The higher DBL means of transfused patients may be due to the higher APACHE II scores.

Conclusion

In conclusion, we found that most of the patients admitted to the ICU had Hb levels that could be accepted as anemic, according to the definition of the WHO. The decrease in mean Hb values continued over time in the following days. Of the patients who were not anemic at the time of admittance, 55.6% (50% in Group E, 63.2% in Group K) had developed anemia by the 3rd day of hospitalization. The mean Hb value before transfusion in our ICU was 7.5±1.3 g/dL (min: 4.7 g/dL, max: 10.5 g/dL). In transfusions done with anemia indication, the mean pre-transfusion Hb values were 6.9±1.1 g/dL (min: 4.7 g/dL, max: 9.2 g/dL). A mean of 37.0±15.7 mL of blood sample per person was taken for diagnostic purposes on the first day of hospitalization. Due to repeated blood samples (mean 147.2±117.1 mL) over time, Hb values decreased significantly, requiring blood transfusion. In patients undergoing transfusion, we determined that only a few cases had febrile reactions and one patient had allergic reactions as transfusion-related complications. The mortality rate was higher in transfused patients than in non-transfused patients; however, transfused patients had higher APACHE II scores, and mortality rates were higher in female patients undergoing transfusion.

Ethics

Ethics Committee Approval: In our study, permission to examine patient records was obtained from the management of Fırat University Hospital and approval was obtained from the Fırat University Non-Interventional Research Ethics Committee (decision no: 18, date: 05.10.2016).

Informed Consent: the data recorded in Enlil Hospital Information Management System of Fırat University Hospital were analyzed retrospectively.

Footnotes

Authorship Contributions

Concept: O.K.B., S.B., R.A., İ.D., Design: O.K.B., A.B., S.B., E.B., İ.D., Data Collection or Processing: O.K.B., S.B., E.B., R.A., Analysis or Interpretation: O.K.B., A.B., E.B., İ.D., Literature Search: O.K.B., S.B., R.A., Writing: O.K.B., A.B., S.B., İ.D.

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ORIGINAL RESEARCH / *ÖZGÜN ARAŞTIRMA*

Factors Affecting Mortality in COVID-19

COVID-19'da Mortaliteyi Etkileyen Faktörler

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ABSTRACT

Objective: Determining the factors affecting mortality may be pivotal in terms of improving survival in the coronavirus disease-2019 (COVID-19). The aim of this study was to determine the demographic, clinical and laboratory characteristics of COVID-19 patients and the factors affecting intensive care unit (ICU) mortality.

Materials and Methods: It was designed as a retrospective cohort study in which patients with a diagnosis of COVID-19 hospitalized in the ICU. The clinical and laboratory parameters were compared between cohorts with mortality and those with survival cohorts. Univariate and multivariate logistic regression analyses were performed for the effect profiles of the parameters on mortality.

Results: The mortality of 58.6% was similar for the three pandemic waves or selected time intervals (p=0.245). Presence of comorbid disease, age, COVID-19 related complications, admission, acute physiology and chronic health evaluation II (APACHE II) and sequential organ failure assessment (SOFA) scores were significantly higher in the mortality cohort (p<0.001). The factors influencing mortality according to the multivariate logistic regression model were hypertension, malignancy (solid and hematologic), neurological illness, age, APACHE-II and SOFA scores, and neutrophil to lymphocyte ratio.

Conclusion: The patients with these risk factors should be monitored with greater caution in terms of the timing and duration of ICU care.

Keywords: COVID-19, mortality, intensive care unit

ÖZ

Amaç: Mortaliteyi etkileyen faktörlerin belirlenmesi, koronavirüs hastalığı-2019'da (COVID-19) sağkalımın iyileştirilmesi açısından çok önemlidir. Bu çalışmanın amacı, COVID-19 hastalarının demografik, klinik ve laboratuvar özelliklerini ve yoğun bakım ünitesi (YBÜ) mortalitesini etkileyen faktörleri belirlemektir.

Gereç ve Yöntem: Bu çalışma YBÜ'deki COVID-19 tanılı hastaların dahil edildiği retrospektif bir kohort çalışması olarak tasarlandı. Klinik ve laboratuvar parametreleri mortalite ve sağkalım kohortları arasında karşılaştırıldı. Parametrelerin mortalite üzerindeki etki profilleri için tek değişkenli ve çok değişkenli lojistik regresyon analizleri yapıldı.

Bulgular: Mortalite %58,6 olup üç pandemi dalgası veya seçilen zaman aralıkları için benzerdi (p=0,245). Komorbid hastalık varlığı, yaş, COVID-19 ile ilişkili komplikasyonlar, başvurudaki akut fizyoloji ve kronik sağlık değerlendirmesi II (APACHE II) ve sıralı organ yetmezliği değerlendirmesi (SOFA) skorları mortalite kohortunda anlamlı olarak daha yüksekti (p<0,001). Çok değişkenli lojistik regresyon modeline göre mortaliteyi etkileyen faktörler hipertansiyon, malignite (solid ve hematolojik), nörolojik hastalık, yaş, APACHE-II ve SOFA skorları ve nötrofil/lenfosit oranıdır.

Sonuç: Bu risk faktörlerine sahip hastalar, YBÜ bakımının zamanlaması ve süresi açısından daha dikkatli izlenmelidir.

Anahtar Kelimeler: COVID-19, mortalite, yoğun bakım ünitesi

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Introduction

The coronavirus disease-2019 (COVID-19), recognized by the reports informing pneumonia cases of unknown etiology at the end of 2019 in Wuhan, China, has spread worldwide, causing millions of deaths (1). Although clarification on the clinical manifestation and pathophysiology of the disease has grown over the past three years, it continues to be an important public health problem. In Türkiye, where the first case of COVID-19 was detected on March 11, 2020, more than 17 million cases of COVID-19 and 101,419 deaths were reported to the World Health Organization (WHO) until October 8, 2023 (2). The crisis of the pandemic dissolved as the disease transformed into a mild respiratory tract infection with substantially less short-term mortality. However, long-term complications and survival are still a matter of debate.

The cumulative rise in the number of critically ill patients during this pandemic increased the demand for intensive care units (ICUs). For this reason, ICU capacity and the number of staff were rapidly expanded, while the quality of the ICU care was diminished in many countries. Similarly, in various periods of the pandemic in Türkiye, the capacity of many ICUs had to be increased. The rates of admission to the ICU and mortality differed greatly among hospitals due to various factors, such as ICU bed capacity, the time between the occurrence of ICU admission criteria and ICU admission, patient characteristics, staff availability, and applied treatment protocols. Determining the factors that may be associated with mortality is important for guiding and improving the ICU follow-up of patients with COVID-19. Several reports investigating the clinical course, mortality, and morbidity related to COVID-19 published from many countries and hospitals revealed that genetic substructure, race, lifestyle, treatment opportunity in hospitals, and staff availability influenced the survival of the patients (3-5). There is limited information focusing on the characteristics and prognosis of Turkish patients with COVID-19 admitted to the ICU, as well as the impact of the disparity of sequential pandemic waves on patient prognosis. The aim of this study was to determine the demographic, clinical, and laboratory characteristics of COVID-19 patients and the factors affecting ICU mortality in Akdeniz University Medical Faculty Hospital, Antalya, Türkiye throughout the pandemic.

Materials and Methods

The current study was carried out in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Akdeniz University Faculty of Medicine, Antalya, Türkiye (approval no: KAEK-335, date:11.05.2022). In addition, this study is retrospectively registered in the ClinicalTrials.gov clinical trials registry (no. NCT06043115).

It was designed as a retrospective cohort study in which patients diagnosed with COVID-19 who were hospitalized in the ICU between 11 March 2020 and 31 March 2022 were included. At the beginning of the pandemic, 8 beds were reserved for COVID-19 patients in our hospital, and while the pandemic progressed, the bed capacity was increased to 30 beds. The data of the patients were obtained from the patient file database and the observation results noted in the patient ICU charts. Patient informed consent was waived due to the retrospective study design. Researchers analyzed only anonymized data.

Patients ≥18 years old with a confirmed diagnosis of the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection, by a positive real-time reverse-transcription polymerase chain reaction test (RT-PCR) performed via nasopharyngeal swab or endotracheal aspirate were included in the present study. Criteria for admission to the ICU included oxygen saturation (SpO_2) below 90% in room air, ratio of partial oxygen pressure to fraction of inspired oxygen (PaO_2/FiO_2) less than 300, respiratory rate of more than 30 breaths per minute or lung infiltrates more than 50% of lung image on tomographic examination, and viral pneumonia with life-threatening conditions such as hemodynamic insufficiency or septic shock. Patients who had a negative SARS-CoV-2 RT-PCR test and whose chest computed tomography findings or symptoms were not compatible with COVID-19 were not included in the study.

Demographic and clinical data derived and analyzed included age, sex, body mass index (BMI), smoking history, comorbidities, vaccination status, acute physiology and chronic health evaluation II (APACHE II) and sequential organ failure assessment (SOFA) scores at admission, blood gas analysis, method of oxygen delivery, ICU and hospital length of stay and COVID-19 related complications. Laboratory findings recorded were blood cell count, fibrinogen, D-dimer, C-reactive protein (CRP), ferritin, creatinine, procalcitonin, and microbial culture results. Additional adjunctive support, including extracorporeal membrane oxygenation (ECMO), prone positioning, renal replacement therapy (RRT) were noted by date. Information on patient-specific therapies, such as administration of antivirals, convalescent plasma and plasmapheresis was also obtained.

Patients were managed following the institutional protocol (Figure 1). Acute respiratory distress syndrome (ARDS) was diagnosed and classified according to The Berlin Definition (6). A lung-protective ventilation strategy was used for all

Figure 1: Institutional COVID-19 protocol

COVID-19: coronavirus disease-19, SpO_2: oxygen saturation, PaO_2: arterial partial oxygen pressure, FiO_2: fraction of inspired oxygen, COPD: chronic obstructive pulmonary disease, ARDS: acute respiratory distress syndrome, AKI: acute kidney injury, DIC: disseminated intravascular coagulation, SARS-CoV-2: severe acute respiratory syndrome coronavirus-2, RT-PCR: real-time reverse-transcription polymerase chain reaction test, CRP: C-reactive protein

patients. Prone positioning was a part of management in all patients if not contraindicated. Patients with a PaO_2/FiO_2 ratio of less than 150 mmHg and a FiO_2 ≥60%, despite positive end-expiratory pressure optimization, were placed in the prone position, (12-16 hours). Patients with severe COVID-19 (as defined by the current WHO COVID-19 clinical management guideline) (7) requiring supplemental oxygen (including high-flow nasal oxygen) or non-invasive ventilation were placed in the awake prone position in 4-hour periods, with a total prone time of 12-16 hours daily. Sepsis-3 criteria were used for the diagnosis of sepsis/septic shock (8). Acute kidney injury (AKI) was defined according to Kidney Disease: Improving Global Outcomes (KDIGO) criteria (9). Co-existing infection was defined as clinical signs of systemic infection with a positive culture of a pathogen other than SARS-CoV-2 obtained from blood or body fluid specimens. Therapeutic dosing anticoagulation (low-molecular weight heparin) was applied to all patients who did not have risk or clinical manifestation of bleeding disorders during the ICU follow-up period. Patients received methylprednisolone at a dose of 1-2 mg/kg/day intravenously for an average of 5-10 days, as described by the current WHO COVID-19 clinical management guidelines (7).

The primary objective of the study was to determine the factors affecting mortality in COVID-19 patients in our ICU. The secondary outcome was to determine whether the pandemic waves had distinct characteristics in terms of factors affecting mortality. Based on the number of COVID-19 cases reported nationally to WHO during the pandemic in Türkiye, the period when the weekly incidence risk exceeds 30 per 100,000 people is defined as a wave (2,10). According to this definition, we examined the pandemic in three consecutive waves (first wave: 11 March 2020 to 31 January 2021, second wave: 1 February 2021 to 30 June 2021, third wave: 1 July 2021 to 31 March 2022).

Statistical Analysis

Statistical analysis was performed using SPSS version 18 statistical software (SPSS Inc., Chicago, Illinois, USA). A value of $p<0.05$ was considered statistically significant. The distribution of the continuous variables was tested using the Kolmogorov-Smirnov test. Frequencies and percentages were calculated for categorical variables. Baseline characteristics were presented as mean ± standard deviation (SD) and median with interquartile range (IQR) for continuous variables and as numbers with percentages for categorical variables. Pearson chi-square test or Fisher exact test were used in the analysis of categorical variables for outcome comparisons between survivors and non-survivors, and the Mann-Whitney U test was used for continuous variables. We used multivariate and univariate logistic regression models to identify risk factors of mortality. Variables that were found to be significant ($p<0.05$) during the univariate analysis were included in the multivariate regression model. The results are expressed as odds ratios (ORs) with 95% confidence intervals (95% CIs). The receiver operating characteristic (ROC) curves were used to determine the distinctive performance of laboratory parameters in predicting mortality in patients. The analysis results, which include the area under the curve (AUC) and cut-off value, were presented along with the sensitivity, specificity, and 95% CIs. The optimal cut-off values of the parameters were calculated with the Youden index.

Results

During the study period, a total of 985 patients with suspected COVID-19 were admitted to the ICU; the data of 619 patients who met the inclusion criteria were analyzed (Figure 2). All patients were discharged or died prior to data collection.

Among the study patients, 256 (41.4%) survived (survival cohort), and 363 (58.6%) died (mortality cohort). Clinical and demographic characteristics of patients are presented in Table 1. The mean age of the patients was 64.2±16.2 years and 69.7% were male. The majority of the study population was male, but the sex distribution was similar between the two mentioned cohorts, while the difference in terms of age

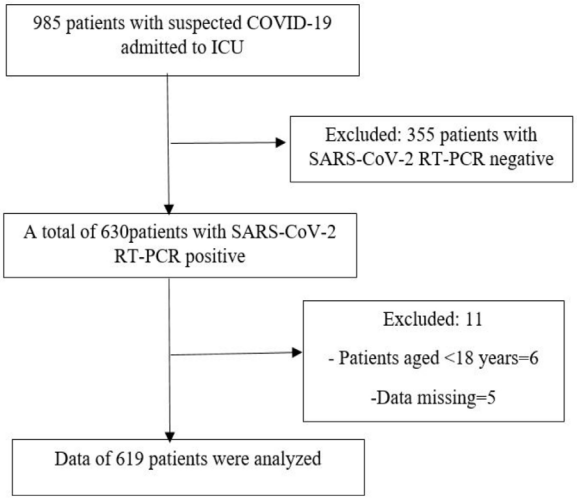

Figure 2: Study flow diagram

COVID-19: coronavirus disease-19, SARS-CoV-2: severe acute respiratory syndrome coronavirus-2, RT-PCR: real-time reverse-transcription polymerase chain reaction test

Table 1. Comparison of the quantitative and qualitative parameters regarding prognosis status (mortality)

Parameters	Overall	Mortality	Survival	p-value	Parameters	Overall	Mortality	Survival	p-value	Parameters	Overall	Mortality	Survival	p-value
Distribution*														
Age, (years) mean ± SD[a]	64.2±16.2	68.3±14.8	58.4±16.4	**<0.001**	**CAD[c]**	146	86 (23.7)	60 (23.4)	0.942	**Malignancy -solid[c]**	75	52 (14.3)	23 (9)	**0.045**
Apache-II score, IQR[b]	12 (0-45)	15 (2-45)	9 (0-38)	**<0.001**	**Obesity Groups(BMI)[c]**					**Malignancy-hematologic[c]**	53	38 (10.5)	15 (5.9)	**0.044**
SOFA score, IQR[b]	4 (0-17)	5 (0-17)	4 (0-13)	**<0.001**	<30	421	236 (65)	185 (72.3)		**IMV duration (day), IQR[b]**	2 (0-103)	6 (0-103)	0 (0-61)	**<0.001**
BMI(kg/m²), mean ± SD[a]	28.5±5.9	28.8±5.9	28.0±5.8	0.125	30-35	120	80 (22)	40 (15.6)	0.187	**Tracheotomy[d]**	8	3 (0.8)	5 (2.0)	0.285
Age groups[c]					35-40	51	32 (8.8)	19 (7.4)		**LOSH-ICU (day), IQR**	8 (1-225)	9 (1-225)	6 (1-64)	**<0.001**
18-55 years	155	62 (17.1)	93 (36.3)		>40	27	15 (4.1)	12 (4.7)		**LOSH (Total) (day), IQR**	16 (1-225)	14 (1-225)	18 (1-182)	**<0.001**
56-63 years	112	54 (14.9)	58 (22.7)	**<0.001**	**CKD[c]**	73	45 (12.4)	28 (10.9)	0.579	**ECMO support[c]**	13	12 (3.3)	1 (0.4)	**0.013**
64-68 years	79	49 (13.5)	30 (11.7)		**Transplantation[c]**	44	30 (8.3)	14 (5.5)	0.183	**Duration of ECMO (day)**	0 (0-64)	0 (0-64)	0 (0-19)	**0.013**
≥69 years	273	198 (54.5)	75 (29.3)		**Neurological illness[c]**	112	77 (21.2)	35 (31.3)	0.016	**Prone possition [c]**	291	126 (34.7)	93 (36.3)	0.679
Gender[c]					**Chronic lung disease[c]**	118	79 (21.8)	39 (15.2)	0.042	**Clinical complications**				
Female	187	110 (30.3)	77 (30.1)	0.952	**Thyroid disease**	44	25 (6.9)	19 (7.4)	0.799	Pneumothorax[c]	47	43 (11.8)	4(1.6)	**<0.001**
Male	432	253 (69.7)	179 (69.9)		**Pregnancy[d]**	10	3 (0.8)	7 (2.7)	0.102	Hemothorax[d]	6	3 (0.8)	3 (1.2)	0.695
Cigarette use[c]					**Reason of ICU admission[c]**					Pulmonary edema[d]	8	3 (0.8)	5 (2.0)	0.285
None	266	158 (43.7)	108 (42.2)	0.104	Respiratory Failure (RF)	420	240 (66.1)	180 (70.3)	**<0.001**	AKI[c]	281	221 (60.9)	60 (23.4)	**<0.001**
Smoker	107	53 (14.7)	54 (21.1)		Sepsis	17	10 (2.8)	7 (2.7)		Requirement of RRT[c]	60	50 (13.8)	10 (3.9)	**<0.001**
Exsmoker	244	150 (41.6)	94 (36.7)		Septic shock	15	8 (2.2)	7 (2.7)		DIC[c]	13	12 (3.3)	1 (0.4)	**0.013**
Vaccination status[c]					Myocardial infarction	12	7 (1.9)	5 (2)		Sepsis[c]	372	304 (83.7)	68 (26.6)	**<0.001**
None	473	299 (82.4)	174 (68)	**<0.001**	RF+septic shock	74	63 (17.4)	11 (4.3)		Septic shock[c]	346	296 (81.5)	50 (19.5)	**<0.001**
Sinovac	81	34 (9.4)	47 (18.4)		Other	81	35 (9.6)	46 (18)		Myocardial infarction[d]	10	7 (1.9)	3 (1.2)	0.535
Biontech	29	12 (3.3)	17 (6.6)		**Oxygen management[d]**					Cardiac arrhythmiad	162	126 (34.7)	36 (14.1)	**<0.001**
Sinovac+Biontech	36	18 (5)	18 (7)		Low flow †	472	252 (69.4)	220 (85.9)	**<0.001**	Thrombosis (DVT, emb.)[c]	24	20 (5.5)	4 (1.6)	**0.012**
Comorbidity[c]	552	339 (93.4)	213 (83.2)	**<0.001**	High flow	5	5 (1.4)	0 (0)		Bleeding[c]	63	49 (13.5)	14 (5.5)	**0.001**
Comorbidity count[c]					NIV	4	4 (1.1)	0 (0)		**PaO_2/ FiO_2(mmHg)** IQR[b]	100 (21-900)	90 (21-550)	125 (40-900)	**<0.001**
None	67	24 (6.6)	43 (16.8)	**<0.001**	IMV	138	102 (28.1)	36 (14.1)		**ARDS[c]**				
1	143	76 (20.9)	67 (26.2)		**IMV duration[c]**					None	52	18 (5.0)	34 (13.4)	**<0.001**
2	158	103 (28.4)	55 (21.5)		0-6 days	431	196 (54.0)	235 (91.8)	**<0.001**	Mild	66	28 (7.8)	38 (15.0)	
3 and over	251	160 (44.1)	91 (35.5)		7-9 days	64	59 (16.3)	5 (2.0)		Moderate	162	82 (22.7)	80 (31.5)	
HT[c]	281	182 (50.1)	99 (38.7)	0.005	10-17 days	71	64 (17.6)	7 (2.7)		Severe	335	233 (64.5)	102 (40.2)	
DM[c]	201	116 (32)	85 (33.2)	0.74	≥18 days	53	44 (12.1)	9 (3.5)						

*:Parameters showing a normal distribution pattern are expressed as mean, standard deviation (SD), and non-normally distributed parameters are expressed as median, as minimum, and as maximum (IQR). Categorical variables were expressed as frequency (N) and percentage (%). The general distribution of the parameter is summarized under the overall title.

†:Includes non-rebreather mask, venturi mask and nasal prongs, [a]:Indepentent-t test, [b]:Mann-Whitney U test, [c]:Pearson's chi-squared test, [d]:Fisher's exact test

HT: hypertension, DM: diabetes mellitus, CAD: coronary artery disease,CKD: chronic kidney disease, DVT: deep venous trombosis, BMI: body mass index, ICU: intensive care unit, IMV: invasive mechanic ventilation, NIV: non-invasive mechanic ventilation, LOSH: lenth of stay in hospital, ECMO: extracorporeal membrane oxygenation, AKI: acute kidney injury, RRT: renal replacement therapy, DIC: disseminated intravascular coagulation, APACHE-II: acute physiology and chronic health evaluation II, SOFA:sequential organ failure assessment, IQR: interquartile range, SD: standart deviation

was significant (p<0.001). The most common comorbidities were hypertension (45.4%), diabetes mellitus (32.4%) and obesity (BMI >30) (32%). One or more comorbidities were detected in 552 (89%) patients. In addition, the presence of comorbid disease was significantly higher in the mortality cohort (p<0.001). Hypertension, chronic lung disease, neurological illness, solid and hematologic organ malignancy were more frequent in patients who died (p=0.005, p=0.042, p=0.016, p=0.045 and p=0.044, respectively). A hundred and ten (17.8%) patients were vaccinated with either Sinovac (13.1%) or BioNTech (4.7%) and with both vaccines (5.8%). The proportion of unvaccinated patients was significantly lower in the survival group (p<0.001). The median APACHE II and SOFA scores were 12 (0-45) and 4 (0-17), respectively, being higher in the mortality cohort (p<0.001). Respiratory failure was the most common cause of ICU admission. 472 patients (76.3%) were on low flow oxygen, which includes non-rebreather mask, venturi mask, and nasal prongs; 138 (22.2%) were on invasive mechanical ventilation (IMV), and 9 (1.4%) were on non-invasive ventilation or high flow nasal oxygen. During the follow-up, 323 out of 472 patients who were receiving low-flow oxygen (<5L/min) required high-flow oxygen or non-invasive ventilation. Likewise, 264 out of 481 patients who did not need IMV on admission needed IMV during ICU follow-up. The median duration of IMV was 2 (0-103) days, which was longer in the mortality cohort (p<0.001). Successful weaning from IMV was achieved in only 7% of patients (29 of 402 patients). The median length of ICU and hospital stay was 8 (1-225) and 16 (1-225) days, respectively. Patients who died had longer ICU stay (9 (1-225) vs. 6 (1-64) days, p<0.001). A large number of patients had moderate to severe ARDS (80.2%) at ICU admission, and most of these patients took part in the mortality cohort (p<0.001). The prone position was applied to 47% of the patients with severe or moderate ARDS, a substantial proportion. Prone position could not be applied to 328 patients for various reasons, such as haemodynamic instability, anatomical difficulty, and increased intracranial pressure. Patients received veno-venous ECMO according to the "ECMO to Rescue Lung Injury in Severe ARDS (EOLIA) criteria" (11). ECMO support was applied in 13 patients, with survival achieved in one. The clinical complications such as sepsis/septic shock (p<0.001), AKI (p<0.001), pneumothorax (p<0.001), disseminated intravascular coagulation (p=0.013), cardiac arrhythmia (p<0.001), thrombosis (p=0.012), and bleeding (p=0.001) were observed more in the mortality cohort.

The neutrophil-to-lymphocyte (N/L), monocyte-to-lymphocyte (M/L), and neutrophil-to-platelet (N/Plt) ratios; eosinophil count; serum creatinine; procalcitonin; CRP; and ferritin values were significantly higher, whereas hemoglobin, platelet, and lymphocyte count values were significantly lower in the mortality cohort. Table 2 depicts the comparison of all laboratory parameters between cohorts. ROC analysis was performed to determine the predictive values and effect levels of parameters regarding mortality, and the results are presented in Table 3 and Figure 3. Univariate and multivariate logistic regression analysis were performed for the effect profiles of the parameters on mortality. Age, SOFA and APACHE II scores, duration of IMV, comorbidity status, hypertension, chronic lung disease, malignancy (solid and hematologic), neurological illness, hemoglobin, lymphocyte count, CRP, N/L, M/L, and N/plt ratio were associated with mortality in the univariate regression analysis. The multivariate model included the parameters that were found to be related to mortality in the univariate analysis. Another analysis was performed to check whether all parameters met the Box-Tidwell assumption. Duration of IMV and lymphocyte count parameters were excluded from the multivariate logistic regression model as they did not meet the assumptions. The factors influencing mortality according to the multivariate-logistic-regression model were hypertension, malignancy (solid and hematologic), neurological illness, age, APACHE-II and SOFA scores, and N/L ratio (Tables 4,5). The cut-off values affecting mortality were >65.5 years for age (sensitivity 64.5% and specificity 63.7%), >11.5 for APACHE-II score (sensitivity 68.4% and specificity 66.4%), >4.5 for SOFA score (sensitivity 61.8% and specificity 71.5%), and >18.45 for N/L ratio (sensitivity 51.5% and specificity 71.9%) (Table 3).

The percentage of COVID-19 patients per pandemic waves was 30% (n=186) in the 1st wave, 18.7% (n=116) in the 2nd wave, and 51.2% (n=317) in the 3rd wave in our study. Mortality was 62.6% in the 1st wave, 58.6% in the 2nd wave, and 56.1% in the 3rd wave period. Mortality was similar for the three pandemic waves (p=0.245). In all pandemic wave periods, mortality was higher over the age of 69. Obesity was found to be a risk factor for mortality in the patients admitted during the 3rd wave period. The number of comorbidities in the 1st and 3rd wave period, the rate of IMV in the 2nd wave period, and the number of unvaccinated patients in the 3rd wave period, were higher in the mortality cohort. Moreover, the rate of severe ARDS was found to be higher in the mortality cohort in all pandemic wave periods (Table 6).

Table 2. Comparison of quantitative and categorical variables according to prognosis (mortality) status				
	Prognosis			**p-value**
	Overall	**Mortality (n=363, %58.6)**	**Survival (n=256, %41.6)**	
Parameters	**Distribution**			
Mean ±SD[1]				
Hemoglobin (g/dL)	11.56±2.27	11.37±2.35	11.84±2.14	**0.011**
Median (IQR)[2]				
CRP (mg/L)	92 (0.89-433)	98.0 (1.74-433)	78.0 (0.89-397)	**0.002**
D-dimer (mg/L)	1.89 (0.13-155.0)	2.19 (0.13-155)	1.69 (0.17-42.4)	0.078
Ferritin (μg/L)	692.5 (3.84-100000)	771.0 (3.84-100000)	572.0 (14.68-85867)	**0.001**
Fibrinogen (mg/dL)	520 (33-4758)	520.0 (33-4319)	506.0 (136-4758)	0.384
Leukocyte count (10^3/μL)	10.46 (0.97-228.6)	10.8 (10.0-228.6)	10.2 (0.97-133.3)	0.728
Platelet count (10^3/μL)	224.5 (16-980)	208.0 (16.0-980.0)	243.5 (24.0-688.0)	**<0.001**
Neutrophil count (10^3/μL)	89.7 (2.6-98)	90.8 (2.6-98)	87.85 (18.2-97.5)	**<0.001**
Lymphocyte count (10^3/μL)	5.8 (0-95.3)	4.8 (0-95.3)	7.35 (1.0-83.0)	**<0.001**
Monocyte count (10^3/μL)	3.7 (0-67)	3.5 (0-67.0)	4.25 (0-26.0)	**<0.001**
Eosinophil count (10^3/μL)	0 (0-32.4)	0 (0-32.4)	0 (0-8.0)	**<0.001**
Neutrophil/Lymphocyte ratio	15.5 (0-271)	18.7 (0-271)	12.05 (0.79-106)	**<0.001**
Monocyte/Lymphocyte ratio	0.63 (0-18.2)	0.73 (0-18.2)	0.53 (0-5.03)	**<0.001**
Neutrophil /Platelet ratio	0.0004 (0.00003-0.0048)	0.0006±0.0006	0.0004±0.0003	**<0.001**
Creatinine (mg/dL)	0.9 (0.17-13.5)	1.04 (0.17-10.09)	0.8 (0.19-13.5)	**<0.001**
Procalcitonin (μg/L)	0.33 (0.01-100)	0.46 (0.01-100.0)	0.19 (0.01-100.0)	**<0.001**
n (%)				
Positive culture result (general)	340	264 (77.6)	76 (22.4)	**<0.001[3]**
Blood culture				
None or <2 positive result	590	342 (94.2)	248 (96.9)	0.177[3]
≥2 positive result(polymicrobial)	29	21 (5.8)	8 (3.1)	
Urine culture				
None or <2 positive result	584	336 (92.6)	248 (96.9)	**0.035[3]**
≥2 positive result(polymicrobial)	35	27 (7.4)	8 (3.1)	
Trachea/sputum culture				
None or <2 positive result	489	253 (69.7)	236 (92.2)	**<0.0013**
≥2 positive result(polymicrobial)	130	110 (30.3)	20 (7.8)	

1: Independent t-test, [2]: Mann-Whitney U test, [3]: Pearson chi-squared test or Fisher's exact test, *: Parameters showing a normal distribution pattern are expressed as mean ± SD, and non-normally distributed parameters are expressed as median, minimum and maximum (IQR). Categorical variables were expressed as frequency (N) and percentage (%). The general distrubition of the parameter is summerised under the overall title.
CRP: C-reactive protein, SD: standard deviation

Table 3. Predictive values and affect levels of parameters regarding mortality

Variable	AUC (95% CI)	p-value	Cut-off	Sensitivity (%)	Specificity (%)
Age (years)	0.679 (0.637-0.722)	**<0.001**	>65.5	64.5	63.7
BMI (kg/m²)	0.546 (0.500-0.592)	**0.049**	>28.35	50.4	60.2
Apache-II score	0.722 (0.682-0.763)	**<0.001**	>11.5	68.4	66.4
SOFA score	0.722 (0.681-0.762)	**<0.001**	>4.5	61.8	71.5
CRP (mg/L)	0.572 (0.526-0.619)	**0.002**	>51.5	73.3	39.2
Lymphocyte count ($10^3/\mu L$)	0.649 (0.606-0.692)	**<0.001**	<496.84	46.9	76.6
Procalcitonin (μg/L)	0.613 (0.562-0.664)	**<0.001**	>0.20	70.1	52.2
D-dimer (mg/L)	0.548 (0.495-0.601)	0.078	>2.49	47.7	62.1
Ferritin (μg/L)	0.595 (0.543-0.648)	**0.001**	>552	65.4	48.9
Fibrinogen (mg/dL)	0.525 (0.470-0.579)	0.384	>519.5	50.4	50.3
Neutrophil/Lymphocyte ratio	0.637 (0.593-0.681)	**<0.001**	>18.45	51.5	71.9
Monocyte/Lymphocyte ratio	0.604 (0.559-0.648)	**<0.001**	>0.605	58.8	58.6
Neutrophil /Platelet ratio	0.594 (0.549-0.639)	**<0.001**	>0.0004	56.1	56.3

CRP: C-reactive protein, BMI: body mass index, APACHE-II: acute physiology and chronic health evaluation II, SOFA: sequential organ failure assessment, AUC: area under curve, CI: confidence interval

Discussion

The results of our study revealed that hypertension, along with identified malignancies (solid and hematologic), neurological illness, age, APACHE-II and SOFA scores, and N/L ratio were independently associated with mortality. However, the sensitivity or specificity percentiles of the factors determined with ROC analysis revealed that none of the cut-off values was solely sufficient for predicting mortality in COVID-19 patients. Mortality was 58.6% and was similar across the three pandemic waves. However, incidence of comorbidity in the 1st and 3rd wave period, IMV in the 2nd wave period, and unvaccinated patients in the 3rd wave period were higher in the mortality cohort.

The reported mortality of critically ill COVID-19 patients varied between centers, with a wide range of 15% to 81.9% (12,13). Differences in the characteristics of the patient population included in the study (ethnicity, comorbidity status, etc.), ICU admission criteria, treatment approach, SARS-CoV-2 variants and ICU resources encountered may be the factors accounting for the disparity of the results. Studies reported from Türkiye indicate that the mortality varied between 36% and 66.5% in critically ill COVID-19 patients (14-19). Most of these reports reflected a short duration of the pandemic, which lasted over 3 years, and some studies included SARS-CoV-2 RT-PCR negative patients with suspicious clinical findings in their study cohort (14,16-18). We included 619 SARS-CoV-2 RT-PCR positive, critically ill patients in our study and mortality was 58.6%. Among the studies reported from Türkiye, our single-center study included a relatively high number of SARS-CoV-2 RT-PCR positive patients admitted to the ICU over a period of two years, covering three pandemic waves.

Multiple waves of pandemics and new variants have emerged since SARS-CoV-2 was first detected in 2019, which may alter patient characteristics and mortality. In a study reporting the data of 2493 COVID-19 ICU patients in Australia, the third wave revealed the highest hospital mortality of the three pandemic waves. Additionally, during the 3rd wave, the most frequent reason for ICU admission was COVID-19 related complications, and the average age of the patients was lower than in the first two waves (20). Sargın Altunok et al. (21) reported similar mortality in hospitalized COVID-19 patients with severe/critical illness for the first and second waves in Türkiye. However, the study covered only the first 8 months of the pandemic, and the basis on which the wave periods were defined was not specified. Apart from this study, there have been no data regarding the clinical course and mortality of ICU patients reflecting the three pandemic waves from Türkiye. In our study, we examined the pandemic process in three consecutive waves over a wide period of time, consisting of the whole pandemic episode. Although mortality was similar in all three wave periods, the number of COVID-19 patients admitted to ICU, and incidence of unvaccinated patients were higher in the third wave period compared with other waves. Additionally, mortality in patients aged 69 and over, was higher in the third wave than in former waves. Older age was pointed out to have an impact on mortality in COVID-19 patients due to increased incidence of comorbidities and systemic

complications (22,23). Univariate and multivariate logistic regression analysis revealed that a cut-off age greater than 65.5 years was significant for the prediction of mortality for COVID-19 in this study. This finding was in agreement with previous studies (24,25). Evidence of one or more comorbidities was identified as a risk factor for death among COVID-19 patients, but it is not completely clear which comorbidity affects mortality more (26,27). Some investigations reported that pre-existing chronic conditions, such as diabetes mellitus, chronic pulmonary disease, kidney disease, hypertension, obesity, cancers, and neurological diseases, were associated with ICU admission and death (28,29). The majority of the patients had one or more comorbidities in our study. The most common comorbidities were hypertension, diabetes mellitus, obesity and coronary artery disease. Additionally, having one or more comorbidities, such as hypertension, malignancy (both solid and hematological), and neurological disease, was determined as an independent risk factor for mortality in multivariate logistic regression analysis. The impact of obesity on mortality in COVID-19 patients is controversial. While

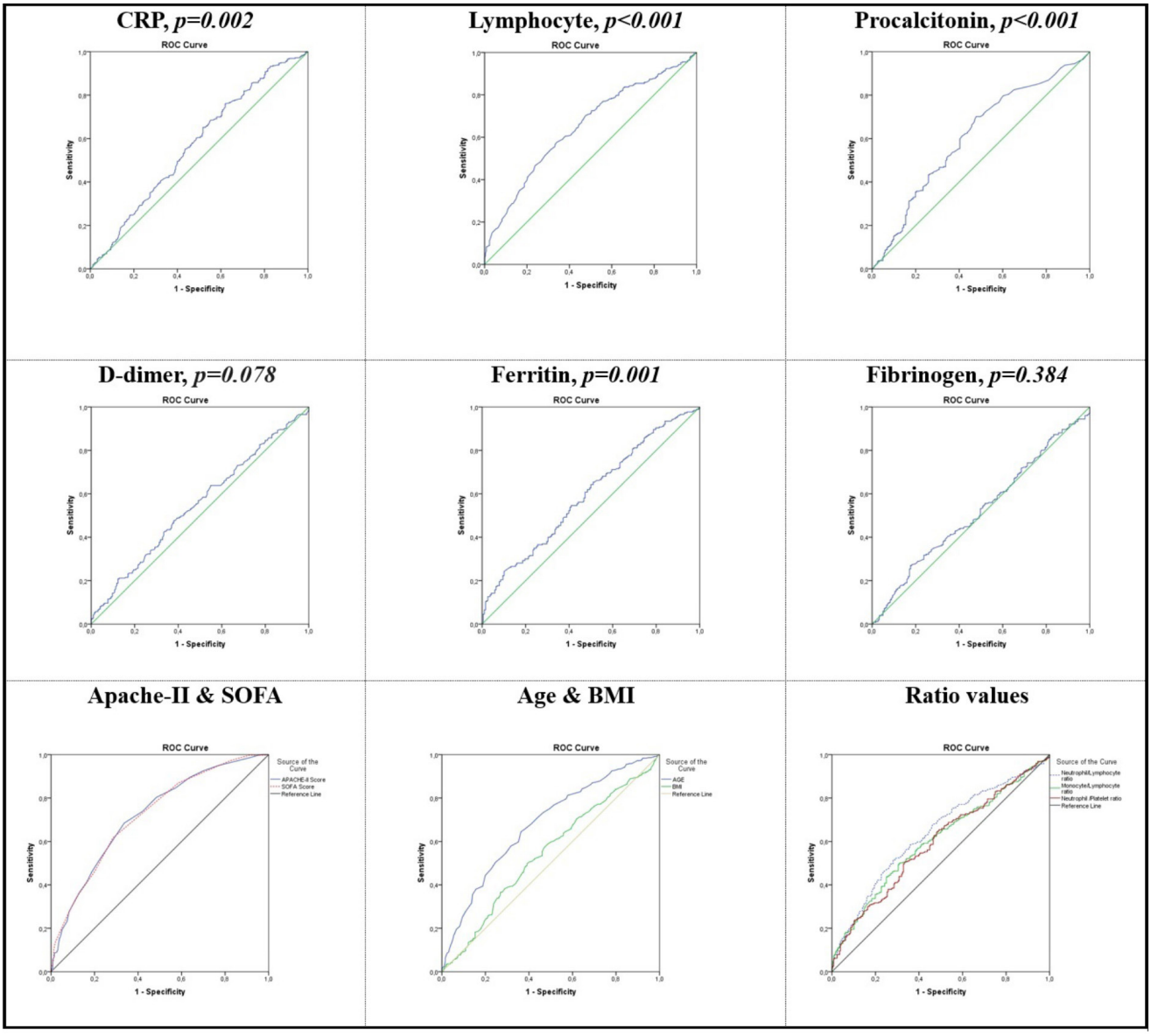

Figure 3. ROC analysis figures of Apache-II score, SOFA score, demographic variables, ratio values regarding laboratory results and laboratory parameters

APACHE-II: acute physiology and chronic health evaluation II, SOFA: sequential organ failure assessment, BMI: body mass index, CRP: C-reactive protein

various studies indicated that obesity was associated with mortality and that the need for hospitalization and mechanical ventilation were high in obese patients (30,31), others reported no risk in terms of mortality in obese patients (22,32). In our study, mortality was higher in patients with a BMI of 30 and above only in the third wave period. This finding may result from the characteristics of SARS-CoV-2 variants encountered or relatively high numbers of obese patients admitted to ICU during the third wave of the pandemic.

Table 4. Univariate and multivariate logistic regression analysis and effect profiles of parameters on mortality

Variables*	Univariate LR		Multivariate LR†	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Age (years)	1.041 (1.030-1.53)	**<0.001**	0.965 (0.953-0.978)	**<0.001**
BMI (kg/m^2)	1.022 (0.994-1.051)	0.126	-	
Duration IMV (days)*	0.829 (0.793-0.867)	**<0.001**	-	
Apache-II score	0.888 (0.863-0.913)	**<0.001**	0.954 (0.923-0.986)	**0.005**
SOFA score	0.708 (0.562-0.769)	**<0.001**	0.797 (0.72-0.883)	**<0.001**
Hemoglobin (g/dL)	1.097 (1.021-1.178)	**0.012**	0.989 (0.909-1.077)	0.807
Lymphocyte(10^3/μL)*	1.031 (1.011-1.050)	**0.002**	-	
CRP (mg/L)	0.997 (0.995-0.999)	**0.013**	1 (0.997-1.002)	0.766
Neutrophil/Lymphocyte ratio	0.974 (0.964-0.984)	**<0.001**	0.985 (0.972-0.998)	**0.021**
Monocyte/Lymphocyte ratio	0.547 (0.416-0.720)	**<0.001**	0.784 (0.562-1.093)	0.151
Neutrophil /Platelet ratio	0.339 (0.240-0.664)	**<0.001**	0.741 (0.435-1.261)	0.269
Procalcitonin (μg/L)	0.996 (0.983-1.008)	0.482	-	
D-dimer (mg/L)	0.981 (0.961-1.001)	0.060	-	
Ferritin (μg/L)	1.000 (0.999-1.000)	0.180	-	
Fibrinogen (mg/dL)	1.000 (0.999-1.001)	0.915	-	

*: The multivariate model includes the significant parameters identified in the univariate analyses. Analysis was conducted to determine whether all parameters met the Box-Tidwell assumption. IMV duration and lymphocyte parameters that did not meet the assumptions were excluded from the multivariate LR model. †: -2LL=659.133 Nagelkerke R2=0.323, Hosmer and Lemeshow test assumption has been met for the model.
BMI: body mass index, APACHE-II: acute physiology and chronic health evaluation II, SOFA: sequential organ failure assessment, CRP: C-reactive protein, IMV: invasive mechanic ventilation, CI: confidence interval

Table 5. Univariate and multivariate logistic regression analysis and effect profiles of parameters on mortality

Variables	Univariate LR		Multivariate LR	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Comorbidity	2.852 (1.682-4.835)	**<0.001**	1.738 (0.967-3.123)	0.065
HT	1.595 (1.152-2.207)	**0.005**	1.463 (1.024-2.089)	**0.036**
DM	1.058 (0.753-1.489)	0.744	-	
CAD	0.986 (0.676-1.438)	0.942	-	
CKD	0.868 (0.526-1.433)	0.580	-	
Thyroid disease	1.084 (0.584-2.013)	0.799	-	
Chronic lung disease	1.548 (1.015-2.361)	**0.043**	1.426 (0.921-2.208)	0.112
Malignancy-solid	1.694 (1.008-2.847)	**0.047**	1.855 (1.076-3.196)	**0.026**
Malignancy-hematologic	1.879 (1.010-3.494)	**0.046**	1.975 (1.043-3.738)	**0.037**
Neurological illness	1.700 (1.099-2.630)	**0.017**	1.59 (1.013-2.495)	**0.044**

The multivariate model includes the significant parameters identified in the univariate analyses, HT: hypertension DM: diabetes mellitus CAD: coronary artery disease CKD: chronic kidney disease, CI: confidence interval

Table 6. Analysis of demographic and clinical characteristics according to mortality during COVID periods						
Variables	**COVID periods**					
	1st wave		**2nd wave**		**3rd wave**	
	Mortalite, n (%)		**Mortalite, n (%)**		**Mortalite, n (%)**	
	Mortality (n=69)	**Survival (n=117)**	**Mortality (n=68)**	**Survival (n=48)**	**Mortality (n=178)**	**Survival (n=139)**
Age groups						
18-55 years	17 (24.6)	17 (14.5)	16 (33.3)	9 (13.2)	60 (43.2)	36 (20.2)
56-63 years	17 (24.6)	12 (10.3)	20 (41.7)	15 (22.1)	21 (15.1)	27 (15.2)
64-68 years	14 (20.3)	17 (14.5)	5 (10.4)	9 (13.2)	11 (7.9)	23 (12.9)
≥69 years	21 (30.4)	71 (60.7)	7 (14.6)	35 (51.5)	47 (33.8)	92 (51.7)
p-value	**0.001**		**<0.001**		**<0.001**	
Gender						
Female	17 (24.6)	35 (29.9)	13 (27.1)	20 (29.4)	47 (33.8)	55 (30.9)
Male	52 (75.4)	82 (70.1)	35 (72.9)	48 (70.6)	92 (66.2)	123 (69.1)
p-value	0.545		0.948		0.582	
Obesity						
No	52 (75.4)	81 (69.2)	33 (68.8)	43 (63.2)	100 (71.9)	112 (62.9)
Yes	17 (24.6)	36 (30.8)	15 (31.2)	25 (36.8)	39 (28.1)	66 (37.1)
p-value	0.467		0.677		0.090	
Obesity groups (BMI kg/m²)						
<30	52 (75.4)	81 (69.2)	33 (68.8)	43 (63.2)	100 (71.9)	112 (62.9)
30-35	13 (18.8)	21 (17.9)	10 (20.8)	15 (22.1)	17 (12.2)	44 (24.7)
35-40	3 (4.3)	11 (9.4)	3 (6.2)	5 (7.4)	13 (9.4)	16 (9)
>40	1 (1.4)	4 (3.4)	2 (4.2)	5 (7.4)	9 (6.5)	6 (3.4)
p-value	0.564		0.917		0.031	
Smoking						
None	28 (40.6)	56 (47.9)	20 (41.7)	29 (42.6)	60 (43.2)	73 (41)
Active smoker	16 (23.2)	15 (12.8)	9 (18.8)	15 (22.1)	29 (20.9)	23 (12.9)
Exsmoker	25 (36.2)	46 (39.3)	19 (39.6)	23 (33.8)	50 (36)	81 (45.5)
Unknown	0 (0)	0 (0)	0 (0)	1 (1.5)	0 (0)	1 (0.6)
p-value	0.181		0.902		0.103	
Vaccination status						
None	110 (94.0)	68 (98.6)	67 (98.5)	44 (91.6)	122 (68.5)	62 (44.7)
Sinovac	3 (2.6)	1 (1.4)	1 (1.5)	3 (6.3)	30 (16.9)	43 (30.9)
Biontec	1 (0.8)	0 (0)	-	-	11 (6.2)	17 (12.2)
Sinovac+Biontec	3 (2.6)	0 (0)	0 (0)	1 (2.1)	15 (8.4)	17 (12.2)
p-value	0.681		0.207		**<0.001**	
Comorbidity						
No	7 (6.0)	13 (18.8)	7 (10.3)	10 (20.8)	10 (5.6)	20 (14.4)
Yes	110 (94.0)	56 (81.2)	61 (89.7)	38 (79.2)	168 (94.4)	119 (85.6)
p-value	**0.006**		0.114		**0.008**	
Oxygen support						
No	24 (20.5)	4 (5.8)	22 (32.4)	1 (2.1)	54 (30.3)	7 (5.0)
Yes	93 (79.5)	65 (94.2)	46 (67.6)	47 (97.9)	124 (69.7)	132 (95.0)
p-value	**0.007**		**<0.001**		**<0.001**	
IMV						
No	6 (5.1)	54 (78.3)	5 (7.4)	37 (77.1)	11 (6.2)	104 (74.8)
Yes	111 (94.9)	15 (21.7)	63 (92.6)	11 (22.9)	167 (93.8)	35 (25.2)
p-value	**<0.001**		**<0.001**		**<0.001**	
ARDS						
None	7 (6.0)	9 (13.0)	2 (2.9)	6 (12.5)	9 (5.1)	19 (13.9)
Mild	74 (63.3)	27 (39.1)	47 (69.1)	21 (43.7)	112 (63.7)	54 (39.4)
Moderate	28 (23.9)	25 (36.2)	14 (20.6)	12 (25.0)	40 (22.7)	43 (31.4)
Severe	8 (6.8)	8 (11.7)	5 (7.4)	9 (18.8)	15 (8.5)	21 (15.3)
p-value	**0.014**		**0.017**		**<0.001**	

Pearson's chi-squared analysis or Fisher's exact tests, BMI: body mass index, IMV: invasive mechanic ventilation, ARDS: acute respiratory distress syndrome

Following the discovery and marketing of COVID-19 vaccines, CoronaVac (Sinovac, Beijing, China; starting January 14, 2021) and BNT162b2 (BioNTech, Mainz, Germany; starting April 2, 2021) were widely used in Türkiye. Studies have shown that all vaccine types were effective in protecting against COVID-19, reducing the severity and mortality of the disease (33,34). The present study found that 82.4% of our mortality cohort was unvaccinated. Moreover, the number of ICU admissions and unvaccinated patients was higher in the 3rd wave period. Some studies have reported that the BNT162b2 vaccine reduced mortality more than the CoronaVac vaccine (35,36). Most of the patients admitted to our ICU had been vaccinated with CoronaVac only (n=81), and a small number of patients had a history of BNT162b2 vaccination (n=29). Relatively less incidence of BNT162b2 vaccination in patients admitted to ICU may reflect the efficacy of the vaccine in terms of reducing morbidity or mortality of SARS-COV-2 however our data was not sufficient to make a strong assumption as most of the patients were unvaccinated of vaccinated with CoronaVac.

SOFA and APACHE II scores are the well-known scoring systems that have long been used to estimate disease severity of ICU patients. Previous studies revealed distinct scoring values to predict mortality in COVID-19 patients (37,38). Higher values of mean APACHE II and SOFA scores in non-survivors and significant differences in ICU admission scores between study cohorts (cut off values for predicting mortality; APACHE II >11.5 and SOFA >4.5) have proven the availability of these scoring systems in predicting ICU mortality. Beigmohammadi et al. (39) reported alike cut off values of APACHE II and SOFA scores for mortality in ICU Patients with COVID-19 as 13 and 5 respectively.

The laboratory parameters associated with mortality in logistic regression analysis were CRP, procalcitonin, ferritin, N/L, M/L, and N/Plt ratio. However, using multivariate logistic regression analysis, only the N/L ratio was independently associated with mortality. Elevated N/L ratio may be a key indicator of mortality in COVID-19 (40). The N/L ratio correlates with the systemic inflammatory status and the disease activity. Neutrophilia may result from inflammation or steroid use in COVID-19 patients (41). The ratio of neutrophils to lymphocytes increases due to the frequently coexisting lymphopenia. The threshold for the N/L ratio was 18 according to the Youden Index, with a 71.9% specificity in our study. There has been no consensus on the optimal cut-off value for N/L ratio to predict mortality, especially for COVID-19. Various studies have reported threshold values for N/L ratio ranging from 3.2 to 27 (41,42). Although the mean fibrinogen and D-dimer values obtained at ICU admission were higher than normal ranges, there was no difference between patients who survived and those who did not. We did not analyze the fibrinogen or D-dimer values during ICU follow-up. Insufficiency of these parameters in predicting mortality in our study may be related to the time of analysis which coincided with the onset of severe respiratory failure.

SARS-CoV-2 causes various serious clinical conditions. It has been reported that development of complications such as ARDS, arrhythmia, myocardial infarction, sepsis/septic shock, AKI, thrombosis, disseminated intravascular coagulation, pneumothorax due to COVID-19, led to an increase in mortality (31,43). The incidence of clinical complications such as severe and moderate ARDS, sepsis/septic shock, AKI, pneumothorax, disseminated intravascular coagulation, cardiac arrhythmia, thrombosis and bleeding was higher in the mortality cohort of our study. Most of the patients had moderate to severe ARDS (80.2%) at admission. The need for IMV was indicated in 64.9% of the patients during ICU admission or follow-up. Prone positioning was reported to improve oxygenation and decrease mortality in non-COVID-19 intubated patients with moderate to severe ARDS (44,45). During the COVID-19 outbreak, the practice of awake prone positioning has also become widespread in terms of improving oxygenation, and reducing the necessity of intubation. However, it was controversial whether prone positioning had a significant effect on mortality in patients who did not receive mechanical ventilation. In a recent systematic review and meta-analysis in COVID-19 patients (intubated and non-intubated), it was stated that the prone position improved oxygenation and reduced the risk of intubation in non-intubated patients, but did not reduce the risk of mortality (46). In this study, the majority of the patient population had moderate to severe ARDS. The prone position was applied to 47% of the patients (awake and intubated) and, in line with the literature, no effect on mortality was observed. ECMO is used as rescue treatment in patients with severe ARDS. Studies have reported that mortality related to ECMO was high and that ECMO had no effect on reducing mortality in COVID-19 patients (47,48). In our study, veno-venous ECMO was performed in 13 patients who had refractory hypoxemia and/or hypercapnia despite mechanical ventilation optimization according to EOLIA criteria (11) and only 1 patient survived.

During the COVID-19 outbreak, the first drugs reported to reduce mortality were corticosteroids (49). Methylprednisolone treatment was reported to be associated with decreased mortality in a single-center observational study from China at the beginning of the pandemic (50). A concurrent preprint

observational study suggested that low-dose (1-2 mg/kg/day) and short-term (5-7 days) methylprednisolone treatment provided faster recovery of clinical symptoms (51). Afterwards, the RECOVERY trial showed that dexamethasone (6 mg/day for 10 days) therapy reduced 28-day mortality in patients who received invasive or non-invasive oxygen therapy (49). Corticosteroids were administered to our patient population throughout all the pandemic waves, and methylprednisolone (1-2 mg/kg/day) was preferred. There are several reasons for preference for methylprednisolone. Firstly, methylprednisolone has high penetration in lung tissue with a longer residence time than dexamethasone, which may be more effective in lung injury (52). Secondly, previous studies have shown the effectiveness of methylprednisolone in treating SARS (53,54). Thirdly, the conventional corticosteroid dose for ARDS was 1-2 mg/kg/day methylprednisolone in past studies (55,56). Finally, reports from China at the beginning of the pandemic showed that methylprednisolone treatment could reduce mortality (50,51). Because methylprednisolone was used as standard therapy in our study population, its effect on mortality could not be evaluated. Corticosteroids are known to play a role in suppressing lung inflammation. However, corticosteroid treatment may also cause suppression of the immune system, which may lead to bacterial/fungal infection and delayed clearance of viruses (57). Co-infections were observed in 54.9% of patients, and polymicrobial infections were detected in 194 (31.4%) patients in our study. Moreover, the mortality was higher in patients with co-infection. Based on data in the literature, the percentage of COVID-19 patients with coinfection or secondary infection is highly variable (ranging between 7.2% and 66.3%) (58,59). The development of co-infection or secondary infection can be affected by many factors such as the nurse/patient ratio, the availability of isolated rooms for a single patient, and the immunosuppressive treatments applied. In our study, there was no control group, in terms of corticosteroids. For this reason, an analysis could not determine whether the corticosteroid increased the co-infection rate or not.

Study Limitations

Our study has several limitations. The first limitation is the absence of external validation due to its retrospective nature. Secondly, the SARS-CoV-2 variant type was missing in the majority of patients, and therefore, the effects of different variants on mortality were not analyzed.

Conclusion

In conclusion, ICU mortality was 58.6% in COVID-19 patients throughout all pandemic waves. Hypertension, malignancy (solid and hematologic), neurological illness, age, APACHE-II and SOFA scores, N/L ratio led to the prediction of mortality with good accuracy, and these parameters were independently associated with mortality. The findings of our study may guide clinicians in taking essential measures in patients who have risk factors associated with mortality.

Ethics

Ethics Committee Approval: This study protocol was reviewed and approved by the Institutional Ethics Committee of Akdeniz University Faculty of Medicine, Antalya, Türkiye (approval no: KAEK-335, date:11.05.2022). The trial was also retrospectively registered at ClinicalTrials.gov (identifier: NCT06043115).

Informed Consent: Patient informed consent was waived due to the retrospective study design. Researchers analyzed only anonymized data.

Footnotes

Author Contributions

Surgical and Medical practice: Ü.A.Y., H.T., Concept: B.Ö., M.Y., Design: M.C., M.Y., Data Collection and Process: B.Ö., H.T., Analysis or Interpretation: Ü.A.Y., A.S.K., Literature Search: B.Ö., A.S.K., Writing: Ü.A.Y., M.C., M.Y.

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

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Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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ORIGINAL RESEARCH / *ÖZGÜN ARAŞTIRMA*

Which Crystaloid Fluid Should be Used for the Treatment of Diabetic Ketoacidosis: A Retrospective Cohort Study

Diyabetik Ketoasidoz Tedavisinde Hangi Kristaloid Sıvı Kullanılmalıdır: Retrospektif Bir Kohort Çalışması

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ABSTRACT

Objective: We aimed to compare the advantages and disadvantages of saline (0.9% NACl) and balanced crystalloid (Isolene or Lactated ringer) solutions in patients with diabetic ketoacidosis (DKA).

Materials and Methods: The study was conducted retrospectively on 80 patients (saline=31, balanced=49) with moderate-to-severe DKA among 129 patients with DKA who were admitted to the adult intensive care unit (ICU) between 2013 and 2023.

Results: The DKA resolution times were similar in the saline and balance groups [12 h (6-16), 9 h (7-12), p=0539]. Statistically, the blood chlorine level after DKA resolution was higher in the saline group than in the balanced group (115±5.5, 110.8±4.4, p<0.001) and the anion gap value was lower [5.9 (3.9-10.6), 9.7 (7.0-12.0), p=0.005]. The blood potassium level after DKA solution was lower than normal in the saline group [3.4(3.1-3.6), 3.6(3.2-4.0), p=0.088]. There were no statistically significant differences between the saline and balanced groups in terms of 1-month mortality rates [0(0), 2(4.1), p=0.524], need for renal replacement therapy [1(3.2), 2(4.1), p=1.000], and ICU stay hours [46 (32-70), 44 (36-68), p=0.961].

Conclusion: The choice of saline or balanced crystalloid solution as the initial resuscitation fluid has no effect on DKA resolution time, mortality rate, or ICU length of stay. However, balanced electrolyte solutions have a lower side effect profile.

Keywords: Diabetic ketoacidosis, saline, balanced crystalloid, resolution, mortality

ÖZ

Amaç: Diyabetik ketoasidozis (DKA) hastalarında salin (%0,9 NACl) ve dengeli kristaloid (İsolen veya Laktatlı ringer) solüsyonlarının avantaj ve dezavantajlarının karşılaştırılması amaçlandı.

Gereç ve Yöntem: Çalışma 2013 ve 2023 yılları arasında erişkin yoğun bakıma ünitesi (YBÜ)'ne Kabul edilen 129 DKA'lı hasta içerisinden orta-şiddetli DKA mevcut olan 80 hasta (salin=31, dengeli=49) üzerinde retrospektif olarak gerçekleştirildi.

Bulgular: DKA resolusyon süresi salin ve dengeli grubunda benzerdi [12 s (6-16), 9 s (7-12), p=0,539]. İstatistiksel olarak salin grubunda dengeli grubuna göre DKA rezolüsyonu sonrası bakılan kan klor düzeyi daha yüksek (115±5,5, 110,8±4,4, p<0,001) ve anion gap değeri ise daha düşüktü [5.9 (3.9-10.6), 9.7 (7.0-12.0), p=0,005]. Salin grubunda DKA resolusyonu sonrası kan potasyum düzeyleri normalden düşüktü [3,4(3,1-3,6), 3,6(3,2-4,0), p=0,088]. Salin ve dengeli grubu arasında 1 aylık mortalite oranları [0(0), 2(4,1), p=0,524], renal replasman tedavi ihtiyacı [1(3,2), 2(4,1), p=1,000] ve YBÜ kalış saati [46 (32-70), 44 (36-68), p=0,961] açısından istatistiksel olarak anlamlı bir fark yoktu.

Sonuç: İlk resolusyon sıvısı olarak salin veya dengeli kristaloid solüsyonun seçiminin DKA resolusyon süresi, mortalite oranı ve YBÜ kalış süresi üzerine bir etkisi yoktur. Bununla birlikte dengeli elektrolit solusyonları daha az yan etki profiline sahiptir.

Anahtar Kelimeler: Diyabetik ketoasidozis, salin, dengeli elektrolit, rezolüsyon, mortalite

Introduction

Diabetic ketosis (DKA) is a metabolic disorder characterized by hyperglycemia, ketosis, and severe dehydration (due to osmotic diuresis) caused by the absence or deficiency of insulin (1). The frequency of diabetic ketoacidosis varies between 2.8% and 6.3% and is increasing gradually (2,3). Although DKA can be observed in all age groups, 80% of individuals are over the age of 18 (3). Although DKA is mostly

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observed in patients with type 1 diabetes (2/3), it can also be observed in patients with type 2 diabetes (4). Although infection is the most common cause of DKA triggering in patients with diabetes mellitus, it can also occur due to events such as not using insulin therapy, trauma, myocardial infarction, cerebrovascular accident, and pancreatitis (3,5).

Due to the presence of deep metabolic acidosis, DKA treatment is usually performed in intensive care units (ICU) (6). The mainstay of DKA treatment is intravenous (IV) replacement for existing insulin deficiency and fluid loss. Crystalloids are considered superior to colloids in IV fluid replacement (7-9). However, the debate continues as to whether saline (0.9% NaCl) or balanced crystalloid solutions are superior (9-10).

The aim of this study was to investigate the clinical advantages and disadvantages of saline and balanced crystalloid solutions as initial resuscitation fluids in patients admitted to the ICU for moderate to severe DKA.

Materials and Methods

Design and Study Population

Patients admitted to the adult ICU for DKA between 2013 and 2023 were retrospectively evaluated. Among the 129 patients admitted to the ICU, those with mild DKA, recurrent ICU hospitalizations due to DKA, those who had mixed fluid replacement (>1 L intake from the other fluid group), those whose blood gas and electrolyte (Na, K, Cl) were not checked every 2-4 hours, and those who were not given crystalloid solutions. Patients with end-stage renal failure, multiple organ failure (MOF), pregnant women, and patients aged 18 years and >90 years were excluded from the study (Figure 1).

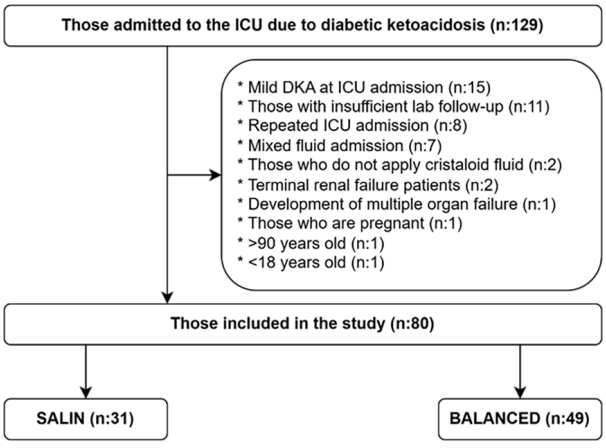

Figure 1: The study flowcharts

These patients were divided into 2 groups, who received saline (0.9% NaCl; pH 5.5) or balanced crystalloid solutions [(Izolen; pH 7.4, Na 140-141 mEq/L, Cl 98-103 mEq/L, K 5-10 mEq/L, Acetate 27-47 mEq/L and others) or (Lactated Ringer; pH 6.5, Na 130 mEq/L, Cl 98-109 mEq/L, K 4-5 mEq/L, Lactate 27-28 mEq/L and others)] as the first resuscitation fluid during ICU follow-up until DKA resolution.

The study was conducted in full accordance with local Good Clinical Practice Guidelines and current legislation. Ethical approval was obtained from the University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital Clinical Research Ethics Committee (decision number: 2023/10, date:22.05.2023).

Protocol

DKA was diagnosed if the following 3 criteria were met:

1.Having a blood glucose level of >250 mg/dL on admission to the hospital or having diabetes mellitus,

2.Having ≥ 2+ ketonuria in urine,

3.Serum HCO3 concentration <15 mmol/L and/or venous Ph<7.3.

Patients with DKA were categorized as mild (serum bicarbonate, 15-18 mEq/L; AG >10; plasma glucose concentration, >250 mg/dL), moderate (serum bicarbonate, 10-15 mEq/L; AG >12; plasma glucose concentration, >250 mg/dL), or severe (serum bicarbonate, <10 mEq/L; AG >12; plasma glucose concentration, >250 mg/dL). AG (Anion GAP) was calculated as follows;

$$AG = (Na+K)-(Cl+HCO_3)$$

After diagnosis of DKA, IV insulin and fluid loading was performed in the first hour before admission to the ICU in all patients. On admission to the ICU, empirical antibiotic therapy was initiated for patients whose clinical and laboratory parameters were compatible with infection (WBC>20,000 X109/L, C-reactive protein (CRP) >5 mg/L or Procalcitonin>0.5 ng/mL).

The follow-up and treatment algorithm of patients diagnosed with DKA admitted to the ICU is summarized below (Figure 2).

Data Collection

Study data were obtained retrospectively from the ImdSoft-Metavision/QlinICU Clinical Decision Support Software' system. Age, sex, body mass index (BMI), comorbidities, white blood cell (WBC), hemoglobin, platelets, blood gas (pH, PCO_2, HCO_3, Base excess, Lactate), glucose,

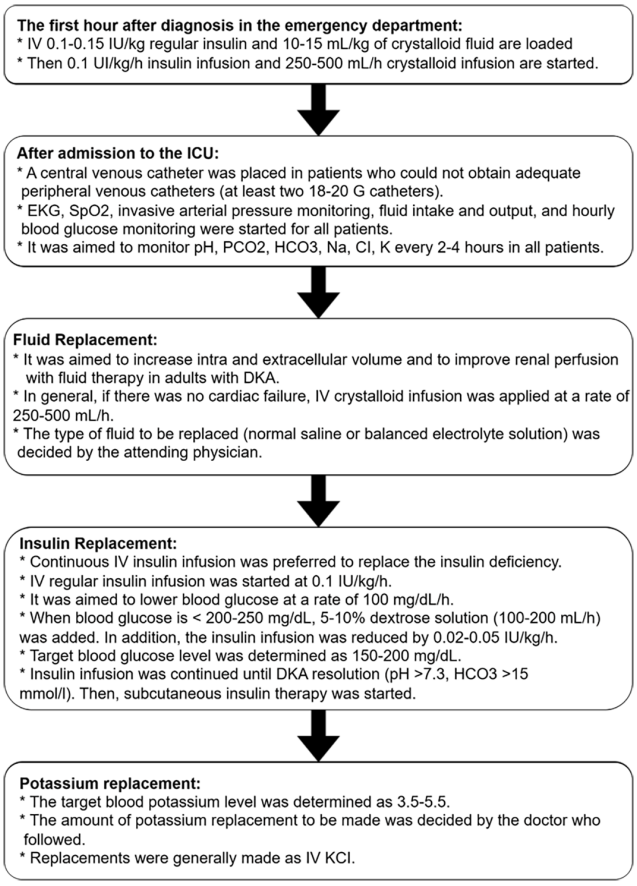

Figure 2: Diabetic ketoacidosis follow-up and treatment algorithm

urea, creatinine, total bilirubin, Na, Cl, K, CRP, and procalcitonin data were collected for all patients at ICU admission. Again, using these data, CCI (Charlson Comorbidity Index), SOFA (Sequential Organ Failure Assessment), and AKI (Acute Kidney Injury) scores were calculated (Supplementary Document). The DKA resolution time (pH≥7.3 and HCO_3 ≥15) was then determined in all patients. Data on total insulin use, crystalloid solutions (normal saline, balanced crystalloid), 5-10% dextrose solution, and amount of KCl replacement used during this period were collected. Finally, data on total LOS (length of stay) in the ICU, the need for RRT (Renal replacement therapy) and in-hospital 1-month mortality were collected for all patients.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, NY, USA). The Shapiro-Wilk test was used to determine whether the data were normally distributed. Categorical variables are given as frequency (n) and percentage (%), numerical variables mean ± standard deviation or median with interquartile range (IQR) Independent-Samples t-test was used to compare quantitative variables with normal distribution between the two groups. Mann-Whitney U test was used for comparisons between two groups of quantitative variables that did not show normal distribution. Pearson's chi-square, continuity correction, or Fisher's exact test were used to compare categorical variables. Statistical significance was set as $p<0.05$.

Results

A total of 80 patients (saline=31, balanced=49) were included in the study. The majority of ICU admissions in both the saline and balanced groups were from the emergency department [n=29(93.5%), n=44(89.8%), p=0.700, respectively,]. Other patients were admitted from external centers and received post-operative or normal in-patient services. There was no statistically significant difference between the saline and balanced crystalloid groups in terms of length of stay (hours) in the emergency department [3.5 (2.0-5.0), 4.0 (2.6-5.8), p>0.077, respectively] (Table 1).

There were no statistically significant differences between the saline and balanced crystalloid groups in terms of age, gender, and BMI (p=0.335, p=0.940, p=0.090, respectively,). There were no statistically significant differences between the saline and balanced crystalloid groups in terms of the CCI and SOFA mortality score (p=0.568, p=0.381, respectively). DKA was most common in type 1 diabetes in both the saline and balanced crystalloid groups 22 (71.0), 38 (77.6), p=0.691, respectively]. The most common cause of DKA in both the saline and balance crystalloid groups was infection [22(71.0), 33(67.3), p=0.926, respectively]. There was no statistically significant difference between the saline and balanced crystalloid groups in terms of DKA severity (p=0.093). There was no statistically significant difference between the saline and balanced crystalloid groups in terms of the rate of development of AKI due to DKA 14 (45.2%), 20 (40.7%), p=0.637, respectively]. There were no statistically significant differences between the saline and balanced crystalloid groups in terms of ICU admission laboratory parameters (p>0.05) (Table 1).

Although DKA resolution time was higher in the saline group, there was no statistical difference with balanced crystalloid solution 12 (6-16), 9 (7-12), p=0.539, respectively]. The amounts of total insulin, fluids and 5-10% dextrose solutions used in IV therapy were similar in both groups (p=0.921, p=0.693, p=0.932, respectively). There was no statistically significant difference between the saline and

balanced crystalloid groups in terms of the number of patients given KCl and amount of KCl replacement (p=1.000, p=0.331, respectively) (Table 2).

There was statistically significant difference between saline group and balanced crystalloid group in terms of the blood chlorine level after DKA resolution (115±5.5, 110.8±4.4, p<0.001, respectively). There was statistically significant difference between saline group and balanced crystalloid group in terms of the anion gap value after DKA resolution [5.9 (3.9-10.6), 9.7 (7.0-12.0), p=0.005, respectively]. There was no statistically significant difference between the saline and balanced crystalloid groups in terms of blood potassium levels

Table 1: Demographic and clinical characteristics

	Saline (n=31)	Balanced (n=49)	p-value
ICU admission type (ED), n(%)	29 (93.5)	44(89.8)	0.700
ED duration (h), median (IQR)	3.5 (2.0-5.0)	4 (2.6-5.8)	0.077
Age, median (IQR)	35 (21-53)	27 (20-48)	0.335
Female, n(%)	16 (51.6)	27 (55.1)	0.940
Body mass index, mean ± SD	23.0±3.1	24.6±4.6	0.090
CCI score, median (IQR)	2 (1-3)	1 (1-2)	0.568
SOFA score, median (IQR)	1 (0-2)	1 (0-2)	0.381
Type-1 diabetes mellitus, n(%)	22 (71.0)	38 (77.6)	0.691
Cause of DKA (Infection), n(%)	22 (71.0)	33 (67.3)	0.926
Severe DKA, n(%)	17 (54.8)	37 (75.5)	0.093
Admission Lab, median (IQR)			
Ph, median (IQR)	7.15 (7.03-7.25)	7.13 (7.07-7.20)	0.607
PCO_2 (mmHg), median (IQR)	18 (10-22)	16.9 (11.7-21.4)	0.953
HCO_3 (mmol/L), median (IQR)	9 (6.5-11.2)	8.2 (7.1-9.8)	0.499
Base excess (mmol/L), mean ± SD	-21.6±5.6	-22.7±4.4	0.336
NA (mmol/L), median (IQR)	134 (132-137)	134 (131-137)	0.886
K (mmol/L), median (IQR)	4.6 (4.2-5.3)	4.5 (3.9-5.0)	0.254
Cl (mmol/L), mean ± SD	102.5±8.4	102.0±6.7	0.757
Anion gap, median (IQR)	24.8 (21.6-30.1)	26.8 (23.0-30.3)	0.412
Lactate (mmol/L), median (IQR)	1.6 (1.2-2.8)	1.4 (1.2-2.3)	0.583
Glukoz (mg/dL), median (IQR)	360 (268-466)	281 (240-351)	0.082
Urea (mg/dL), median (IQR)	38 (31-54)	30.3 (19.3-50.0)	0.091
Creatınıne (mg/dL), median (IQR)	0.95 (0.79-1.18)	0.89 (0.73-1.13)	0.716
Total Bilirubin (mg/dL), median (IQR)	0.32 (0.2-0.5)	0.25 (0.18-0.44)	0.534
CRP(mg/L), median (IQR)	10.5 (1.95-43.75)	13.5 (5.2-56.0)	0.474
Procalcitonin (ng/ml), median (IQR)	0.5 (0.2-2.5)	0.75 (0.27-3.74)	0.537
Hemoglobin (g/dL), median (IQR)	12.4 (10.9-13.3)	12.7 (11.0-13.7)	0.448
Platelet ($X10^9$/L), mean ± SD	300±133	297±120	0.904
WBC ($X10^9$/L), mean ± SD	17.6±5.8	18±7.9	0.824
AKI, n(%)	14 (45.2)	20 (40.7)	0.637
AKI-1	12 (38.7)	18 (36.7)	
AKI-2	2 (6.5)	2 (2.0)	
AKI-3	0 (0)	1 (2.0)	

ED: emergency department, CCI: Charlson comorbidity index, SOFA: sequential organ failure assessment, DKA: diabetic ketoacidosis, CRP: C-reactive protein, WBC: white blood cells, AKI: acute kidney injury

after DKA resolution [3.4 (3.1-3.6), 3.6 (3.2-4.0), p=0.088, respectively]. There were no statistically significant differences between the saline and balanced crystalloid groups in terms of blood pH, PCO_2, HCO_3, base excess, and sodium levels after DKA resolution (p>0.05) (Table 2).

There was no statistically significant difference between the saline and balanced groups as the first resuscitation fluid in terms of mortality, LOS in the ICU, and RRT (p=0.524, p=0.961 p=1.000, respectively) (Table 2).

The range of increases in blood Cl levels and decreases in the amount of anion gap were more pronounced in the saline group than in the balanced group. On the other hand, the ranges of improvement in blood PCO_2, HCO_3, and base excess values were lower in the saline group. The range of changes in other laboratory parameters (pH, Na, K) was similar between the groups (Figure 3).

Table 2: Treatment outcomes of patients receiving saline and balanced crystalloid solutions

	Saline (n=31)	**Balanced (n=49)**	**p-value**
DKA resolution time(Hour), median (IQR)	12 (6-16)	9 (7-12)	0.539
IV replacements therapies, median (IQR)			
Total insulin, IU	40 (26-64)	42 (28-56)	0.921
Total dextrose (5-10%), L	1 (1-2)	1 (1-2)	0.932
Total fluid, L	4 (2.0-7.0)	3.5 (3.0-5.3)	0.693
KCl, mEq	40 (40-90)	50 (50-100)	0.331
Number of patients given KCl, n(%)	4 (12.9)	7 (14.3)	1.000
After resolution lab			
Ph, median (IQR)	7.35 (7.33-7.38)	7.34 (7.31-7.38)	0.232
PCO_2 (mmHg), median (IQR)	27.8 (25.5-31.0)	28.3 (26.0-33.5)	0.390
HCO_3 (mmol/L), median (IQR)	17.0 (16-18)	17.3 (16-19)	0.317
Base excess (mmol/L), mean ± SD	-9.22±2.2	-8.58±2.8	0.283
Anion gap, median (IQR)	5.9 (3.9-10.6)	9.7 (7.0-12.0)	0.005*
Na (mmol/L), median (IQR)	135 (132-139)	134 (131-137)	0.454
K (mmol/L), median (IQR)	3.4 (3.1-3.6)	3.6 (3.2-4.0)	0.088
Cl (mmol/L), mean ± SD	115.0±5.506	110.8±4.4	<0.001*
RRT need, n(%)	1 (3.2)	2 (4.1)	1.000
LOS in ICU (Hour), median (IQR)	46 (32-70)	44 (36-68)	0.961
Mortality, n(%)	0 (0)	2 (4.1)	0.524

*p<0.05, DKA: diabetic ketoacidosis, IV: intravenous, Lab: laboratory, RRT: renal replacement therapy, LOS: length of stay, ICU: intensive care unit

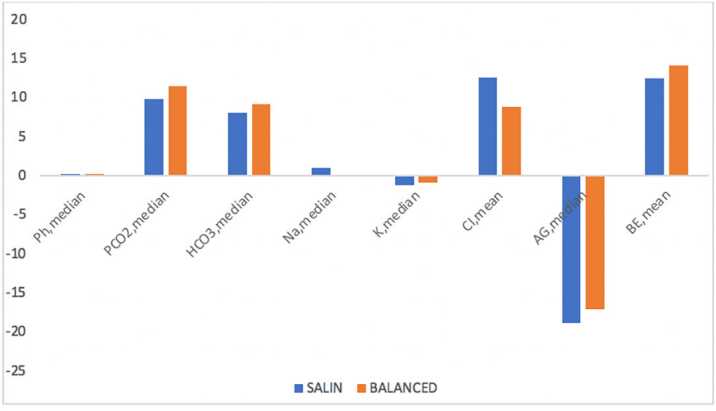

Figure 3: Comparison of the range of change in laboratory values among patients treated with saline and balanced fluid

Discussion

We conducted this study to determine the advantages and disadvantages of saline and balanced crystalloid solutions as the initial resuscitation fluid in patients developing DKA. We did not detect any differences between saline and balanced crystalloid solutions in terms of DKA resolution time, 1-month mortality rate, and ICU length of stay. At the same time, the choice of saline or balanced electrolyte solution did not change the total amount of insulin used. In two prospective randomized controlled trials in 2011 and 2012 comparing the use of saline and balanced crystalloid solutions in the treatment of DKA, no superiority of either crystalloid solution was found (10-12). In a retrospective study of 85 patients in the emergency department in 2018, no difference was found in the time to resolution of DKA with the choice of crystalloid solution (13). Subsequently, in a post hoc secondary subgroup analysis of 172 patients that included 2 randomized controlled trials on emergency room and ICU patients in 2020, balanced crystalloid solution therapy was associated with faster resolution of DKA (14). Finally, in a meta-analysis of 8 randomized controlled trials involving a total of 482 patients comparing saline and balanced crystalloid solutions in 2022, it was found that the use of saline caused a slight increase in the risk of DKA resolution time and hospital stay compared with the use of balanced crystalloid solutions (1). In our study, the DKA resolution time was longer in patients receiving saline therapy, but this difference was not statistically significant. When these studies are evaluated together, no evidence that saline solutions are superior to balanced crystalloid solutions has been presented. On the contrary, a significant number of these studies showed that the use of saline can lead to hyperchloremic acidosis and prolonged DKA resolution time.

In our study, when DKA resolution was achieved, an increase in the blood chlorine level was observed in both groups. However, the increase in the blood Cl level range was much more pronounced in the saline group than in the balanced group. At the same time, the range of decrease in the anion gap content was much more pronounced in the saline replacement group. On the other hand, the range of recovery of blood PCO_2, HCO_3, and base deficit was lower in the saline group. Studies have shown that hyperchloremic acidosis, low anion gap, and renal HCO_3 loss may develop due to rapid and high-volume IV infusion of high-volume acidic saline solution (1,15). Therefore, although DKA regresses with insulin replacement in the saline replacement group, metabolic acidosis due to hyperchloremia may develop. In addition, although the duration of DKA resolution was longer in the saline group, the amount of HCO_3 increase and the range of base excess recovery amount may have been lower. It was observed that hyperchloremia developed in the balanced group but not in the saline group. This may be due to the use of saline solution to replace insulin, potassium, and other IV drugs.

The number and amount of patients who received potassium replacement were similar between the groups. The potassium level measured after DKA resolution was lower in the saline group but within the lower limits in both groups. When DKA develops due to insulin deficiency, potassium levels tend to decrease intracellularly and increase extracellularly (3). Later, with the initiation of insulin therapy, hypokalemia may develop due to the shift of potassium into the cell (4). Therefore, potassium must be replaced. The low potassium levels measured after resolution of DKA in our patient population, especially in the saline group, suggest that potassium replacement was inadequate.

In both patient groups, the proportion of patients who developed AKI upon admission to the hospital was similar. AKI may develop due to renal perfusion impairment, as well as deterioration in all tissues due to severe volume deficit due to osmotic diuresis. High-volume replacement is needed for the treatment of AKI (16). However, there are concerns that renal vasoconstriction and decreased glomerular filtration rate may occur due to hyperchloremia associated with saline infusion (15,17). In our study, although the AKI rates were high in both groups upon admission, the need for RRT was similarly low. In a study evaluating 15,802 critically ill patients hospitalized in multicentric ICU in 2018, no statistically significant difference was found between the use of saline or balanced crystalloid solutions, the need for new RRT, and the rate of development of permanent renal dysfunction (18).

Both patient groups consisted mostly of young patients who did not have any additional comorbidities other than diabetes mellitus. Therefore, CCI scores were low in both groups. The SOFA scores used to predict mortality were low in both patient groups. The low SOFA score was consistent with the low overall mortality rate. Although SOFA scores were low, most patients in both patient groups had severe DKA.

Patients with type 1 diabetes mellitus constituted the majority of the patients. Although DKA can be observed in type 2 diabetes mellitus due to insulin resistance, it is most likely to occur in type 1 diabetes mellitus, which mainly develops due to insulin insufficiency (4,6). In our study, as in the literature, the most common cause of DKA in both patient groups was

infection (3,5). Correspondingly, both patient groups had higher WBC count, CRP level, and procalcitonin level.

The current study has several limitations: Firstly, the study was retrospective. Due to the retrospective nature of the study, some patients who were not followed up frequently and in accordance with the study protocol were excluded from the study. However, considering the original studies on DKA, it was important to ensure that a significant number of patients with DKA were examined. Second, the study was single-centered. Third, although the amount of intravenous insulin and crystalloid loading administered within the first hour after DKA diagnosis is standardized, the lack of recorded data on the exact amount of treatments administered during the period until ICU admission is an important limitation. The mean length of stay in the emergency room was similar between the groups. Although the mean length of stay in the emergency department before ICU admission was similar in both groups, we did not include the treatment administered in the emergency department in our evaluation of both patient groups. We planned to compare the treatment after ICU admission.

Conclusion

The saline was superior to the balanced crystalloid solution as the initial resuscitation fluid in patients with DKA. On the contrary, rapid and high-volume saline solution use can lead to the development of hyperchloremic metabolic acidosis. Greater attention should be paid to adequate potassium replacement regardless of whether a saline solution or a balanced solution is used. In addition, potassium replacement with potassium phosphate is more appropriate for preventing hyperchloremia.

However, no effect of selecting saline or balanced crystalloid solution on mortality and ICU stay was observed. The advantages of saline solutions, such as their cost and ease of supply, may make them a reason for centers with limited resources. However, for DKA treatment, we recommend the use of balanced crystalloid solutions as the first choice because they have a lower side effect profile.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital Clinical Research Ethics Committee (decision number: 2023/10, date:22.05.2023).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: M.A., C.Y.Ö., Concept: M.A., C.Y.Ö., Design: M.A., C.Y.Ö., Data Collection or Processing: M.A., C.Y.Ö., Analysis or Interpretation: M.A., Literature Search: M.A., Writing: M.A.

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ORIGINAL RESEARCH / *ÖZGÜN ARAŞTIRMA*

Potential Drug-Drug Interaction Detection Using the UpToDate Mobile Application in Intensive Care: A Retrospective, Observational Study

Yoğun Bakımda UpToDate Mobil Uygulaması Kullanılarak Potansiyel İlaç-İlaç Etkileşiminin Tespiti: Retrospektif, Gözlemsel Bir Çalışma

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ABSTRACT

Objective: This study aimed to investigate the frequency of potential drug-drug interactions (pDDI) and the effect of the number of drugs used on pDDIs using the UpToDate drug interactions application.

Materials and Methods: Patients aged >12 years who were treated in the intensive care unit for 3 days in 2016 were included in the study. pDDIs were detected by entering the drugs used for >24 hours into the UpToDate application. The total number of mild, moderate, and severe pDDIs, number of medications used, length of stay, age, number of chronic diseases, mechanical ventilation (MV) support, hospitalization diagnoses, and APACHE II score were statistically compared.

Results: Although the pDDI was found to increase with the number of medications administered, it did not show an exact association with the number of days of hospitalization. However, it was higher among patients who received MV support, had a high APACHE II score, and died. pDDI was observed least in the postoperative follow-up group.

Conclusion: The pDDI increased as the number of medications used by critically ill patients increased.

Keywords: Critically ill patient, intensive care unit, drug-drug interaction, adverse drug reactions, UpToDate

ÖZ

Amaç: Bu çalışmada UpToDate ilaç etkileşimleri uygulaması ile potansiyel ilaç-ilaç etkileşimlerinin (PİİE) sıklığı ve kullanılan ilaç sayısının PİİE üzerindeki etkisinin araştırılması amaçlandı.

Gereç ve Yöntem: Çalışmaya 2016 yılında 3 gün ve daha fazla yoğun bakım ünitesinde tedavi gören 12 yaş üstü hastalar dahil edildi. 24 saatten fazla kullanılan ilaçların UpToDate uygulamasına girilmesiyle PİİE'ler tespit edildi. Hafif, orta ve ağır PİİE toplam sayısı ile kullanılan ilaç sayısı, kalış süresi, yaş, kronik hastalık sayısı, mekanik ventilasyon (MV) desteği, hastaneye yatış tanıları ve APACHE II skoru istatistiksel olarak karşılaştırıldı.

Bulgular: Uygulanan ilaç sayısı arttıkça PİİE'nin arttığı bulunurken, hastanede yatış gün sayısı ile kesin bir ilişki göstermediği belirlendi. Ancak MV desteği alan, APACHE II skoru yüksek olan ve ölen hastalarda bu oran daha yüksekti. PİİE en az postoperatif takip tanı grubunda görüldü.

Sonuç: Kritik hastalarda kullanılan ilaç sayısı arttıkça PİİE'nin arttığı belirlendi.

Anahtar Kelimeler: Kritik hasta, yoğun bakım ünitesi, ilaç-ilaç etkileşimi, advers ilaç reaksiyonları, UpToDate

Introduction

Drug-drug interactions are often unpredictable and undesirable, regardless of their positive or negative effects. Decreased absorption, decreased metabolism, kidney problems, and polypharmacy are among the reasons that increase drug-drug interactions in critically ill patients (1).

Many different types of medications are used in intensive care patients because of systemic diseases and organ failures (2). Drug-related adverse events are twice as frequent as in normal care (3). It has been reported that 23% of clinically important adverse events in intensive care unit (ICU) are related to drug-drug interactions (4). An excessive number of drugs increases the possibility of interaction (5,6). As a result, morbidity and mortality increase (7).

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Potential drug-drug interaction (pDDI) is the possibility of drugs changing each other's effects, and it is possible to detect it with computer programs. 40-80% of patients are exposed to at least one pDDI during their stay in the ICU (8). The number of pDDIs is reportedly related to the number of medications taken daily (1).

pDDIs can be detected using programs such as Stockley's Drug Interactions, Micromedex Drug Interactions, and Epocrates (1). In addition, mobile applications such as UpToDate (Lexicomp Drug Interactions) and MedScape, which can be accessed via smartphones and computers, are used to detect pDDIs (9,10).

This study aimed to investigate the frequency of pDDI detected using the UpToDate Drug Interactions mobile application, the effect of the number of drugs used on pDDI, and its relationship with factors affecting intensive care mortality.

Materials And Methods

Design of the Study

Approval for the research was received from the Ethics Committee of Cerrahpaşa Faculty of Medicine (number: 419987, date: 08.11.2017). The study was planned as a retrospective cross-sectional study.

The study was performed in a single center in the 12-bed tertiary ICU of a university hospital. Patients admitted to intensive care in 2016 were included in the study. The treatment plans were scanned, and the names of the drugs used for each patient were recorded one by one in the Excel file.

The criteria for inclusion in the study were admission to intensive care, age >12 years, and treatment for 3 days or more. Patients whose files could not be accessed or whose treatment plans were missing were excluded from the study.

Patient length of stay, age, number of chronic diseases, mechanical ventilation (MV) support, hospitalization diagnosis, outcome, names and number of medications used daily, and acute physiology and chronic health evaluation II (APACHE II) scores were recorded. Drugs used for >24 hours were considered data. Medications prescribed in single doses were not recorded. During the analysis phase, hospitalization diagnoses were grouped under certain diagnostic groups.

All medications were obtained from the paper treatment plans. The names, routes of administration, and doses of the drugs were recorded in an Excel file, with a separate column for each patient each day. The treatment plan applied for each day was entered into the UpToDate mobile application, and the pDDIs that occurred on the relevant day were recorded. The same procedure was performed repeatedly for each patient on each hospitalization day, and pDDIs were recorded.

pDDI detection using UpToDate

The generic names or active ingredients and routes of administration of the drugs administered to a patient within a day were entered into the UpToDate (Lexicomp Drug Interactions) mobile application. The results were obtained for each pair of drugs with potential interactions grouped as A, B, C, D, and X. Group A was not included in the data. B-C interactions were recorded as mild, D interactions as moderate, and X interactions as severe. This process was repeated for each patient's treatment plan each day. Interaction types and numbers were recorded on separate days.

The UpToDate screening tool uses different databases to detect the presence or absence of significant interactions for a given drug pair. If conflicting evidence is presented between these databases, scientific literature and prospectus information are used to provide clinical practice recommendations to clinicians (10). In the program, the pDDI is grouped as A, B, C, D, and X, and the interaction group of each drug pair is taken as the result output.

Meanings of groups A, B, C, D, and X:

In group A, there were no known drug-drug interactions.

In group B, the mentioned drugs may interact, but there is no clinical evidence of their concomitant use.

In group C, the indicated agents may interact with each other in a clinically significant manner. The benefits of using these two drugs together usually outweigh the risks. An appropriate monitoring plan should be established to prevent possible adverse effects. Dosage adjustments may be necessary for some patient groups.

In group D, the data suggest that the two drugs interact with each other in a clinically meaningful manner. Patient-specific evaluation should be conducted to determine whether the benefits of concomitant treatment outweigh the risks. Precautions should be taken to determine the benefits and/or minimal toxicity of the use of active substances. These actions include close monitoring, empirical dosage changes, and the selection of alternative agents.

In group X, the indicated agents may interact with each other in a clinically significant manner. The risks associated with the combined use of these agents generally outweigh the benefits. These agents are generally contraindicated.

Statistical Analysis

Each patient's total mild, moderate, and severe pDDIs, length of stay, age, number of chronic diseases, MV support, hospitalization diagnosis groups, and total and average number of drug use were statistically compared with the APACHE II score. Patients are listed in order from least to most according to the total and daily number of medications used during hospitalization. The results were then divided into 5 consecutive groups. The mean of each group was calculated. The groups were statistically compared according to mild, moderate, and severe pDDI.

The suitability of the variables to normal distribution was examined using visual (histogram and probability graphs) and analytical methods (Kolmogorov-Smirnov Test). It was determined that not all data had a normal distribution. Descriptive analyses are presented as percentages, and mean ± standard deviation (SD) and median (minimum-maximum) values are given for continuous variables. In data that did not conform to the normal distribution, Mann-Whitney U test was used for comparison analyzes between two groups. Comparisons between more than two groups were performed using the Kruskal-Wallis test. Pairwise comparisons of groups with significant Kruskal-Wallis test results were performed using the Mann-Whitney U test with Bonferroni correction. The Friedman test was used to evaluate more than two repeated measurements in dependent groups. The results are within the 95% confidence interval, and the margin of statistical error is accepted as 0.05. Statistical evaluation was performed using the Statistical Package for Social Sciences (SPSS) for Windows 25.0 (IBM SPSS Inc., Chicago, IL) program.

Results

Patient Characteristics

The number of patients admitted for treatment in the intensive care unit was 835. 276 of these patients were found suitable for statistical evaluation (Figure 1).

55.4% of the patients included in the study were male and 44.6% were female. The average age is 60.98±17.11 (age range 14-88). 62% of the patients were 60 years or older (Table 1).

The average APACHE II score was 22.22±7.35. Patients were divided into 5 groups according to hospitalization diagnosis (Appendix Tables 1-3).

The total mild pDDI was 28.5, and the daily mild pDDI was 3.32. The moderate pDDI was 3 and 0.36, respectively, while the severe interaction was zero for both (Table 2).

Total pDDI according to the total number of drugs

Patients were divided into 5 groups of 20% each according to the total number of medications ordered in the ICU (Appendix 1). Mild pDDI increased as the number of drug uses increased ($p<0.001$). In the pairwise group comparisons, except for the first-second and second-third group comparisons, the moderate pDDI increased as the number of drugs used increased ($p<0.001$). Severe pDDI was found to be higher in the group taking the most medication than in the two groups taking the least amount of medication ($p<0.001$). The pDDI decreased in all groups from mild to severe (Table 3).

Table 1. Patient characteristics

	n(%)
Male	153 (55.4)
Age (Mean ± SD)	60.98±17.11
BMI (Mean ± SD)	24.60±5.89
Disease history	
Cardiovascular system	54.7%
Respiratory system	37%
Gastrointestinal system	31.2%
Neurological system	22.8%
Renal system	19.9%
Hospitalization diagnostic group	
Respiratory system disease	118 (42.8)
Shock	89 (32.2)
Postoperative follow-up	35 (12.7)
Neurological system disease	25 (9.1)
Urinary system disease	9 (3.3)
MV support	
There is	183 (66.3)
None	93 (33.7)
Intensive care result	
Transfer to service	180 (65.2)
Ex	96 (34.8)
Total length of stay	
Ort ±SS	10.76±11.63
Ortanca (IQR)	7 (5-12)
Length of stay	
3-10	192 (69.6)
11-20	50 (18.1)
21-30	21 (7.6)
31 and over	13 (4.7)
Total number of ordered medicines	
Mean ± SD	111.61±130.85
Median (IQR)	69.00 (38.25-130.75)
Daily number of ordered medicines	
Mean ± SD	9.77±3.18
Median (IQR)	9.59 (7.67-12.00)

SD: standard deviation, IQR: inter quartile range, MV: mechanical ventilation

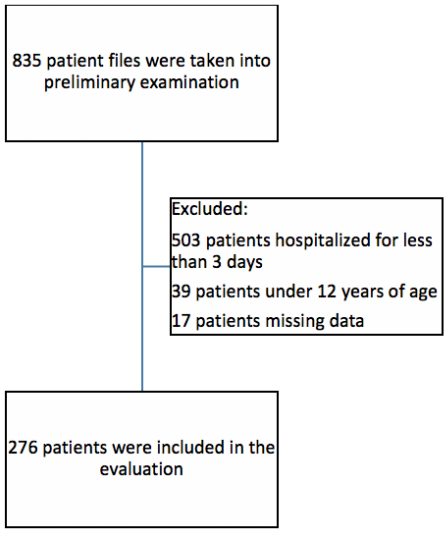

Figure 1. Flow Diagram

Table 2. Potential drug-drug interaction-median (IQR)		
	Total	**Daily**
Mild interaction	28.50(7.00-69.00)	3.32(1.23-6.62)
Moderate interaction	3(0-9.00)	0.36(0-1.00)
Severe interaction	0(0-0)	0(0-0)
IQR: inter quartile range		

Daily pDDI according to daily drug number

Patients were divided into 5 groups of 20% each according to the daily number of medications ordered in the ICU (Appendix 1). It was determined that mild pDDI was lowest in the first group and second group, and there was no significant difference between the next three groups. The moderate pDDI was lowest in the first group, and the difference between the first and fifth groups was significant ($p<0.001$). The severity of pDDI was higher in the fifth group than in the first and second groups ($p=0.001$). The pDDI decreased from mild to severe in all groups (Table 4).

Total pDDI according to the length of stay

Patients were divided into 4 groups according to length of stay (Table 5). Moderate pDDI was found in less patients hospitalized for 3-10 days ($p<0.001$). Severe pDDI was more common in patients hospitalized for 21-30 days than in those hospitalized for 3-10 days ($p=0.010$). pDDI decreased from mild to severe interaction in all groups ($p<0.001$).

Total pDDI according to the hospitalization diagnostic groups

Patients divided into 5 groups according to hospitalization diagnosis (Appendix 1) and were compared according to the degree of pDDI (Table 6). Mild and moderate pDDIs

Table 3. Total pDDI according to total number of, median (IQR)				
Total number of drugs Mean (SD)	**Mild**	**Moderate**	**Severe**	**p-value[2]**
1) 22.75±5.91	3 (0-6)	0 (0-1)	0 (0-0)	<0.001
2) 44.69±7.91	9 (5-19.5)	0 (0-4)	0 (0-0)	<0.001
3) 71.09±8.97	32 (18.5-49)	3 (0-7.5)	0 (0-2.5)	<0.001
4)113.15±18.22	53 (34.5-74.5)	6 (1-10.5)	0 (0-2)	<0.001
5) 302.91±183.94	138 (67.5-189.5)	19.5 (6.5-35)	0 (0-9)	<0.001
p-value[1]	<0.001	<0.001	<0.001	

[1]: Tests used in comparison between groups: Kruskal-Wallis test, $p<0.05$ was considered significant. In pairwise group comparisons, Bonferroni correction was applied, and the Mann-Whitney U test was performed,
[2]: Tests used for intra-group comparison: Friedman test, $p<0.05$ was considered significant.
pDDI: potential drug-drug interaction, IQR: inter quartile range, SD: standard deviation

Table 4. Daily pDDI according to the mean number of medications per day, median (IQR)				
Mean number of drugs	**Mild**	**Moderate**	**Severe**	**p-value[2]**
1) 5.51±1.19	1 (0-1.83)	0 (0-0.33)	0 (0-0)	<0.001
2) 8.01±0.48	2.25 (0.82-3.66)	0 (0-0.78)	0 (0-0)	<0.001
3) 9.53±0.44	4.57 (2.53-7.06)	0.50 (0-1.04)	0 (0-0.42)	<0.001
4) 11.34±0.67	4.87 (3.20-9.54)	0.75 (0.10-1.11)	0 (0-0.23)	<0.001
5) 14.37±1.75	5.93 (3.20-8.40)	0.90 (0.21-1.44)	0 (0-0.49)	<0.001
p-value[1]	<0.001	<0.001	0.001	

[1]: Tests used in comparison between groups: Kruskal-Wallis test, $p<0.05$ was considered significant. In pairwise group comparisons, Bonferroni correction was applied, and the Mann-Whitney U test was performed,
[2]: Tests used for intra-group comparison: Friedman test, $p<0.05$ was considered significant.
pDDI: potential drug-drug interaction, IQR: interquartile range

were observed less frequently in the postoperative follow-up group than in the neurological, respiratory, and shock groups (p<0.001). Severe pDDI was also less common in the postoperative follow-up group than in the respiratory system and shock groups (p=0.017). The pDDI decreased from mild to severe in all groups. Total pDDI results according to survival and MV are shown in Table 7.

Total pDDI according to the number of systemic diseases

Patients were divided into 3 groups according to the number of systemic diseases they had before admission. Mild pDDI was found to be more common in groups with more systemic disease (p<0.001). There was no significant difference between the groups in terms of moderate pDDI (p=0.285). Severe pDDI was more common in patients with 3 or more systemic diseases than in those with no systemic disease (p=0.022). The pDDI decreased in all groups from mild to severe (Table 8).

Total pDDI according to the APACHE II score

Patients were divided into 3 groups in terms of APACHE II score, and pDDI values were compared. Mild and moderate pDDI scores were higher in the 2 groups with an APACHE II score of 20 or more (p<0.001 and p<0.006). There was no significant difference in severe pDDI (p=0.713). The pDDI decreased in all groups from mild to severe (Table 9).

Table 5. Total pDDI according to length of stay median (IQR)

Length of stay (days)	Mild	Moderate	Severe	p-value[2]
3-10 (n=192)	14.00 (4-36)	1.00 (0-5)	0 (0-0)	<0.001
11-20 (n=50)	62.50 (29-107)	8.00 (2-19)	0 (0-3)	<0.001
21-30 (n=21)	143.00 (54-171)	20.00 (7-34)	0 (0-11)	<0.001
31 (n=13)	279.00 (147-370)	32.00 (11-61)	0 (0-8)	<0.001
p-value[1]	<0.001	<0.001	0.010	

[1]: Tests used in comparison between groups: Kruskal-Wallis test, p<0.05 was considered significant. In pairwise group comparisons, Bonferroni correction was applied, and the Mann-Whitney U test was performed,
[2]: Tests used for intra-group comparison: Friedman test, p<0.05 was considered significant.
pDDI: potential drug-drug interaction IQR: interquartile range

Table 6. Total pDDI according to hospitalization diagnosis median (IQR)

Hospitalization diagnosis group	Mild	Moderate	Severe	p-value[2]
Neurological system (n=25)	41 (26-73)	8 (2-16)	0 (0-0)	<0.001
Postoperative follow-up (n=35)	7 (3-19.5)	0 (0-2)	0 (0-0)	<0.001
Respiratory system (n=118)	36 (9-76)	3 (0-9)	0(0-2)	<0.001
Shock (n=89)	27 (7-73)	3 (0-9)	0 (0-1)	<0.001
Urinary system (n=9)	11 (7-36)	3 (1-4)	0 (0-0)	0.001
p-value[1]	<0.001	<0.001	0.017	

[1]: Tests used in comparison between groups: Kruskal-Wallis test, p<0.05 was considered significant. In pairwise group comparisons, Bonferroni correction was applied, and the Mann-Whitney U test was performed,
[2]: Tests used for intra-group comparison: Friedman test, p<0.05 was considered significant.
pDDI: potential drug-drug interaction IQR: interquartile range

Table 7. Total pDDI according to survival and mechanical ventilation median (IQR)

ICU Result	Mild	Moderate	Severe	p-value[2]
Alive (n=180)	16 (5-42)	1.5 (0-7.5)	0 (0-0)	<0.001
Exitus (n=96)	57.5 (29.5-107)	4.5 (2-15.5)	0 (0-2)	<0.001
p-value[1]	<0.001	<0.001	0.107	
MV Support				
Yes (n=183)	37 (12.5-84)	4 (1-12.5)	0 (0-1)	<0.001
No (n=93)	9 (4-36)	0 (0-4)	0 (0-0)	<0.001
p-value[1]	<0.001	<0.001	0.243	

[1]: Tests used in comparison between groups: Kruskal-Wallis test, p<0.05 was considered significant,
[2]: Tests used for intra-group comparison: Friedman Test, p<0.05 was considered significant.
pDDI: potential drug-drug interaction IQR: interquartile range, ICU: Intensive Care Unit, MV: Mechanical Ventilation

Table 8. Total pDDI according to the number of systemic diseases median (IQR)				
Number of Systemic Diseases	**Mild**	**Moderate**	**Severe**	**p-value[2]**
No (n=23) 1-2 (n=138) ≥3 (n=115)	6 (1.5-25.5) 24.5 (5-57) 39 (14.5-92)	2 (0-9) 3 (0-8) 3 (0-12)	0 (0-0) 0 (0-0) 0 (0-2.5)	<0.001 <0.001 <0.001
p-value[1]	<0.001	0.285	0.022	

[1]: Tests used in comparison between groups: Kruskal-Wallis test, p<0.05 was considered significant. In pairwise group comparisons, Bonferroni correction was applied, and the Mann-Whitney U test was performed,
[2]: Tests used for intra-group comparison: Friedman test, p<0.05 was considered significant.
pDDI: Potential Drug-Drug Interaction, IQR: interquartile range

Table 9. Total pDDI according to the APACHE II Score as a median (IQR)				
APACHE II Score	**Mild**	**Moderate**	**Severe**	**p-value[2]**
0-19 (n=101) 20-29 (n=136) Thirty or more (n=39)	14 (4-41) 30 (9-73) 45 (29.5-108.5)	2 (0-6) 3 (0-10) 5 (1-18)	0 (0-0) 0 (0-0) 0 (0-2)	<0.001 <0.001 <0.001
p-value[1]	<0.001	<0.006	0.713	

[1]: Tests used in comparison between groups: Kruskal-Wallis test, p<0.05 was considered significant. In pairwise group comparisons, Bonferroni correction was applied, and the Mann-Whitney U test was performed,
[2]: Tests used for intra-group comparison: Friedman test, p<0.05 was considered significant.
pDDI: potential drug-drug interaction IQR: interquartile range, APACHE II: acute physiology and chronic health evaluation

Discussion

In this study, we determined that as the number of medications administered during intensive care stays increased, the potential mild, moderate, and severe drug-drug interactions detected by UpToDate increased. Additionally, an increase in the length of stay in the ICU was associated with an increase in pDDI.

Mild pDDI detected was approximately 10 times more common than moderate pDDI. Mild pDDI has a minimal impact on a patient's clinic, or medication use is more likely to benefit the patient. Moderate and severe pDDI is more clinically significant and was found to be highest in the patient group who used the most medication.

According to the results of our study, mild and moderate interactions increased with the duration of ICU stay, whereas no clear results were obtained for severe interactions. This situation suggests that even though the patient's stays is long, physicians are careful not to use drugs together, which may cause serious interactions. However, the possible reasons why pDDIs are less common in the postoperative group are the shorter length of stay and the lower number of medications used. Similarly, the fact that severe pDDI, but not moderate pDDI, was found more frequently in patients with more diseases before ICU admission can be explained by the possibility of using multiple medications in patients with multiple diseases. Another explanation may be that intensive care physicians have low levels of knowledge about the drugs used outside intensive care.

In the study conducted by Uijtendaal et al. (11), who obtained similar results to those obtained in the current study, 54% of the patients were exposed to at least one pDDI on 27% of the hospitalization days. In the same study, the number of days and number of patients exposed to ≥1 pDDI increased in patients with long-term stay in the ICU, high expected mortality rate according to APACHE IV, chronic diseases, and high number of medications used, in patients who received MV support, and who died in intensive care. In addition, similar to our results on the effect of length of stay, Gutiérrez-Valencia et al. (12) found in their study that the number of medications used temporarily during ICU stay increased significantly and PIIE increased due to this increase.

In the meta-analysis conducted by Fitzmaurice et al. (13) to investigate pDDIs in ICUs, it was emphasized that 58% of patients admitted to the ICU may be exposed to at least one pDDI. It has been stated that higher-risk drugs are typically given to critically ill patients compared with other patient populations; therefore, pDDIs may occur between 1 and 10 times per patient. In another meta-analysis, 67% of ICU patients were exposed to at least one pDDI (14). In this study, the daily and total values of mild pDDI were significantly higher than those of moderate and severe pDDI. However, our findings of moderate and severe

interactions, which are more clinically significant, were similar to those of Fitzmaurice et al. (13).

Many studies (2, (2,15,16), such as Jain et al. (17), have emphasized that as age increases, systemic diseases increase, and the number of drugs used may increase accordingly. It has been observed that the pDDI increases with the number of drugs used. Similar results were obtained in our study.

Rodrigues et al. (18) showed that the duration of intensive care stay was longer in patients with more severe pDDIs. In our study, mild, moderate, and severe pDDIs increased as the duration of intensive care stay increased. Depending on the severity of the critical illness, the length of stay of patients in ICUs may vary, and patients may receive complex treatments during this period. The cause and effect relationship between patients with a high number of pddises and prolonged stay in intensive care is not clear. Although long periods of stay in the ICU increase the risk of pDDI, negative clinical responses caused by pDDI may also prolong the stay of patients in the ICU.

It has been shown that prolonged mechanical ventilation due to sedation, fluid overload, and exceeding therapeutic drug concentrations are less common in ICUs where clinical pharmacologists play an active role (19). Although pharmaceutical care is practiced across many disciplines, critically ill patients require additional evaluation due to the complexity of medication regimens and disease states. We are aware of the importance of clinical pharmacologists as a part of a multidisciplinary team. In addition to all these positive aspects, they can also contribute to the training of intensive care teams.

Medication errors are more common in patients with multiple drug use, long hospital stays, and organ failure. In this regard, we believe that ICUs are very important in terms of treatment planning, administration, monitoring, and evaluation of results. Electronic order systems warn healthcare professionals about the appropriate dosage, correct drug selection, and drug-drug interactions when creating a treatment plan. For this reason, we believe it is useful to use an electronic order system that warns the physician who decides on the treatment and the nurses who apply it to minimize the margin of error in ICUs where a patient-based treatment plan is made.

Although drug combinations causing interactions were not recorded in our study, combinations of combivent and quetiapine and of combivent and carvedilol are the most common combinations that cause severe pDDI. In our study, severe pDDI was detected much less frequently than moderate and mild pDDI. We believe that this may have occurred because physicians are better aware of the contraindicated use of drug combinations.

Some enteral nutrition products and blood products are not available in the database used to detect pDDI. The interactions of the ingredients in these treatments with other drugs were not evaluated.

As a result, in the current study, in the screening performed on critically ill patients with the UpToDate mobile application, it was determined that the PDDI increased as the number of drugs used in the ICU increased, and that there was a relationship between length of stay and pDDI rates.

Ethics

Ethics Committee Approval: Approval for the research was received from the Ethics Committee of Cerrahpaşa Faculty of Medicine (number: 419987, date: 08.11.2017).

Informed Consent: The study was planned as a retrospective cross-sectional study.

Footnotes

Authorship Contributions

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

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Appendix Table 1. Patient characteristics	
Sex	**n(%)**
Male Female	153(55.4) 123(44.6)
Age	
(Mean ± SD) Median (Min-Max)	60.98±17.11 62.00(14-88)
Age Groups	**n(%)**
12-19 20-39 40-59 60 and older	6(2.2) 29(10.5) 70(25.4) 171(62.0)
BMI	
(Mean ± SD)	24.60±5.89
BMI	**n(%)**
Underweight (<18.5) Normal weight (18.5-24.9) Overweight (≥25)	29(10.5) 125(45.3) 122(44.2)
BMI: body mass index	

Appendix Table 2. Distribution of patients' clinical condition characteristics	
APACHE II (Mean ± SD)	**Score 22.22±7.35**
Hospitalization diagnosis	**n(%)**
Acute respiratory failure Septic shock Postoperative follow-up Postoperative respiratory distress Postoperative hemorrhagic shock Care after cardiopulmonary resuscitation Sepsis AKI, metabolic acidosis Hemorrhagic shock Ischemic cerebrovascular event Subdural hematoma Gunshot wound Decompensated heart failure Multitrauma Renal transplantation Status epilepticus	95(34.4) 41(14.9) 35(12.7) 23(8.3) 22(8.0) 14(5.1) 12(4.3) 8(2.9) 6(2.2) 5(1.8) 5(1.8) 4(1.4) 3(1.1) 1(0.4) 1(0.4) 1(0.4)
Hospitalization diagnostic group	**n(%)**
Respiratory system disease shock Postoperative follow-up Neurological system disease Urinary system disease	118(42.8) 89(32.2) 35(12.7) 25(9.1) 9(3.3)
MV support	**n(%)**
There is None	183(66.3) 93(33.7)
APACHE II Score: Acute Physiology and Chronic Health Evaluation (II) score, AKI: acute kidney ınjury, MV: mechanical ventilation	

Appendix Table 3. Hospitalization diagnoses and diagnosis groups	
Respiratory system diseases	Acute respiratory failure, postoperative respiratory distress
Shock	Gunshot ınjury, decompensated heart failure, hemorrhagic shock, multitrauma, postoperative hemorrhagic shock, sepsis/septic shock
Postoperative follow-up	Postoperative follow-up
Neurological system diseases	Ischemic CVO, post CPR care, status epilepticus, subdural hematoma
Urinary system diseases	Renal transplantation, acute kidney ınjury, metabolic acidosis
CVE: cerebrovascular Event, CPR: cardiopulmonary resuscitation	

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ORIGINAL RESEARCH / *ÖZGÜN ARAŞTIRMA*

Analysis of Medication Inventory System for Intensive Care Unit: A Hospital Example

Yoğun Bakım Ünitesi İçin İlaç Envanter Sistemi Analizi: Bir Hastane Örneği

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ABSTRACT

Objective: Optimizing health benefits becomes essential given the limitations of universal healthcare resources. Therefore, this study aims to conduct an always, better, and control (ABC) and vital, essential, and desirable (VED) analysis of medications in the intensive care unit (ICU) of a tertiary care hospital. The primary objective is to enhance medication inventory management and control costs. The research will assess clinical and operational actions, examine research databases, and review published literature to achieve these objectives. Given that drug expenses constitute a significant portion (30-40%) of total medication costs in ICUs, this study will focus on evaluating selective inventory control techniques, including ABC, VED, and ABC-VED matrix analysis.

Materials and Methods: Examining 546 medications in 2020, 634 in 2021, and 662 in 2022, this study collected three years of data to conduct a comprehensive analysis. The applied methodologies included ABC, VED, and ABC-VEN matrix techniques.

Results: In 2020, Category I, comprising AV+AE+AD+BV+CV, had 79 drugs, constituting 74% of the total cost and representing 14% in variety. Category II (BE+CE+BD) included 259 drugs, accounting for 47% of the total cost and 47% of the total drug variety. In comparison, Category III (CD) comprised 208 drugs, representing 38% of the total cost and variety share. In 2021 and 2022, similar patterns were observed within the categories, with varying drug counts and percentages.

Conclusion: Given rising costs and the integration of expensive innovations in critical care, the study highlights the critical role of economic evaluations in the ICU. Implementing robust inventory control measures is crucial for effective medication management in ICUs, contributing to cost-effectiveness and improved resource utilization in healthcare systems.

Keywords: ICU, drug management, inventory management, ABC-VED analysis

ÖZ

Amaç: Bu çalışma, özellikle yoğun bakımda belirgin olan evrensel sağlık hizmetleri kaynak kıtlığı bağlamında, sınırlı kaynaklar dahilinde sağlık faydalarını optimize etme zorluğunu ele almaktadır. İlaç giderlerinin toplam ilaç maliyetlerinin %30-40'ını oluşturduğu üçüncü basamak bir hastanenin yoğun bakım ünitesine (YBÜ) odaklanan bu çalışmanın temel amacı, her zaman, daha iyi ve kontrol (ABC) ve hayati, temel ve arzu edilir (VED) ve ABC-VED matris analizi gibi seçici envanter kontrol tekniklerini değerlendirmektir.

Gereç ve Yöntem: 2020 yılında 546, 2021 yılında 634 ve 2022 yılında 662 ilacın incelendiği bu çalışmada, kapsamlı bir analiz yapmak için üç yıllık veri toplanmıştır. Uygulanan metodolojiler arasında ABC, VED ve ABC-VEN matris teknikleri yer almıştır.

Bulgular: 2020 yılında, AV+AE+AD+BV+CV'den oluşan Kategori I'de toplam maliyetin %74'ünü oluşturan ve çeşitlilik açısından %14'lük bir paya sahip olan 79 ilaç yer almıştır. Kategori II (BE+CE+BD) toplam maliyetin %47'sini oluşturan ve çeşitlilikte %47'lik bir paya sahip 259 ilaç içerirken, Kategori III (CD) toplam maliyetin %38'ini oluşturan ve çeşitlilikte %38'lik bir paya sahip 208 ilaç içermekteydi. 2021 ve 2022'de, ilaç sayıları ve yüzdeleri değişmekle birlikte, kategoriler içinde benzer modeller gözlenmiştir.

Sonuç: Artan maliyetler ve pahalı yeniliklerin kritik bakıma entegrasyonu göz önüne alındığında, bu çalışma YBÜ'de ekonomik değerlendirmelerin kritik rolünü vurgulamaktadır. Sağlam envanter kontrol önlemlerinin uygulanması, YBÜ'lerde etkili ilaç yönetimi için çok önemlidir ve sağlık sistemlerinde genel maliyet etkinliğine ve gelişmiş kaynak kullanımına katkıda bulunur.

Anahtar Kelimeler: YBÜ, ilaç yönetimi, envanter yönetimi, ABC-VED analizi

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Introduction

Intensive care involves a multidisciplinary team providing specialized, focused healthcare services to critically ill patients (1). The intensive care unit (ICU) is a specialized unit within a hospital equipped with advanced technology and a diverse team of experts, providing intensive care, including both invasive and non-invasive monitoring of the patient's physiological indicators for precise care adjustments (2). ICUs are characterized by a combination of unique features, including the severity of patients' clinical conditions, significant variability in length of stay, the potential for rapid deterioration of clinical conditions, a limited number of service beds, and strict policies against stockpiling medications (3).

ICUs are resource-intensive units within the healthcare system. Intensive care services are costly (4,5). ICU care requires intensive resources, including physicians, nurses, medical devices, medical supplies, and medications. In terms of hospital organization, ICUs account for one-third of the total service production costs (6,7). The high expenses associated with ICUs can be attributed to the aging patient population, the need for specialists from various fields, advanced medical devices, and the intensive and frequent use of medications. Patient lengths of stay in the ICU and personnel, medication, and material costs are fundamental factors that affect ICU costs. ICU medication expenses constitute approximately 30-40% of the total drug costs associated with hospital admissions, surpassing medication expenses in other departments (8). Moreover, the increase in medication costs in the ICU is nearly twice that of medication costs outside the ICU (8). Recognizing the significant role of medication usage in increasing overall ICU expenses and in effectively controlling costs is essential. Concerns arise due to factors such as the rising prices of commonly used ICU medications, the dominance of generic manufacturers, drug shortages, and regulatory changes, all of which contribute to the cost increases of ICU medications, constituting a significant portion of hospital drug budgets (9).

Inventory is a comprehensive record of an organization's assets, including items such as stocked goods, medications, and equipment (10). Managing medication inventory focuses on minimizing costs and increasing efficiency while maintaining exceptionally high service standards for each item. Medication inventory management emphasizes cost control and improved operational efficiency. Various inventory management strategies are employed to examine medication expenses. Some standard inventory management methods include always, better, and control (ABC) analysis, HML analysis, vital, essential, and desirable (VED) analysis, FSN analysis, SDE analysis, GOLF analysis, and SOS analysis (11,12). Two frequently used methods are ABC analysis (classifying medications based on budgetary consumption) and VED analysis (12,13). Among these methodologies, the ABC-VED analysis is widely preferred because it enables the evaluation of medication expenses while considering their impact on patient health and costs. The ABC analysis model provides an accurate and impartial depiction of budget distribution for inventory.

In contrast, VED analysis assists in prioritizing medications for supply and use within a medication supply system. Specifically, ABC, VED, and the ABC-VED matrix analysis are crucial for efficient resource allocation and cost-effective medication inventory management in hospitals and other healthcare organizations, balancing quality healthcare delivery and medication expenses. Existing literature contains numerous studies on medication inventory management in hospitals (14,15). Additionally, there are studies specific to ICUs (16).

This study aims to conduct an ABC-VED analysis of medications used in the ICU of a tertiary care hospital at the institutional level to enhance medication inventory management and control these medications to manage the increasing medication costs in the ICU. Additionally, it investigates clinical and operational actions, research databases, and published literature.

Materials And Methods

Compared to the traditional maximum-minimum system, the ABC system offers cost-effective benefits and enhances financial control, ultimately encouraging inventory management efficiency (17). The ABC classification technique, derived from the Pareto principle in inventory management, (18) prioritizes high-value, high-usage items over others. Approximately 20% of inventory items contribute to about 80% of the total sales value; the following 30% contribute to approximately 15%, and the remaining 50% contribute to approximately 5% (19-21).

Healthcare institutions may face budget constraints that hinder their ability to acquire all necessary medications, and VED analysis provides a systematic approach to prioritize medication procurement and inventory maintenance by categorizing medications into vital, essential, and desirable categories based on their importance from a healthcare perspective (22).

An ABC-VED matrix combines ABC and VED analyses to establish a prioritization management system divided into

three categories (I, II, and III). Category I includes AV, AE, AD, BV, and CV sub-items; Category II includes BE, CE, and BD sub-items; and Category III includes the remaining items in the CD sub-category. The first letter in these subcategories represents the classification in the ABC analysis, and the second letter represents the classification in the VED analysis (12,31).

Application

This research is a retrospective cross-sectional study covering the evaluation of medications used in the 37-bed Anesthesia and Internal Medicine ICUs of a 1005-bed university hospital in 2020, 2021, and 2022. The area where the study was conducted, the methods used, and the sources from which data were collected are components of the research that do not require ethical approval. The sample of this single-center quantitative research consists of 662 medications used in the ICU. This list covers all medications used in the Anesthesia and Internal Medicine ICUs generic drugs. Medications used in other ICUs in the hospital (surgical, coronary, pediatric, neonatal) were excluded. Data on the quantity of usage and purchase unit prices of medications used in the ICUs were obtained from the hospital's automation system. A structured data collection format adapted from Management Sciences for Health (MSH), as used by Jobira et al., (14) was used to collect the necessary data for the ABC analysis. A total of 27 vital medications that must be continuously available in intensive care were identified. Medications with a lower level of criticality for ICU patients and can be stocked in the hospital were categorized as essential. Medications with the lowest criticality, whose absence would not adversely affect the health of ICU patients, were categorized as desirable. Assigning a VED status to each medication was verified by the research group through discussion until a consensus was reached among the responsible intensivists. All medications in the ICU medication inventory were categorized into "V", "E", or "D" categories using a judgmental method (12).

Statistical Analysis

The information regarding the yearly consumption and expenses associated with each pharmaceutical item during the fiscal years 2020 to 2022 was gathered. These data were subsequently entered into a Microsoft Excel spreadsheet. Statistical analysis was conducted using the statistical functions available in Microsoft Excel.

For the ABC analysis, the total annual consumption of all medications was determined by multiplying the unit cost by the annual consumption. The obtained values were then ranked in order of monetary value. Subsequently, medications were categorized into A, B, and C groups with shares of 70%, 20%, and 10%, respectively, based on cumulative consumption (14,23).

For the VED analysis, medications were evaluated by the intensive care responsible physicians and categorized accordingly (14,24).

The data obtained from the ABC and VED analyses were organized into a matrix to classify medications types I, II, and III. With this consolidation, Category I includes items from the AV, AE, AD, BV, and CV subcategories; Category II includes items from the BE, CE, and BD subcategories; and Category III includes the remaining items in the CD subcategory (15,25).

ABC Analysis

The distribution of medications used in intensive care units for the years 2020, 2021, and 2022, according to the ABC analysis, is presented in Table 1. In 2020, there were 26 medications in intensive care in the A stock group, constituting 4.76% of the total medications. There were 43 medications in the B stock group, representing 7.88% of the total medications. The C stock group had 477 medications, making up 87.36%. Moving to 2021, there were 35 medications in the A stock group in intensive care units, representing 5.52% of the total medications. There were 53 medications in the B stock group, constituting 8.36% of the total medications. In the C stock group, there were 546 medications, making up 86.12% of the total medications. In 2022, there were 30 medications in the A stock group in intensive care, accounting for 4.53% of the total medications. There were 60 medications in the B stock group, representing 9.06% of the total medications. In the C stock group, there were 572 medications, comprising 86.40% of the total medications.

Regarding expenditures in 2020, A stock group materials accounted for ₺3,203,395.57, B stock group accounted for ₺915,559.60, and C stock group accounted for ₺456,761.41. The total expenditure for that year was ₺4,575,716.58. In 2021, the A stock group's share of total expenditure increased to ₺4,176,166.07, while the B and C groups accounted for ₺1,153,423.77 and ₺581,847.17, respectively. The total expenditure for that year was ₺5,911,437.01. In 2022, A stock group materials, amounted to ₺6,128,067.47, B stock group to ₺1,764,823.62, and C stock group to ₺860,459.70. The total expenditure for 2022 was ₺8,753,350.79.

VED Analysis

According to the VED analysis in Table 2 for the year 2020, when examining the drugs used, there were 62 drugs in the V category, representing 11% of the total drugs and accounting for 16% of the costs. The E category included 252 drugs, constituting 46% of total drugs and representing 57% of the costs. The D category included 232 drugs, constituting 42% of total drugs and accounting for 27% of the costs.

In 2021, there were 59 drugs in the V category, representing 9% of the total drugs and accounting for 15% of the costs. The E category included 303 drugs, constituting 48% of total drugs and representing 58% of the costs. The D category included 272 drugs, constituting 43% of total drugs and accounting for 26% of the costs.

In 2022, there were 68 drugs in the V category, representing 10% of the total drugs and accounting for 16% of the costs. The E category included 311 drugs, constituting 47% of total drugs and representing 58% of the costs. The D category included 283 drugs, constituting 43% of total drugs and accounting for 27% of the costs.

ABC-VED Matrix Analysis

An ABC-VED matrix is formed by merging ABC and VED analyses to develop a prioritized management system into three categories (I, II, and III). Category I comprises AV, AE, AD, BV, and CV; Category II includes BE, CE, and BD. Category III encompasses the remaining items in the CD sub-category (Table 3). The first letter denotes the ABC classification, and the second indicates the VED classification. Based on the data for the year 2020, within Category I (AV+AE+AD+BV+CV),

Table 1. ABC analysis table

Year	Stock group	Item count	Item count percentage (%)	Total expenditure (₺)	Total expenditure percentage (%)
2020	A	26	4.76%	₺3,203,395.57	70.01%
	B	43	7.88%	₺915,559.60	20.01%
	C	477	87.36%	₺456,761.41	9.98%
	Total	546	100.00%	₺4,575,716.58	100.00%
2021	A	35	5.52%	₺4,176,166.07	70.65%
	B	53	8.36%	₺1,153,423.77	19.51%
	C	546	86.12%	₺581,847.17	9.84%
	Total	634	100.00%	₺5,911,437.01	100.00%
2022	A	30	4.53%	₺6,128,067.47	70.01%
	B	60	9.06%	₺1,764,823.62	20.16%
	C	572	86.40%	₺860,459.70	9.83%
	Total	662	100.00%	₺8,753,350.79	100.00%

Table 2. VED analysis table

Year	VED group	Count (number)	Amount (₺)	Count (%)	Amount (%)
2020	V group	62	₺743,205.28	11%	16%
	E group	252	₺2,594,302.34	46%	57%
	D group	232	₺1,238,208.96	42%	27%
	Total	546	₺4,575,716.58	100%	100%
2021	V group	59	₺914,319.77	9%	15%
	E group	303	₺3,433,294.78	48%	58%
	D group	272	₺1,563,822.46	43%	26%
	Total	634	₺5,911,437.01	100%	100%
2022	V group	68	₺1,383,492.49	10%	16%
	E group	311	₺5,039,423.24	47%	58%
	D group	283	₺2,330,435.06	43%	27%
	Total	662	₺8,753,350.79	100%	100%

Table 3. ABC-VED matrix analysis table					
Year	**ABC and VED matrix analysis**	**Count**	**Amount (₺)**	**Variety (%)**	**Cost (%)**
2022	Category I (AV+AE+ AD+BV+CV)	92	₺6,626,027.46	14%	76%
	Category II (BE+CE+BD)	320	₺1,811,117.56	48%	21%
	Category III (CD)	250	₺316,205.77	38%	4%
	Total	662	₺8,753,350.79	100%	100%
2021	Category I (AV+AE+ AD+BV+CV)	85	₺4,516,027.46	13%	76%
	Category II (BE+CE+BD)	311	₺1,097,203.78	49%	19%
	Category III (CD)	238	₺298,205.77	38%	5%
	Total	634	₺5,911,437.01	100%	100%
2020	Category I (AV+AE+ AD+BV+CV)	79	₺3,396,027.46	14%	74%
	Category II (BE+CE+BD)	259	₺953,483.35	47%	21%
	Category III (CD)	208	₺226,205.77	38%	5%
	Total	546	₺4,575,716.58	100%	100%

79 drugs account for 74% of the total cost and represent a 14% share in terms of variety. Category 1 drugs commonly used in the ICU according to their ATC names are albumin, amphotericin B, cefotaxime, and sodium chloride. These medications are essential for managing critical care patients' medical needs. Category II (BE+CE+BD) consists of 259 drugs and represents 47% of the total cost, with a 47% share in terms of variety. Category III (CD) is composed of 208 drugs, each representing 38% of the total cost and a 38% share in terms of variety.

In the data for the year 2021, within Category I (AV+AE+AD+BV+CV), 85 drugs account for 76% of the total cost and represent a 13% share in terms of variety. Category II (BE+CE+BD) consists of 311 drugs and represents 49% of both the total cost and variety. Category III (CD) is composed of 238 drugs, representing 38% of the total cost and 38% of the variety.

According to the data for the year 2022, within Category I (AV+AE+AD+BV+CV), 92 drugs account for 76% of the total cost and represent a 14% share in terms of variety. Category II (BE+CE+BD) consists of 320 drugs and represents 48% of the total cost, with a 48% share in terms of count. Category III (CD) is composed of 250 drugs, representing 38% of the total cost and having a 38% share in terms of variety.

Results

The analysis of the medication inventory system in the ICU, combining ABC, VED, and ABC-VED matrix analyses, highlights critical patterns in drug usage and expenditure from 2020 to 2022. The ABC analysis demonstrates that while the C stock group consistently includes the highest number of medications each year (over 86%), its financial impact remains minimal compared to the A stock group, which, despite having the lowest item count, contributes the highest share of total expenditures. Over the three years, expenditures for A group medications rose significantly from ₺3.2 million in 2020 to ₺6.1 million in 2022, reflecting the high costs associated with essential ICU drugs. This trend underscores the importance of stringent management strategies for high-cost items to optimize resource allocation and reduce financial strain in critical care settings.

The VED analysis further reveals that vital (V) and essential (E) medications dominate the expenditure landscape, emphasizing their crucial role in patient care. The ABC-VED matrix analysis offers a comprehensive view by integrating cost significance and clinical importance, categorizing medications into three priority levels. Category I drugs, including high-cost and critical medications, consistently accounted for over 74% of total costs across all years, highlighting their indispensability in ICU operations. Effective inventory management, particularly for Category I medications, is essential for ensuring cost-efficiency, uninterrupted supply, and enhanced healthcare outcomes in ICUs. This study reinforces the need for continuous monitoring, precise demand forecasting, and strategic procurement practices to manage ICU medication inventories effectively.

Discussion

This research evaluates the inventory management of drugs used in intensive care units through ABC-VED analysis.

Ensuring rapid access to essential resources, including drugs, is crucial for effective healthcare delivery in ICU settings. Conducting ABC or VEN analysis independently has certain limitations. ABC analysis disregards the importance of drugs, while VED analysis overlooks the cost dimension of drugs (26). Therefore, ABC-VEN matrix analysis is essential to harness the advantages of both approaches and identify items requiring strict control (13,27). In healthcare services, using scientifically sound techniques for drug inventory management is imperative to enhance the efficiency and effectiveness of healthcare service delivery (28). Given that limited resources and increasing demand characterize the healthcare environment, healthcare institutions must prioritize the efficient allocation of resources to minimize errors and maximize benefits (15). In a healthcare setting, inventory must be managed to ensure continuity of essential patient care services while achieving optimal inventory levels with minimal working capital utilization (15).

Based on the ABC analysis conducted in the current study, drugs classified as Class A represented 4.76% of the total quantity supplied in 2020, 5.52% in 2021, and 4.53% in 2022. In Class A, the number of item categories has increased each year. Classes B and C seem to have experienced fewer fluctuations in the number of item categories. The total expenditure in 2020 is approximately ₺4.6 million. Despite having less than 10% of the total expenditure, Class C leads in the number and variety of item categories. In 2021 and 2022, the total expenditure amounted to ₺5.9 million and ₺8.7 million, respectively. Class C had more item categories in both years than the other groups (22,16). Although they have limited quantities, the proper management of Class A drugs is essential because their neglect can lead to increased hospital expenditures and, consequently, affect the overall provision of healthcare services (29,15). Class A drugs require stringent monitoring, data-based accurate demand forecasting, strict budget control, minimum safety stock, regular inventory checks, and well-defined regulation and control protocols (14).

Regarding V Group drugs, there were 62 in 2020, 59 in 2021, and 68 in 2022. This indicates that the number of items classified as critical has increased. 13 For E Group items, there were 252 in 2020, 303 in 2021, and 311 in 2022. These data generally show that the number of essential items has increased and is significant for healthcare services. The number of D Group items was 232 in 2020, 272 in 2021, and 283 in 2022. This suggests that the number of desired items remains relatively stable. Focusing on 2022, the number of V Group items has increased, while the number of items in the E and D Groups has remained relatively constant. This indicates an increasing importance of critical items and the need for greater attention to the inventory management of such items. Regarding expenditure percentage, V Group items represented 16% of total expenditures in 2020, 15% in 2021, and 16% in 2022. This emphasizes the significance of these items significance in terms of quantity and cost. E Group items represented 57% of total expenditures in 2020 and 58% in both 2021 and 2022 (12). This accounts for a significant portion of the cost and remains relatively constant. D Group items represented 27% of total expenditures in 2020, 26% in 2021, and 27% in 2022. This group has a lower cost share and a relatively stable share (22).

According to the results of the analysis, it is evident that specific categories are important in drug consumption for the years 2020, 2021, and 2022. Firstly, the drugs within Category I (AV+AE+AD+BV+CV) represented a significant portion of the total cost, accounting for 74%, 76%, and 76% in the respective years (14,29). This category has a high-cost impact and makes up a substantial portion of hospital drug expenditures, while having a lower share in terms of variety, with percentages of 14%, 13%, and 14% noted for specific sub-categories (22,16). This highlights the need for intensive care unit managers to monitor these drugs and continually review them for cost-effectiveness.

Category II (BE+CE+BD) is more significant and notable in cost and variety than other categories. This category represented 47%, 49%, and 48% of the total cost in 2020, 2021, and 2022, respectively. It also had a share of 47%, 49%, and 48% in variety during these years. This reflects the diversity of hospital inventory and suggests that drug costs are distributed more evenly. These drugs play a significant role in the daily operation of the hospital (30).

Category III (CD) has a more balanced structure in terms of cost and variety. It represents 5% of the total cost in all three years and has a 38% share in terms of variety. These drugs can be supplied annually or semi-annually, reducing order costs, maintaining a reasonable holding cost, and preventing the blocking of a significant amount of capital (24).

Moreover, the evolving significance of specific drug categories over the years underscores the importance of closely monitoring consumption patterns and expenditure distribution. Category I drugs consistently contribute a substantial portion of total costs, highlighting the need for intensive care unit managers to continually review these drugs for cost-effectiveness. Category II drugs play a significant role in daily hospital operations, reflecting the diversity of hospital

inventory. In contrast, Category III drugs exhibit a more balanced structure in terms of cost and variety, allowing for efficient supply management.

In conclusion, the comprehensive analysis conducted in this study emphasizes the critical role of ABC-VED analysis in optimizing drug inventory management within ICU settings. By closely monitoring consumption patterns and expenditure distribution, healthcare institutions can make informed decisions to enhance resource utilization, ensuring the continuity of essential patient care services while maximizing cost-effectiveness.

Conclusion

In conclusion, this study underscores the importance of conducting an ABC-VED analysis of drugs in ICUs. The implementation of ABC-VED analysis has provided valuable insights into medication consumption patterns and expenditure distribution, highlighting critical areas for effective inventory management.

Category I drugs (AV, AE, AD, BV, CV) have emerged as significant contributors to total medication costs across all three years despite representing a limited variety. These drugs' meticulous monitoring and continual assessment are essential for achieving cost-effectiveness and optimal resource allocation within the ICU.

Category II drugs (BE, CE, BD) exhibit a notable presence in terms of both cost and variety, reflecting the diverse inventory requirements of the hospital. Careful management of these drugs is necessary to ensure efficient utilization of resources.

Category III drugs (CD) demonstrate a more balanced structure in terms of cost and variety, which is crucial in maintaining adequate inventory levels while minimizing costs.

In conclusion, the findings emphasize the importance of adopting comprehensive inventory management strategies, such as ABC-VED analysis, to optimize medication inventory management and control costs effectively in ICU settings. By closely monitoring medication consumption patterns and expenditure distribution, healthcare institutions can make informed decisions to enhance resource utilization and ensure the continuity of essential patient care services while maximizing cost-effectiveness.

Furthermore, sharing inventory classification and analysis results with pharmacy managers has influenced decisions regarding the intensive care unit's procurement, storage, and continuous monitoring of inventory items. This research is a valuable tool for healthcare institutions seeking to optimize their drug inventory management, streamline operations, and allocate resources efficiently in the ever-evolving healthcare landscape.

Ethics

Ethics Committee Approval: The area where the study was conducted, the methods used, and the sources from which data were collected are components of the research that do not require ethical approval.

Informed Consent: The sample of this single-center quantitative research consists of 662 medications used in the ICU.

Footnotes

Authorship Contributions

Surgical and Medical Practices: A.D., A.N.G., Concept: A.D., A.N.G., Design: A.D., Ö.Ö., A.N.G., Data Collection or Processing: A.D., Ö.Ö., Analysis or Interpretation: A.D., Ö.Ö., A.N.G., Literature Search: A.D., Ö.Ö., Writing: A.D., A.N.G.

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ORIGINAL RESEARCH / *ÖZGÜN ARAŞTIRMA*

Evaluation of Enteral Nutrition Applications in Pediatric Intensive Care Units in Türkiye

Türkiye'deki Çocuk Yoğun Bakım Ünitelerinde Enteral Beslenme Uygulamalarının Değerlendirilmesi

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ABSTRACT

Objective: Enteral nutrition practices in pediatric intensive care units (PICUs) in Türkiye and all around the world are mostly performed in accordance with an expert opinion due to the inadequacy of evidence-based practices. Therefore, different approaches are observed in enteral nutrition applications. This research aimed to evaluate the enteral nutrition practices in PICUs in Türkiye.

Materials and Methods: The research was carried out through the online survey database between February 2021 and June 2021 by reaching 73 out of 93 PICUs according to the 2019 data of the Ministry of Health of the Republic of Türkiye. The "clinical identification form" and "the clinic's evaluation form for enteral nutrition practices" were prepared by the researcher and expert opinion was taken. The data were analyzed with the SPSS 21.0 program.

Results: As a standard, the first preferred method was the gastrointestinal tract (98.6%) followed by the intermittent feeding method (93.2%). The commonly used criteria to evaluate enteral feeding tolerance included gastric residual volume (GRV), vomiting, increased abdominal pressure, and diarrhea. 61.6% of PICUs routinely measured GRV in patients who were on enteral feeding, whereas 31.5% did not routinely measure it but measured GRV only in patients with signs of intolerance. The frequency of GRV measurement was 50.7% in patients who were on intermittent feeding, and it was performed before each feeding.

Conclusion: It was determined that the routine GRV control was frequently performed in enterally fed patients in PICUs, and the first preferred enteral feeding method was the intermittent gastric route. However, it is noteworthy that the use of written enteral nutrition protocols in PICU was insufficient. In accordance with these findings, we recommend implementing practices to encourage the use of the enteral nutrition protocol in the PICU.

Keywords: Enteral nutrition, pediatric intensive care, gastric residual volume, intensive care nurse

ÖZ

Amaç: Türkiye'de ve dünyadaki çocuk yoğun bakım ünitelerinde (ÇYBÜ) enteral beslenme uygulamaları kanıta dayalı uygulamaların yetersizliği sebebiyle büyük ölçüde uzman görüşü doğrultusunda yürütülmektedir. Bu duruma bağlı olarak enteral beslenme uygulamalarında farklı yaklaşımlar görülmektedir. Araştırma, Türkiye'de bulunan çocuk yoğun bakım ünitelerindeki enteral beslenme uygulamalarını değerlendirmek amacıyla planlanmıştır.

Gereç ve Yöntem: Araştırma, Şubat 2021- Haziran 2021 tarihleri arasında online surveey veri tabanı üzerinden Türkiye Cumhuriyeti Sağlık Bakanlığı 2019 verilerine göre toplam 93 ÇYBÜ'nin 73'üne ulaşılarak yapılmıştır. Veriler araştırmacı tarafından hazırlanan ve uzman görüşü alınan "klinik tanımlama formu" ve "kliniğin enteral beslenme uygulamalarını değerlendirme formu" kullanılarak elde edilmiştir.

Bulgular: Standart olarak ilk tercih edilen yol ve yöntem, %98,6 oranında gastrointestinal yol ile %93,2 oranıyla aralıklı beslenme yöntemidir. Enteral beslenme tolerasyonunu değerlendirmede en sık kullanılan kriterler sırasıyla; gastrik rezidüel volüm (GRV) miktarı, kusma, abdominal basınç artışı ve ishaldir. ÇYBÜ'lerinin %61,6'sı rutin olarak enteral beslenmeye başlanan her hastada GRV ölçmekte ve % 31,5'i ise rutin olarak bakmayıp sadece intolerasyon belirti/bulgusu olan hastalarda GRV ölçmektedir. GRV ölçüm sıklığı aralıklı beslenme yönteminin kullanıldığı hastalarda en fazla % 50,7 oranıyla her beslenme öğünü öncesinde yapılmaktadır.

Sonuç: ÇYBÜ'lerinde enteral beslenen hastalarda rutin GRV kontrolünün sıklıkla yapıldığı ve ilk tercih edilen enteral beslenme yönteminin aralıklı gastrik yol olduğu belirlendi. Bununla birlikte ÇYBÜ'nde yazılı enteral beslenme protokolü kullanımının yetersiz olduğu dikkati çekmektedir. Bu sonuçlar doğrultusunda ÇYBÜ'nde enteral beslenme protokolü kullanımının teşvik edilmesi konusunda uygulamalar yapılması önerilebilir.

Anahtar Kelimeler: Enteral beslenme, çocuk yoğun bakım, gastrik rezidüel volüm, yoğun bakım hemşiresi

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Introduction

The needs of patients in intensive care units (PICUs) are quite different from those in wards due to factors such as trauma, stress, and metabolic response to critical illness. In case of a strong metabolic response, in critically ill patients, malnutrition is inevitable if adequate nutritional support cannot be provided. As a result of malnutrition, there is an increase in morbidity and mortality due to impaired immune functions, delayed wound healing, and increased duration of infection (1-4).

Malnutrition is mostly observed in cases of prolonged starvation in intensive care patients since these patients are severely ill, and early enteral feeding cannot be initiated (2). In addition to undernutrition, overnutrition causes energy imbalance in patients under treatment in the PICU. In particular, children with fluid restriction, whose nutrition is interrupted due to multiple interventions, and who experience nutritional intolerance are at great risk of malnutrition (2,5).

The American Society for Parenteral and Enteral Nutrition (ASPEN) recommended the use of the enteral route for feeding support in the clinical guideline for nutritional support in critically ill pediatric patients, which was published in 2017 (4). It has been reported that enteral nutrition supports intestinal physiology, prevents intestinal villus atrophy, preserves the intestinal barrier, reduces intestinal permeability, protects against ischemic-reperfusion injury by stimulating intestinal blood supply, improves regional and systemic immune response, and increases epithelial development (3,6). Even a small amount of enteral nutrition improves intestinal perfusion and intestinal barrier function and supports enteral hormone release owing to its trophic effect (6).

In a multicenter study investigating the relationship between the protein intake and 60-day mortality in critically ill children, the mortality rate was found to be lower in children who took 60% or more of the desired protein amount (3). Mehta et al. (7) reported in a study, conducted with patients in the PICU who were on enteral and parenteral feeding, that the prevalence of mortality and infection was lower in enterally fed children compared to those who were on parenteral feeding. In a study performed by Mikhailov et al. (8), hospital costs were significantly lower in the early fed group, although there was no significant difference in the length of hospital stay. This was observed in critically ill children who stayed in the PICU for at least 96 hours and were on enteral feeding (25% of the target calories in the first 48 hours).

Consequently, even though enteral nutrition is frequently applied in the PICU, it is mostly performed based on the opinion of clinical experts due to the lack of evidence both nationally and internationally. However, this situation has led to the emergence of different approaches in enteral nutrition practices. In the light of this information, this descriptive study was carried out to determine the necessity of enteral nutrition in PICUs in Türkiye and to evaluate the methods and practices used in the initiation of feeding and during feeding.

Materials and Methods

This research was carried out through an online survey between February and June 2021. The form prepared by the researcher was transferred to the online platform and sent to the responsible nurses working in the PICU.

a) Participants and sampling

There are a total of 93 PICUs in Türkiye according to the 2019 data of the Republic of Türkiye Ministry of Health, General Directorate of Public Health. The population of the research consisted of 93 nurses (one responsible nurse from each unit was included in the research) working in the PICUs of public, private, and university hospitals. This study aimed to reach the entire population, and therefore no sample selection was made. The sample of the study consisted of 73 PICU that replied and sent back the entire form (response rate: 78.5%). The inclusion criterion was the presence of a 3rd level ICU in hospitals. To carry out the research, the nurses in charge of the PICUs were reached through the Nursing Commission formed by the Pediatric Emergency Medicine and Intensive Care Association to represent the nurses working in this field. One head nurse from each unit was asked to answer the questionnaire through the common communication network of the nursing commission.

b) Data collection tools

In the study, data were collected using the "clinical identification form" and "the clinic's evaluation form for enteral nutrition practices". The forms prepared by scanning the literature 9-11 were sent to nurses, physicians and academicians who are experts in the field, and the suitability of the content of the questions was evaluated. The pre-application of the online forms was carried out with five pediatric intensive care nurses with different levels of education and experience (specialist, doctor, associate professor, and professor). In accordance with the feedback, necessary corrections were made and the form was finalized.

Clinical identification form: consisted of a total of 7 questions describing the educational levels of the nurses who

agreed to participate in the study, and the characteristics of the nurse/doctor/patient attendant working in the unit.

The clinic's evaluation form for enteral nutrition practices consists of 20 questions about nutritional practices such as the presence of an enteral nutrition protocol in the institutions of the nurses participating in the study, the presence of a pediatric nutrition assessment scale, the time to start feeding, the time to reach full energy level, and the status of gastric residual volume (GRV) measurement.

Data were collected through a total of 27 questions in both forms. It took 5-10 minutes to fill out the questionnaire.

Statistical Analysis

The data obtained in the research were analyzed using the SPSS (Statistical Package for Social Sciences) 21.0 program. Number, percentage, mean, and standard deviation values were used as descriptive statistical methods to evaluate the data.

Ethical Issues

Permission for the research was obtained from the Ethics Committee of Okan University (no:133, date: 17.02.2021). To conduct the study, permission was obtained from the Pediatric Emergency Medicine and Intensive Care Association Board of Directors (on 07.04.2021). Before starting the study, a reminder text containing information about the purpose, target population, data collection, and storage of the research was provided. The online form became available after the approval of the consent form.

Results

Characteristics of the responsible nurses and institutions participated in the study

When the characteristics of the responsible nurses and institutions that participated in the study were investigated, 71.2% of the nurses who answered the questionnaire had a bachelor's degree. Considering the number of patients per nurse in the day/night shift, 47.9% of them were in charge of following two patients at night and two patients during the day, whereas 24.7% of them were following three patients at night and two patients during the day. The titles of the physicians working in the unit were examined as well. The findings revealed that the percentage of units consisting of a physician holding a rank of associate professor or professor was 54.8%, while the percentage of units with a pediatrician was 13.7%. It is determined that 27.4% of them work with one assistant during night shifts and two personnel during day shifts. The average number of nurses working in the PICUs was found to be 25.55±15.75. Considering the number of nurses with certificates in the units, it was observed that an average of 6.14±8.91 nurses had an intensive care nursing certificate, and 4.49±10.17 nurses had a pediatric intensive care nursing certificate (Table 1).

Characteristics of the enteral nutrition applications in the pediatric intensive care units (PICU)

Considering the characteristics of the enteral nutrition practices in the PICUs, 24.7% of them used a written "pediatric

Table 1. Characteristics of health workers and ınstitutions participating in the study

Features	Frequency (n)	Percent (%)
Education status		
High school	2	2.7
Associate degree	3	4.1
Bachelor's degree	52	71.2
Postgraudate	16	21.9
Day/night working time		
8 h during daytime, 16 h during nighttime	57	78.1
10 h during daytime, 14 h during nighttime	4	5.5
12 h during daytime, 12 h during nighttime	4	5.5
Other/24 h	8	11.0
Total number of patients per nurse in day/night shift		
2/2 patien	35	47.9
3/2 patient	18	24.7
3/3 patient	17	23.3
4 or more/3 or more patient	3	4.2
Physicians working in the unit		
Pediatric specialist	10	13.7
Pediatric intensive care specialist	23	31.5
Associate professor and/or professor	40	54.8
Number of patient attendants working in night /day shifts		
1/1 person	13	17.8
1/2 person	20	27.4
1/3 person	7	9.6
2/2 person	11	15.1
2/3 person	12	16.4
3 and more/ 4 and more	10	13.8
The average number of nurses working in units	25.55	15.37
The average number of nurses with intensive care nursing certification	6.14	8.91
The average number of nurses with pediatric intensive care nursing certification	4.49	10.17

enteral nutrition protocol", while 47.9% of the units used the Pediatric Nutrition Risk Assessment Scale. Among the scales used (n=35), 19.2% were Strong Kids Scale, 2.7% were Gomez Scale and 6.8% were Nutritional Risk Score (NRS) 2002. Seventeen point eight percent of them did not specify the name of the scale used. When the target times to initiate enteral nutrition in the PICUs are examined, it was detected that 78.1% of the units had a target time of 24 hours to initiate enteral nutrition after patient admission. Additionally, 42.5% had a target time of within the first 48 hours to reach full energy level. Almost all of the units stated that the gastrointestinal tract (nasogastric/PEG/gastrostomy) was the standard initial feeding route (98.6%). There were 18 units (24.7%) who answered "Yes" to the application of post-pyloric nutrition. 13.7% of these units (n=18) reported that they preferred the post-pyloric route when the gastrointestinal tract could not be tolerated. It was determined that the initially preferred feeding method in the units was mostly intermittent feeding (93.2%). When the criteria used to evaluate feeding tolerance in the units were examined, it was observed that 90.4% of them were based on GRV criteria, 80.8% on increased abdominal pressure criteria, 87.7% on vomiting criteria, 35.6% on diarrhea criteria, and 4.1% on tachypnea criteria. (Table 2).

When enteral feeding practices were evaluated in children placed in the prone position, it was observed that 58.9% of the units fed the children enterally. Twenty-eight of the children on enteral nutrition (n=43,) were fed intermittently. Considering the state of enteral nutrition practice in children with noninvasive ventilation, it was determined that 90.4% of the units provided enteral feeding to children who were on noninvasive ventilation, and 48 of the children (n=66) on enteral feeding were fed intermittently (Table 2).

Gastric residual volume (GRV) measurement in the PICUs and applications for GRV

GRV measurement and applications in the PICUs were examined. The findings revealed that GRV was measured in every patients who routinely started enteral feeding in 61.6% of the units. On the other hand, the findings revealed that in 31.5% of the units, "GRV was measured only in patients with signs of intolerance, which was not routinely checked". GRV measurements were performed "in the assessment of bleeding risk" in 1.4% of the units and "only at the request of a physician" in 5.5% of the units. When the frequency of GRV measurement in intermittently fed patients was examined, it was determined that 50.7% measured before each meal, 13.7% did measurements only if the child vomited, and 11% measured every three hours. Meanwhile, the frequency of GRV measurement in continuously fed patients was studied and the findings demonstrated that 38.4% of them measured only when the child vomited, 13.7% of them measured every 8 hours, and 12.3% of them measured every 4 hours. 57.5% of the units used the expression "no special injector size" for GRV measurement. When the methods used in the decisions to cessation of feeding or skip meals were examined, it was found that the physicians made the decision in 65.8% of the patients, nurses and physicians together made the decision in 16.4% of the patients, and only the nurses made the decision in 12.3% of the patients. Forty-one point one percent of the units used a threshold value or formula to stop feeding according to the amount of GRV. 16.4% reported that the threshold value used was considered as "If GRV is at least half of the previous feeding amount". Considering the method used when evaluating excessive GRV, 4.1% of the units used the maximum volume in mL. In addition, the amount found by the ratio of the amount of last feeding, to the amount of gastric residue was used in 95.9% of the units. It was observed that 52.1% of the units, when questioned about the method of resuming feeding, which had been stopped due to the high GRV amount, provided the answer "Nutrition is gradually increased according to the tolerance status by switching to minimal enteral nutrition" (Table 3).

Discussion

The purpose of feeding the child in the PICUs should include determining the energy needs correctly and providing them appropriately. Nutritional requirements for each child should be determined according to the progression of the disease and individual needs. It is known that adequate nutrition of children in the ICU affects the prognosis positively and reduces the length of hospital stay, highlighting the significance of this issue (4,5,12).

It was determined that only 24.7% of the units enrolled in the study used a written "pediatric enteral nutrition protocol" (Table 2). Similar to this study, Martinez et al. (11) reported that only 9 units in 31 PICUs used an enteral nutrition protocol in an international multicenter cohort study. The low use of the protocol might result in reaching the targets for enteral nutrition taking longer and affect the prognosis of the patient. Petrillo-Albarano et al. (13) concluded that children on enteral nutrition achieved their nutritional goals in a shorter time and improved enteral nutrition tolerance. In the guide published by ASPEN in 2017, it is recommended to prepare protocols in line with current guidelines to perform the most effective enteral nutrition in PICUs (4). As mentioned in the literature,

Table 2. Evaluation and initiation of enteral nutrition needs of units and enteral nutrition applications in special situations		
Features	**Frequency (n)**	**Percent (%)**
Status of using "pediatric enteral nutrition protocol" written in the unit		
Yes	18	24.7
No	55	75.3
Pediatric nutrition risk assessment scale usage status		
Yes	**35**	**47.9**
Strong Kids Scale	14	19.2
Gomez Scale	2	2.7
NRS 2002	5	6.8
Waterlow malnutrition scale	1	1.4
"Yes" was said, but the name of the scale was not specified	13	17.8
No	**38**	**52.1**
Target time to start enteral feeding after patient admission		
Within the first 24 hours	57	78.1
Within the first 48 hours	8	11.0
Within the first 72 hours	3	4.1
Other/varies according to patient's condition	5	6.8
Target time to reach full energy level		
Within the first 24 hours	22	30.1
Within the first 48 hours	31	42.5
Within the first 72 hours	16	21.9
Other/varies according to patient's	4	5.5
First preferred enteral feeding route as standard		
Gastrointestinal tract (nasogastric/PEG/gastrostomy)	72	98.6
Postpyloric tract (duodenal/jejunal)	1	1.4
Post-pyloric feeding application		
Yes	**18**	**24.7**
In cases where the gastrointestinal tract cannot be tolerated	10	13.7
In case of stomach/intestinal surgical operation	3	4.1
In chronic patients who need to receive nutritional support for a long time (home care)	3	4.1
In the presence of a pre-existing jejunostomy in the patient	1	1.4
In patients who are applied continuous feeding method	1	1.4
No	**55**	**75.3**
First preferred enteral feeding method as standard		
Intermittent feeding	68	93.2
Continuous feding	4	5.5
Depends on the patient	1	1.4
Standard feeding frequency		
2 hours apart (12 x feeding)	1	1.4
3 hours apart (8 x feeding)	48	65.8
4 hours apart (6 x feeding)	13	17.8
For 20 hours	1	1.4
For 24 hours	1	1.4
Depends on age/patient	8	11.0
Criteria used to assess enteral feeding tolerance*		
Gastric residual volume	66	90.4
Abdominal pressure increase	59	80.8
Vomiting	64	87.7
Diarrhea	26	35.6
Tachypnea	3	4.1

Table 2. Continued		
Features	**Frequency (n)**	**Percent (%)**
Enteral nutrition application status in children given prone position		
Yes, feeding	**43**	**58.9**
No special feeding method is preferred Intermittent feeding Continuous feeding	9 28 6	12.3 38.4 8.2
No, not feeding	28	38.4
Other/Prone position not used at all	2	2.7
The state of applying enteral nutrition in children undergoing non-invasive ventilation		
Yes, feeding	**66**	**90.4**
No special feeding method is preferred Intermittent feeding Continuous feeding	11 48 4	15.1 65.8 5.5
No, not feeding	**7**	**9.6**

maintaining nutrition in accordance with the protocols of ICUs is a critical parameter that will positively affect the general condition of the patient.

Most of the units (78.1%) participating in the study declared that the target time to start enteral nutrition after patient admission is the first 24 hours. In addition, 98.6% of the units stated that the preferred enteral feeding route is the gastrointestinal route (Table 2). ASPEN's 2017 guideline has reported that enteral nutrition should be initiated in critically ill children within the first 24 to 48 hours after admission, and the gastrointestinal route is the first choice (4). In ESPNIC's 2020 guideline, it is recommended to start enteral nutrition within the first 24 hours after admission of critically ill children to the ICU, if there are no contraindications (12). It is noteworthy that the information taken into consideration and applied by units about enteral nutrition, as described in this study, is in accordance with the recommendations of significant guides listed in the literature.

Three-quarters (75.3%) of the units included in this study did not use the post-pyloric alimentary tract. The units that did use it indicated that they did so "in cases where the gastrointestinal tract could not be tolerated" (Table 2). This result is in line with the guidelines of ASPEN (2017).

When the participants were asked about the enteral nutrition method, which is the first choice as a standard in the unit, 68 units stated that they prefer intermittent feeding, 4 units use continuous feeding, and 1 unit indicated that the feeding style could change depending on the patient's condition (Table 2). In a study investigating enteral nutrition practices in the PICUs of England, it was reported that more than half of the PICUs used continuous feeding, which differs from our findings (9). Campos-Miño et al. (14) identified that the continuous feeding method, with a rate of 57.4%, was used more than the intermittent method, similar to the results of the study in England. When different studies are examined, the continuous feeding method is applied more frequently in most of the PICUs around the world (15,16). Recent findings indicate that intermittent feeding is preferred in PICUs since intermittent feeding is closer to the natural feeding rhythm that the body is accustomed to, and the fasting period experienced during intermittent feeding is more beneficial for body metabolism (16). Therefore, this method has been preferred in recent years. In addition, studies comparing intermittent and continuous feeding methods in the past indicated that the bolus method was generally used as the intermittent method, which may adversely affect the results. Since the concept of intermittent feeding has developed further cyclical and bolus feeding methods, it encompasses a wider range than the concept of continuous feeding. It is thought that the intermittent feeding method might, therefore, be preferred more frequently in our country.

When the criteria used by the units that participated in this study to evaluate the tolerance of enteral nutrition were questioned, the primary criterion identified for feeding intolerance was the amount of GRV with 90.4%, which was then followed by vomiting with 87.7%, increased abdominal pressure with 80.8%, and diarrhea with 35.6% (Table 2). Martinez et al. (17) defined nutritional intolerance in their study in a manner similar to the criteria used in our research. In a study by Tume et al. (9), the frequency of the criteria used to define nutritional intolerance was 100% GRV, 67% vomiting, 50% diarrhea, and 44% increased abdominal pressure. Compared to our results, the 10% difference for the GRV criterion, which ranks first, may suggest that this criterion could

Table 3. Gastric residual volume (GRV) measurement and applications for GRV		
Features	**Frequency (n)**	**Percent (%)**
GRV measurement status		
It is measured in every patient who is routinely started on enteral feeding	45	61.6
It is measured only in patients with signs/signs of intolerance and not routinely checked	23	31.5
Measured in bleeding risk assessment	1	1.4
Only at the request of a physician	4	5.5
When the frequency of GRV measurement in intermittent fed patients was		
Before each feeding meal	37	50.7
3 hours apart	8	11.0
4 hours apart	3	4.1
6 hours apart	1	1.4
Once per shift	7	9.6
Only if the child is vomiting	10	13.7
Other/ only at the request of a physician/ situations that pose a risk to the child	7	9.6
Frequency of GRV measurement in continuously fed patients		
3 hours apart	5	6.8
4 hours apart	9	12.3
6 hours apart	8	11.0
8 hours apart	10	13.7
1 time in 24 hours	4	5.5
2 times in 24 hours	3	4.1
Only if the child is vomiting	28	38.4
Other/ this method is not applicable/ only at the request of a physician	6	8.2
Does the injector used in GRV measurement have a certain size?		
Yes	31	42.5
No	42	57.5
Methods used in decisions to stop feeding or skip meals		
In this regard, it is acted in accordance with the written procedure	4	5.5
Nurses decide	9	12.3
Physicians decide	48	65.8
Other/ doctor and nurse decide together	12	16.4
Threshold value or formula used for cessation of feeding according to the amount of GRV		
Yes	**30**	**41.1**
If GRV is at least half of the previous feeding amount	12	16.4
If GRV appears to be at least 1/3 of the previous feeding consumption	9	12.3
If GRV is equal to or more than the previous feeding amount	1	1.4
If you have a GRV of 400 mL or more	1	1.4
Threshold value or formula not specified even though yes is said	7	9.6
No	**43**	**58.9**
Method used when evaluating whether the amount of GRV is excessive		
Maximum volume in “mL”	3	4.1
Ratio of last feeding amount and gastric residue amount	70	95.9
The method of resumption of feeding, which was stopped due to the high amount of GRV		
Nutrition is gradually increased according to the tolerance status by switching to minimal enteral nutrition	38	52.1
In the first 24 hours, feeding is started with low amounts and gradually increased according to the tolerance status	35	47.9

be gradually excluded, as it raises the question of whether GRV measurement is necessary.

In this study, it was observed that only 58.9% of critically ill children placed in the prone position could be fed enterally (Table 2). In critically ill patients placed in the prone position, there is concern that the endotracheal tubes, venous access lines, and nasogastric tubes might be inadvertently displaced or removed. In addition, since the body is in a flatter plane, this position is believed to increase the risk of nutritional complications due to high pressure in the abdominal region and the use of high-dose sedation and paralytic agents. However, Savio et al. (18) claimed that there was no difference between the supine and prone positions in terms of enteral feeding intolerance. Furthermore, Sangers et al. (19) concluded that the amount of GRV was higher in the supine position, compared to the prone position, in a prospective observational study with 147 newborn babies.

The use of non-invasive ventilation (NIV) in PICUs has increased significantly in recent years (20). Although the use of NIV causes a decrease in the intubation process in critically ill patients, it may cause delays in initiating enteral nutrition. During NIV application, administering positive pressure to the mouth and nostrils to allow entry of air into respiratory and gastrointestinal systems may contribute to complications such as increased abdominal pressure and vomiting. Furthermore, the sedation used during NIV administration might increase the risk of aspiration by weakening airway protective reflexes (21). Enteral nutrition was applied during NIV in 90.4% of the units included in this study (Table 2). Kogo et al. (22) compared the mortality of two groups of patients who received NIV: those in whom enteral feeding was initiated and those in whom it was not. It was reported that there was no significant difference in mortality between the two groups. Although there was a risk of enteral feeding complications during NIV administration, enteral feeding could be initiated if undertaken with caution (22). Tume et al. (23) found that enteral nutrition was applied to 80% of the critically ill children who received NIV, with a very low pulmonary aspiration rate of 1.5%.

In 61.6% of the units included in the study, it was detected that the GRV was "measured in every patient who routinely started enteral nutrition", whereas in 31.5% of the units it was "measured only in patients with signs of intolerance, which were not routinely checked" (Table 3). Tume et al. (9) reported that GRV was routinely measured in units at a much higher rate (96%) than our study. This difference might be related to the recent discussions on the necessity of GRV measurements and the fact that the study published before 2020 stated that GRV was measured routinely in almost all cases. In addition, the "not recommending routine GRV measurement in critically ill children" principle in the ESPNIC12 guideline was published in 2020.

When the frequency of GRV measurement was questioned in the units using intermittent and continuous feeding methods and those participating in the study, the most common answer was "before each meal" (50.7%), which was followed by "only if the child vomits" (13.7%). In the cases that use the continuous feeding method, 38.4% answered "only if the child vomits", which was followed by "8 hours apart" with 13.7%, and "4 hours apart" with 12.3% (Table 3). In their study with newborn babies, Dorling et al. (10) demonstrated that the frequency of GRV measurement in intermittent feeding method was "at regular intervals of 4-6 hours" with a rate of 43.3%, "in the presence of clinical indications" with 28.9% and "every feeding" with a rate of 22.2%. The findings are similar to the findings of our study; however, the answer "before each nutritional meal", was in third place. In the study conducted in England, it was found that 75% of both intermittent and continuous feeding methods were controlled "with an interval of 4 hours", unlike our research (9) In our study, a high rate of GRV measurements "only if the child vomits" in children who are fed continuously was interpreted as an indication that no routine measurement has been made in recent years, due to the recent approach of GRV measurement, and the current recommendations of the guidelines (ESPNIC, 2020).

When the decisions to stop feeding or skip meals due to high GRV were questioned, it was observed that 65.8% were made by the physicians, 16.4% were made by a physician and a nurse together, 12.3% were made by the nurses, and the written protocols were applied to 5.5% (Table 3). Dorling et al. (10) reported that the first decision regarding the GRV content was made by the "nurse in charge of the patient's care", the "specialist physician" in the second place, and the "senior nurse in charge of the shift" in the third place. Although the results of the study seemed similar to our research, it is also important to note that nurses in our country are not effective enough in decision-making.

When the units participating in this study were asked whether there was a threshold value or a formula used for cessation of feeding according to the amount of GRV, 43 (58.9%) of the units stated that they did not use a threshold value or formula, while the remaining 30 units (41.1%) stated that they did. 12 of the units stated "if at least half of the previous feeding amount has GRV", 9 of them stated "if at least 1/3 of the previous feeding amount has GRV", and 7

of them stated that "the content was not written even though it was stated that the threshold value or formula was being used" (Table 3). In their study, Tume et al. (9) questioned the GRV threshold value; the findings were "5mL/kg and more GRV", "10mL/kg and more GRV", "Total volume taken in 2/4/6 hours and more GRV", and "At least 50% of the previous 4-hour feeding amount and more GRV", in descending order of findings. In this study, it was observed that although most of the units measured GRV, they did not use the threshold value or formula required to make the decision to stop feeding, and those who stated that they used the threshold value or formula used widely varying values. This situation shows that there is no common definition of high GRV in our country, and each institution follows a different approach.

In case of questioning the method used when evaluating whether the amount of GRV was high, it was observed that 95.9% of the participants used "the ratio of the last nutrition amount and the amount of GRV", while the remaining 4.1% unit used the "maximum volume in mL" method (Table 3). In the study conducted in a PICU in England, the answers were "maximum volume in mL/kg body weight" and "percentage of maximum volume of the applied amount", respectively (9) The high GRV amount in our study was calculated based on the last feeding amount, instead of taking the child's weight into account, unlike this research.

Study Limitations

Not all PICUs in Türkiye could be reached. This research was carried out with the nurses in charge of the PICU and may not reflect the approaches and practices of other nurses working in the unit. It has been determined based on the self-reports/statements of the participants who use the nutrition protocol in the units and cannot be presented as definitive information on the nature of the protocols.

Conclusion

In conclusion, it was determined that routine GRV control in enterally fed patients was frequently performed in PICUs, with 61.6% of the units using it routinely and 31.5% in case of intolerance. It was found that the initially preferred route of the units was the intermittent gastric method of enteral feeding. The use of written enteral nutrition protocols in the PICU was insufficient (24.7%).

In accordance with these results, the use of enteral nutrition protocols in the PICUs should be encouraged. Institutional protocols should be developed and intensive care workers should be informed through in-service training. To maintain enteral nutrition more effectively, in the PICUs, it might be recommended to establish "nutrition support teams" at the institutional level and to determine evidence-based best practices in enteral nutrition by conducting randomized controlled studies.

Ethics

Ethics Committee Approval: Permission for the research was obtained from the Ethics Committee of Okan University (no:133, date: 17.02.2021).

Informed Consent: The online form became available after the approval of the consent form.

Footnotes

Authorship Contributions

Concept: T.Y., D.S.D., Design: T.Y., D.S.D., Data Collection or Processing: T.Y., Analysis or Interpretation: D.S.D., G.U., Literature Search: T.Y., D.S.D., G.U., Writing: T.Y., D.S.D., G.U.

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