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Critically Ill Obstetric Patients in Intensive Care Unit: A Single-center Ten-year Retrospective Cohort Study

Yoğun Bakım Ünitesindeki Kritik Obstetrik Hastalar: Tek Merkezli On Yıllık Geriye Dönük Kohort Çalışması

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Abstract

Objective: In critically ill obstetric patients (COPs), an exacerbation of both a pre-pregnancy disease and newly emerging additional diseases during and after pregnancy may occur. There are limited data on intensive care unit (ICU) follow-up of COPs in literature. The aim of this retrospective study was to evaluate the COPs that we have followed in ICU in the last 10 years, to investigate the frequency and the reasons of admission to the ICU, and the factors affecting outcomes and mortality.

Method: This study was planned retrospectively on COPs who were followed up in the ICU of University of Health Sciences Turkey, İstanbul Bağcılar Training and Research Hospital between 2011 and 2021.

Results: A total of 220 patients aged 18-50 years, who were diagnosed as COPs, were included in the study. The most frequent admission type to the ICU was after caesarian section (n=129, 58.6%) and the most frequent indication was obstetric hemorrhage (n=56, 25.4%). The average length of stay in the ICU was 2 days (3.5±4), the average length of hospitalization was 6 days (9.1±7.9), the rate of discharge from the ICU was 95.5%, and mortality rate was 4.5%. Gestational age was lower (p<0.05) and first 24 hours acute physiological and chronic health evaluation II and sequential organ failure assessment scores were found significantly higher in the mortal cases (p<0.001).

Conclusion: The most frequent admission type to ICU was due to cesarean section (n=129, 58.6%) and the most common indication for admission was obstetric hemorrhage (n=56, 25.4%). Mortality rate was determined as 4.5%. In COPs, we should be prepared for complications that may arise, and these patients should be followed up and treated appropriately.

Keywords: Critically ill obstetric patient, intensive care unit, maternal mortality

Öz

Amaç: Kritik obstetrik hastalarda (KOPs) hem gebelik öncesi var olan bir hastalığın hem de gebeliğin kendisi ve sonrasında yeni ortaya çıkan ek hastalıkların şiddetlenmesi söz konusudur. Literatürde KOPs'nin takibine yönelik sınırlı sayıda veri bulunmaktadır. Bu çalışmanın amacı yoğun bakım ünitemizde son 10 yılda takip ettiğimiz KOPS'nin retrospektif taranması ile yoğun bakım ünitesine (YBÜ) kabul sıklığı, nedenleri, sonuçları ve mortaliteye etki eden faktörleri araştırmaktır.

Yöntem: Çalışmamız Sağlık Bilimleri Üniversitesi, İstanbul Bağcılar Eğitim ve Araştırma Hastanesi YBÜ'de 2011-2021 tarihleri arasında yatan KOPs üzerinde retrospektif olarak planlandı.

Bulgular: KOPs tanısı alan 18-50 yaş arası 220 hastanın bilgileri çalışmaya dahil edildi. YBÜ'ye hasta kabulü sebebi en sık sezaryen (n=129, %58,6), en sık kabul endikasyonu ise kanama idi (n=56, %25,4). YBÜ yatış süresi ortalama 2 (3,5±4) gün, hastanede yatış süresi ise 6 (9,1±7,9) gün olup, YBÜ'den taburculuk oranı %94,5, mortalite oranı %4,5 olarak tespit edildi. Mortalite görülen hastalarda gestasyonel yaş daha düşük (p<0,05), ilk 24 saat akut fizyoloji ve kronik sağlık değerlendirmesi II skoru, ardışık organ yetmezliği değerlendirme skoru anlamlı olarak daha yüksek bulundu (p<0,001).

Sonuç: YBÜ'ye hasta kabulü en sık sezaryen (n=129, %58,6) sebebiyle; en sık kabul endikasyonu ise obstetrik kanama idi (n=56, % 25,4). Mortalite oranı %4,5 olarak tespit edildi. KOPs ortaya çıkabilecek komplikasyonlara karşı hazırlıklı olunmalı ve bu hastaların takip ve tedavileri uygun şekilde yapılmalıdır.

Anahtar kelimeler: Kritik obstetrik hasta, maternal mortalite, yoğun bakım

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Introduction

Critically ill obstetric patients (COPs) usually consist of young and healthy individuals. In this patient population, an exacerbation of both a pre-pregnancy disease and newly emerging additional diseases during and after pregnancy may occur. In addition, as a result of the complications associated with the applied procedures, a series of events that may result in the death of the mother and the baby can be observed (1,2).

The third of the Millennium Development Goals determined by the United Nations has been determined as reducing the maternal mortality rate in the world (3). According to the 2018 report of the World Health Organization, while the maternal mortality rate was 239/100.000 births in developing countries, it was 12/100.000 births in developed countries (4). According to the data published by the Ministry of Health of the Republic of Turkey in 2019, the maternal mortality rate was 13.1/100.000 live births (5). When maternal mortality rates are examined, it is found that most of them are due to obstetric causes and can be prevented with a quality care. In order to protect maternal and infant health, it is important to detect obstetric problems at the earliest stage and to apply the appropriate intervention as quickly as possible (6).

In the literature, the rate for admission to intensive care unit (ICU) varies between 0.7% and 16%, depending on the level of development (7-10). COPs admitted to the ICU may exacerbate due to both a pre-pregnancy disease and a new comorbidity during and after pregnancy (11). Most of the COPs (75%) are admitted to the ICU, usually due to postpartum complications (12).

In our country, the number of studies on COPs followed in the ICU, explaining maternal mortality and morbidity, is limited and these studies reported low mortality rates (13). The aim of this study is to evaluate the COPs we have followed in our ICU in the last 10 years, to investigate the causes and consequences of admission to ICU and the factors affecting mortality and morbidity retrospectively. These data, which we presented in our study, are important in terms of increasing scientific awareness and for expectant mothers to get the necessary follow-up and treatment before they become COPs.

Materials and Methods

This retrospective study was planned in patients followed up for obstetric reasons in University of Health Sciences Turkey, İstanbul Bağcılar Training and Research Hospital ICU between 2011 and 2021, after getting approval from University of Health Sciences Turkey, İstanbul Prof. Dr. Cemil Taşcıoğlu City Hospital Clinical Research Ethics Committee, dated 19.04.2021 and numbered 169.

COPs aged 18 years and older, who were treated in the ICU for at least 24 hours, were retrospectively included in the study. Patients who were under the age of 18 years, who had a length of stay in the ICU for less than 24 hours, and who were admitted to the ICU for the second time after discharge were excluded from the study. Demographic characteristics of the patients, maternal age (years), gestational age (weeks), first 24 hours acute physiological and chronic health evaluation (APACHE) II score, sequential organ failure assessment (SOFA) score, duration of mechanical ventilation (days), length of ICU stay (days), length of hospital stay (days) and ICU outcome were recorded. The number of discharged patients and patients who developed mortality in the ICU were recorded. The type of admission to the ICU, e.g. after caesarean section, being transferred from other hospitals or from Obstetrics Clinic of hospital, was reported. Specific interventional procedures in the ICU, invasive mechanical ventilation (IMV) and non-invasive mechanical ventilation (NIMV), high-flow nasal oxygenation (HFNO), oxygen requirement by mask, need for intubation or tracheotomy, need for plasmapheresis, need for renal replacement therapy, vasoactive agent use, nosocomial infections encountered 48 hours after ICU admission and up to day 10, and the localizations of infection were evaluated. Maternal age, gestational age, APACHE II and SOFA scores of surviving and mortal patients were compared and their effects on mortality were investigated. Univariate and multivariate logistic regression analyses were performed to evaluate mortality in patients.

Statistical Analysis

In the descriptive statistics of the data, mean, standard deviation, median, minimum, maximum, frequency, and ratio values were used. The distribution of variables was assessed with the Kolmogorov-Smirnov test, and the Mann-Whitney U test was used to analyze quantitative independent data. A univariate model was used to find the level of effect on mortality, and a multivariate model logistic analysis was used to find the independent factors that were effective. All statistical analyses were conducted by using SPSS 27.0 program (IBM, USA).

Results

All data of 220 COPs followed up in the ICU of hospital were evaluated in ten years. The distribution of patients

according to the years in our study was 2011 (n=15), 2012 (n=16), 2013 (n=14), 2014 (n=16), 2015 (n=15), 2016 (n=28), 2017 (n=28), 2018 (n=60), 2019 (n=6), 2020 (n=10), and 2021 (n=12).

Demographic and clinical characteristics of the patients were indicated in Table 1. The mean maternal age was 30 (30.7±8.1) years, the mean gestational age was 32 (31.5±3.1) weeks, the median APACHE II score was 16 (5-35), and the median SOFA scores was 2 (0-16). On the other hand, the mean duration of IMV was 1 (2.2±2.9) days, the mean duration of ICU stay was 2 (3.5±4) days; and the mean duration of hospitalization was 6 (9.1±7.9) days. The discharge rate from the ICU was found as 95.5% (n=210), and the mortality rate was 4.5% (Table 1).

Mortality was higher in patients with lower gestational age [30 (29.5±4.18)] compared to those with higher gestational age [32 (31.6±2.98)] ($p<0.05$), and mortality was also higher in patients with higher APACHE II scores [28 (25-35)] and SOFA scores [13 (9-16)] than in those with lower APACHE II [15 (5-35)] and SOFA scores [2 (0-2)] ($p<0.001$). Comparison of the surviving patients and patients with mortality in terms of maternal age, gestational age and APACHE II and SOFA scores are presented in Table 2.

Logistic regression analysis showed that gestational age, APACHE II and SOFA scores were significantly correlated with mortality ($p<0.05$) ($p<0.001$) (Table 3).

Table 1. Demographic and clinical variables

		Min-max	Median	Mean ± SD/n-%
Maternal age (year)		18-50	30	30.7±8.1
Gestation weeks		20-36	32	31.5±3.1
APACHE II score		5-35	16	-
SOFA score		0-16	2	-
Length of mechanical ventilation (days)		1-2	1	2.2±2.9
Length of ICU stay (days)		2-3	2	3.5±4.0
Length of hospital stay (days)		4-10	6	9.1±7.9
ICU outcome (n%)				210/95.5
The reasons for mortality (n%)	Mortality			10/4.5%
	Septic shock			4/1.8%
	CSD			3/1.35%
	DIC			2/0.9%
	Preeclampsia/ eclampsia			1/0.45%

APACHE II: Acute physiology and chronic health evaluation score, SOFA: Sequential organ failure assessment score, ICU: Intensive care unit, MOF: Multiple organ failure, CSD: Cardiovascular system diseases, DIC: Disseminated intravascular coagulation, SD: Standard deviation

The most common type of admission was after caesarean section (n=129; 58.6%). Twenty eight patients (12.7%) were transferred from other hospitals and 63 (28.7%) were transferred from obstetrics clinic of our hospital. The ICU indications were obstetric hemorrhage in 56 patients (25.4%), preeclampsia/eclampsia in 42 patients (19.1%), atypical hemolytic uremic syndrome (HUS) in 31 patients (14.1%), hemolysis elevated liver enzymes low platelet syndrome in 21 patients (9.5%), septicemia in 20 patients (9.1%), shock due to ectopic pregnancy rupture in 16 patients (7.3%), cardiovascular system diseases in 14 patients (6.3%), pulmonary embolism in 7 patients (3.2%), neurological system diseases in 6 patients (2.7%), pneumonia in 5 patients (2.3%), disseminated intravascular coagulation (DIC) in 1 patient (0.45%), and diabetic ketoacidosis in 1 patient (0.45%). Pregnant and COPs with a diagnosis of Coronavirus disease-2019 (COVID-19) were not followed up in our ICU (Table 4).

A total of 131 (59.4%) patients were supported by mechanical ventilation. IMV was performed in 120 patients (54.5%). One hundred eighteen patients (53.6%) were intubated due to respiratory failure and hemodynamic instability. These causes were determined as atonic obstetric hemorrhage, septicemia, HUS, respiratory, neurological and cardiovascular system diseases. Two patients (0.9%)

Table 2. Comparison of patients with mortality and patients who were discharged in terms of their demographic and clinical parameters [data are mean ± SD/median (min-max)]

	Mortality	Discharged	p
Maternal age (year)	30 (31.00±5.83)	30 (30.71±8.16)	0.909[m]
Gestation week	29.55±4.18	31.63±2.98	**0.034**[m]
APACHE II score	28 (25-35)	15 (5-35)	**<0.001**[m]
SOFA score	13 (9-16)	2 (0-9)	**<0.001**[m]

APACHE II: Acute physiology and chronic health evaluation score, SOFA: Sequential organ failure assessment score. [m]Maternal age and gestational week: Mean ± SD, scores were median (min-max), SD: Standard deviation

Table 3. Regression analysis of the factors affecting mortality

	Univariate model			Multivariate model		
	OR	**95% CI**	**p**	**OR**	**95% CI**	**p**
Maternal age	1.00	0.93-1.08	0.908[LR]	0.90	7.02-1.17	0.467[LR]
Gestational age	0.84	0.71-0.98	**0.034**[LR]	0.79	4.74-1.33	0.385[LR]
APACHE II	1.35	1.18-1.54	**<0.001**[LR]	0.78	5.53-1.11	0.181[LR]
SOFA	2.24	1.54-3.28	**<0.001**[LR]	3.47	1.40-8.60	**0.007**[LR]

APACHE II: Acute physiology and chronic health evaluation score, SOFA: Sequential organ failure assessment score, CI: Confidence interval, OR: Odds ratio, [LR]: Lojistic regresyon (forward LR)

Table 4. Diagnosis at the admission and indication to the ICU over the 10-year period (n, %)

Admission type	**n**	**(%)**
After caesarian section	129	58.6
Transferred from other hospitals	28	12.7
From obstetrics clinic of our hospital	63	28.7
ICU indication	**n**	**(%)**
Obstetric hemorrhage	56	25.4
Preeclampsia/eclampsia	42	19.1
Atypical hemolytic uremic syndrome	31	14.1
HELLP syndrome	21	9.5
Sepsis	20	9.1
Ectopic pregnancy rupture	16	7.3
Cardiovascular system diseases	14	6.4
Pulmonary embolism	7	3.2
Neurologic system diseases	6	2.7
Pneumonia	5	2.3
DIC	1	0.45
Diabetic ketoacidosis	1	0.45
Other	0	0.0

HELLP: Hemolysis, elevated liver enzymes low platelet syndrome, DIC: Disseminated intravascular coagulation, ICU: Intensive care unit

Table 5. Specific interventions performed at the ICU (n, %)

	Number of patients	
	(n)	**(%)**
Mechanical ventilation	131	59.5%
Non-invasive mechanical ventilation	11	5.0%
Invasive mechanical ventilation	120	54.5%
High flow nasal oxygen	15	6.80%
Mask	74	33.7%
Intubated	118	53.6%
Tracheostomy	2	0.90%
Plasmapheresis	8	3.6%
Renal replacement therapy (continuous hemofiltration)	32	14.5%
Vasoactive agent use	61	27.7%
Blood transfusion	151	68.6%
Whole blood	68	31.0%
Fresh frozen plasma	110	50.0%
Platelet suspension	62	28.2%
Erythrocyte suspension	139	63.2%
Fibrinogen	40	18.1%

ICU: Intensive care unit

underwent tracheostomy due to prolonged mechanical ventilation. On the other hand, 11 (5.0%) received NIMV support. Fifteen (6.81%) patients required HFNO and 74 (33.6%) patients received oxygen support via face mask.

Plasmapheresis was applied to 8 (3.63%) patients due to atypical HUS. Continuous renal replacement therapy was applied to 32 (14.5%) patients who developed acute renal failure (ARF) and were hemodynamically unstable. Vasoactive agent was used in patients (n=61, 27.7%) to provide hemodynamic stabilization. Totally 151 blood and protects transfusion were performed. One hundred thirty nine units of erythrocyte suspension (ES), 110 units of fresh frozen plasma (FFP), 68 units of whole blood, 62 units of platelet suspension, and 40 flacon fibrinogen were transfused (Table 5).

Nosocomial infections were observed at a rate of 20% in COPs. Most commonly, the infection was localized in genitourinary system (52.3%) and that was followed by soft tissue (22.7%), deep tracheal aspirate (18.2%) and systemic circulatory tract (6.8%). The microbiological analyses revealed the most common infectious agents as *Escherichia coli* (27.3%), *Klebsiella pneumonia* (20.4%), and *Acinetobacter baumanii* (18.2%) (Table 6).

Table 6. Infection data of patients (n, %)

	(n)	**(%)**
Infection occurring after 48 hours	44	20.0
Localizations of infection		
Urine	23	52.3
Soft tissue	10	22.7
Deep tracheal aspiration	8	18.2
Blood	3	6.8
Microorganism		
Escherichia coli	12	27.3
Klebsiella pneumoniae	9	20.4
Acinetobacter baumannii	8	18.2
Candida albicans	7	15.9
Klebsiella oxytoca	2	4.5
Staphylococcus aureus	2	4.5
Proteus mirabilis	1	2.3
Pseudomonas aeruginosa	1	2.3
Staphylococcus agalactiae	1	2.3
Staphylococcus epidermis	1	2.3

Discussion

The mean maternal age of 220 COPs followed in our multidisciplinary ICU was found as 30 (30.7±8.1) years, and the mean gestational age was 32 (31.5±3.1) weeks. The mean gestational and maternal ages of the survival and mortality patients in our study were higher when compared

to the study of Demirkiran et al. (14). It was similar to the study of Dirik et al. (1). The rate of discharge or mortality was similar to that in the studies of Dirik et al. (1), Tezcan Keleş et al. (2) and Demirkiran et al. (14). The reasons for maternal mortality, which were more common in young mother population in our study, may be lack of follow-up, being inexperienced in pregnancy, and presence of a serious disease.

Complications occurring during emergency cesarean section are the most important reasons for hospitalization in the ICU in the perioperative and postoperative period. Consistent with other studies, most of our patients were admitted from the operating room. It has been reported in various studies that patients were transferred to further centers for further follow-up and surgical intervention (9,15). Similarly, 12.7% of the patients who were admitted to the ICU constitute the group of patients referred from other hospitals for further examination and treatment. Although the number of studies on critical COPs is limited, studies have found a correlation between transfer from another hospital and mortality (16-19). In our study, all 220 patients whose follow-up and treatment processes were completed were discharged to the obstetrics clinic of our hospital. No patient was transferred to another center.

Mechanical ventilation support is needed mostly due to pregnancy-related complications (20). Like our results, in the literature, the need for mechanical ventilation support has been reported between 19% and 60%, (8,19,21). In the studies conducted by Tripathi et al. (22) and Togal et al. (23), this rate was 64-85% and was higher than that in our study. The duration of mechanical ventilation of obstetric patients was reported as 3.8±3.5 days in the study conducted by Tezcan Keleş et al. (2) and 4.9 days in the study conducted by Dirik et al. (1). In our study, the mean duration of mechanical ventilation was 1 (2.2±2.9) days. The reason for this was that the weaning processes of the patients were preferred to be performed after their transfer to the ICU rather than in the operating room due to perioperative hemodynamic instability. The mean length of stay in ICU was 4.4 days in the study conducted by Platteau et al. (24), 8 days in the study conducted by Demirkiran et al. (14), 7 days in the study conducted by Togal et al. (23) and 6 days in the study conducted by Dirik et al. (1), while it was 2 (3.5±4) days in our study.

In COPs, prognosis can be predicted by using the APACHE II scoring system (25). Lapinsky et al. (26) defended the opposite of this view in their study (9). In our study, the median APACHE II and SOFA scores were found to be higher in non-survived patients, similar to the studies of Dirik et al. (1) ($p<0.001$). In addition, SOFA score was determined as the only independent factor among the risk factors affecting mortality, similar to the study of Dirik et al. (1) ($p<0.05$).

In COPs, the mortality rate changes between 5% and 27%; however, it has been stated that the causes of mortality include hypertensive diseases (eclampsia and severe preeclampsia), obstetric hemorrhages, sepsis, amniotic fluid embolism, and DIC (27,28). Moreover, inadequate antenatal care significantly increases the risk of pregnancy-related death (29). Hypertensive diseases and obstetric hemorrhages are the two most common obstetric causes requiring ICU (30-32). These three reasons for admission differ due to geography, race, socio-economic status, environmental factors, and different surgical techniques performed (33). Eclampsia is the major cause of maternal mortality in developing countries (34). Demirkiran et al. (14) reported in their study that 73.6% of COPs were admitted due to eclampsia and 11.2% of them due to hemorrhage. Tezcan Keleş et al. (2), on the other hand, reported that COPs were admitted most frequently because of hypertensive diseases (38.7%). Akköz Çevik (28) reported that the major reason for admission to the ICU was obstetric hemorrhages (57%). Ülger et al. (35) reported that the most common reason for admission to the ICU was postpartum hemorrhage (31%) and that was followed by preeclampsia/eclampsia (26%). In the study of Arıcı et al. (27), 46% of the patients had postpartum hemorrhage and 5% of the patients had preeclampsia/eclampsia while Singh et al. (36) reported that 43% of the patients admitted had postpartum bleeding and 31% of the patients had preeclampsia/eclampsia. Our results, similar to all these studies, showed that 25.4% of the patients admitted had obstetric hemorrhage and 19.1% of the patients admitted had preeclampsia/eclampsia.

COVID-19 patients were followed up in our ICU and hospital clinical services between March 15, 2019 and April 20, 2021. Since there was no indication to our ICU between these dates, no obstetric patient with a diagnosis of COVID-19 was hospitalized. A limited number of COPs were admitted to our ICU postoperatively and from the emergency department. For this reason, the number of COPs decreased at the time of our study.

Infection and sepsis are among the important causes of maternal mortality in COPs and this rate has increased within the last 10 years (37,38). The main cause of maternal sepsis is genitourinary infections due to curettage (39).

Group A Streptococcus, staphylococcus, Escherichia coli, anaerobic bacteria and *Candida* are the most common microorganisms causing infections (10). Shields et al. (39) reported an ICU admission rate of 38% with a diagnosis of sepsis. Hedriana et al. (40) reported an ICU admission rate of 24%, Wanderer et al. (31) reported an ICU admission rate of 7.1% and Pollock et al. (7) reported an ICU admission rate of 5.0% due to sepsis. Our ICU acceptance rate due to maternal sepsis was 9.1%. Genitourinary infection was the most common reason for nosocomial infection with a rate of 52.3%. The most common microorganism causing the infection was *Escherichia coli* with a rate of 27.3%, in our study.

Hemorrhage is a common complication in pregnancy and is still almost the most frequent cause of maternal mortality (9,14,41). The rate of hospitalization in the ICU due to pregnancy-related hemorrhage varies significantly. Limited number of studies in the literature reported precise values for blood loss (14). In our study, 56 patients (25.4%) were hospitalized in the ICU due to obstetric hemorrhage and 16 patients (7.6%) were hospitalized due to early uterine rupture. We transfused ES, FFP, platelet, fibrinogen and whole blood, when necessary, and all patients treated for hemorrhage were discharged, except 2 patients who died because of DIC. The mortality of the women due to bleeding during or after childbirth is largely due to their inability to access adequate obstetric care on time (42). Concomitant hemorrhage treatment and the strategy of using blood products are extremely important.

ARF, preeclampsia-eclampsia, postpartum hemorrhage, sepsis, and atypical HUS are frequently seen in obstetric patients due to secondary renal and systemic alterations (33,43). Although its incidence is low, it can be a major cause of morbidity and mortality. Özçelik et al. (13) and Jonard et al. (43) performed dialysis on 14.6% and 29% postpartum patients, respectively. Özçelik et al. (13) reported that plasmapheresis was performed in 21 patients (43.8%) in the postpartum period, and Zhao et al. (37) performed plasmapheresis in 17 patients (3.46%). Like Zhao's study, 3.6% patients received plasmapheresis treatment due to atypical HUS in our ICU.

Study Limitations

The major limitation of our study was its retrospective design. Some of the patient data could not be reached due to insufficient medical records. Another limitation is that it is a single-center study.

Conclusion

This study investigated the way and reasons for admission of COP patients to the ICU and the invasive procedures applied. Our retrospective data showed our mortality rate to be 4.5%. In CPOs, lower gestational age and higher APACHE II and SOFA scores were found to be associated with mortality. There are limited data on the follow-up of COPs in our country. We believe that more studies are needed at the national level in order to determine the factors affecting mortality and morbidity better in this specific patient group.

Ethics

Ethics Committee Approval: This retrospective study was planned in patients followed up for obstetric reasons in University of Health Sciences Turkey, İstanbul Bağcılar Training and Research Hospital ICU between 2011 and 2021, after getting approval from University of Health Sciences Turkey, İstanbul Prof. Dr. Cemil Taşcıoğlu City Hospital Clinical Research Ethics Committee, dated 19.04.2021 and numbered 169.

Informed Consent: Informed consent was obtained prior to intensive care admission.

Peer-review: Externally and internally peer-reviewed.

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