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Risk factors for multiorgan failure and mortality in severe sepsis patients who need intensive care unit follow-up

Ece ÖZ¹
Cüneyt SALTÜRK²
Zuhal KARAKURT²
Özlem YAZICIOĞLU MOÇİN²
Nalan ADIGÜZEL²
Gökay GÜNGÖR²
Özkan DEVRAN³
Merih KALAMANOĞLU⁴
Gülbanu HORZUM²
Adnan YILMAZ²

¹ Department of Chest Diseases, Faculty of Medicine, Medeniyet University, Istanbul, Turkey

² İstanbul Medeniyet Üniversitesi Tıp Fakültesi, Göğüs Hastalıkları Anabilim Dalı, İstanbul, Türkiye

³ Medical Intensive Care Unit, Süreyyapaşa Chest Diseases and Chest Surgery Training and Research Hospital, Istanbul, Turkey

⁴ Süreyyapaşa Göğüs Hastalıkları ve Göğüs Cerrahisi Eğitim ve Araştırma Hastanesi, Yoğun Bakım Ünitesi, İstanbul, Türkiye

⁵ Clinic of Chest Diseases, Yedikule Chest Diseases and Chest Surgery Training and Research Hospital, Istanbul, Turkey

⁶ Yedikule Göğüs Hastalıkları ve Göğüs Cerrahisi Eğitim ve Araştırma Hastanesi, Göğüs Hastalıkları Kliniği, İstanbul, Türkiye

⁷ Clinic of Chest Diseases, Kartal Kosuyolu High Specialization Training and Research Hospital, Istanbul, Turkey

⁸ Kartal Koşuyolu Yüksek İhtisas Eğitim ve Araştırma Hastanesi, Göğüs Hastalıkları Kliniği, İstanbul, Türkiye

SUMMARY

Risk factors for multiorgan failure and mortality in severe sepsis patients who need intensive care unit follow-up

Introduction: Multiorgan failure (MOF) is a primary cause of morbidity and mortality in sepsis patients in intensive care units (ICU). Finding risk factors and solving preventable problems of MOF in patients who have sepsis can be a favourable step for decreasing mortality. We aimed to examine multiorgan failure and mortality related risk factors in intensive care unit patients who have sepsis.

Materials and Methods: A retrospective data collection and prognostic cohort study was performed. Between January 2009-March 2010, patients accepted to the 22-bed pulmonary intensive care unit with the diagnosis of sepsis were enrolled. Patients' demographic data, ICU severity scores, application of mechanical ventilation, causative agent of sepsis, number of ICU days and presence of mortality were recorded. Logistic regression analysis was carried out for risk factors.

Results: 347 patients with sepsis were involved in the study. 43 of the patients (12.4%) developed MOF and overall mortality rate was 14.9% (n= 52). Presence of resistant pathogen, presence of shock, application of TPN and high APACHE II score were found to be risk factors for MOF [p= 0.015 Odds ratio (OR) 3.47 confidence interval (CI): 1.27 - 9.47, p= 0.001, OR: 30.8 CI: 11.41 - 83.49, p= 0.028, OR: 3.08, CI: 1.13 - 8.39, p= 0.003, OR: 1.10, CI: 1.04-1.18, respectively]. Risk factors for overall mortality were

Yazışma Adresi (Address for Correspondence)

Dr. Cüneyt SALTÜRK
Süreyyapaşa Göğüs Hastalıkları ve Göğüs Cerrahisi
Eğitim ve Araştırma Hastanesi, Göğüs Hastalıkları Kliniği,
Yoğun Bakım Ünitesi, İSTANBUL-TURKEY
e-mail: csalturk@yahoo.com

presence of nosocomial infection, high 3rd day SOFA score, presence of shock, application of TPN and sedation ($p=0.005$, OR: 3.39, CI: 1.45 - 7.93; $p=0.001$, OR: 1.51, CI: 1.27 - 1.81; $p=0.014$, OR: 3.24, CI: 1.27 - 8.25; $p=0.003$, OR: 3.64, CI: 1.54 - 8.58; $p=0.001$, OR: 3.38, CI: 1.51 - 7.57, respectively).

Conclusions: In sepsis patients who need ICU follow up, presence of resistant pathogen, presence of shock, application of TPN and high APACHE II scores are risk factors for developing MOF. Thus, rational use of antibiotics, reducing the use of TPN, application of infection control programmes and prevention of shock will further reduce multiorgan failure and mortality.

Key words: Intensive care unit, multiorgan failure, sepsis, mortality

ÖZET

Yoğun bakımda takip edilen sepsisli hastalarda çoklu organ yetmezliği ve mortalite için risk faktörleri

Giriş: Çoklu organ yetmezliği (ÇOY) yoğun bakım ünitelerinde önde gelen morbidite ve mortalite nedenlerinden biridir. Sepsis hastalarında ÇOY gelişimine katkı sağlayan risk faktörlerinin tespit edilmesi ve önlenebilir problemlerin çözümlenmesi mortaliteyi azaltmada önemli bir adım olabilir. Bu çalışmada yoğun bakımda yatan sepsis hastalarında ÇOY ve mortalite ile bağlantılı risk faktörlerinin araştırılması amaçlanmıştır.

Hastalar ve Metod: Retrospektif veri toplamaya dayalı prognostik kohort çalışması gerçekleştirilmiştir. Ocak 2009-Mart 2010 tarihleri arasında, 22 yataklı solunumsal yoğun bakım ünitesine sepsis tanısı ile yatırılan hastalar çalışmaya dahil edilmiştir. Hastaların demografik verileri, Yoğun bakım ünitesi (YBÜ) ciddiyet skorları, mekanik ventilasyon uygulaması, sepsise neden olan ajan, yoğun bakımda kalış süreleri ve mortalite varlığı kayıt edilmiş olup risk faktörleri için lojistik regresyon analizi uygulanmıştır.

Bulgular: Çalışmaya 347 sepsis hastası dahil edilmiştir. Kırk üç hastada (%12.4) ÇOY gelişmiş olup genel mortalite oranı %14.9'dur ($n=52$). ÇOY gelişimi için risk faktörleri dirençli patojen ve şok varlığı, total parenteral beslenme (TPB) ve yüksek APACHE II skoru olarak bulunmuştur. (sırasıyla $p=0.015$ Odds oranı (OR) 3.47 güven aralığı (CI): 1.27 - 9.47, $p=0.001$, OR: 30.8 CI: 11.41 - 83 - 49, $p=0.028$, OR: 3.08, CI: 1.13 - 8.39, $p=0.003$, OR: 1.10, CI: 1.04 - 1.18). Genel mortalite risk faktörleri ise nozokomiyal infeksiyon varlığı, üçüncü gün yüksek SOFA skoru, şok varlığı, sedasyon ve TPB'dir. (sırasıyla $p=0.005$, OR: 3.39, CI: 1.45 - 7.93; $p=0.001$, OR: 1.51, CI: 1.27 - 1.81; $p=0.014$, OR: 3.24, CI: 1.27 - 8.25; $p=0.003$, OR: 3.64, CI: 1.54 - 8.58; $p=0.001$, OR: 3.38, CI: 1.51 - 7.57).

Sonuç: Yoğun bakımda takibi gereken sepsis hastalarında dirençli patojen varlığı, şok, TPB uygulanması ve yüksek APACHE II skoru ÇOY gelişimi açısından risk faktörleridir. Bu nedenle akılcı antibiyotik kullanımı, TPB uygulamasının azaltılması, infeksiyon kontrol programlarının uygulanması ve şokun önlenmesi çoklu organ yetmezliği ve mortaliteyi azaltacaktır.

Anahtar kelimeler: Yoğun bakım ünitesi, çoklu organ yetmezliği, sepsis

INTRODUCTION

Sepsis is a major challenge in intensive care units (ICUs) as it was determined one of the leading causes of death (1). As early identification and treatment are essential, a "surviving sepsis campaign" has been implemented in the worldwide ICUs (2,3).

Multiorgan failure (MOF) is a major threat to the survival of patients with sepsis (4). It has been shown that patients with severe sepsis typically die due to MOF (5). In these patients, inappropriate activation of the immune system seems to contribute to organ dysfunction (6). Finding risk factors and overcoming preventable reasons of MOF in patients with sepsis may reduce mortality.

In this retrospective study, we primarily aimed to investigate MOF-related risk factors in patients with severe sepsis. Our secondary aim was to examine the factors affecting overall mortality in these patients.

MATERIALS and METHODS

We designed a retrospective, observational, cohort study in a 20-bed, level III ICU of a tertiary teaching

hospital for chest diseases between January 2009 and March 2010. During the study period, a total of eight pulmonology specialists worked in the ICU, which they staffed 24 hours a day. This study was approved by the local ethics committee of Sureyyapasa Chest Diseases and Thoracic Surgery Teaching and Research Hospital, Istanbul, Turkey. Three hundred and forty seven patients admitted to the ICU with respiratory failure and sepsis were evaluated (Figure 1). All patients had acute respiratory failure and most of them had chronic obstructive pulmonary disease (COPD). All patients stayed in the ICU for more than 24 hour. In all patients, the etiology of sepsis was originated from a respiratory system disease. Patients were grouped according to having MOF or not and also to their survival status.

Demographic data, initial arterial blood gas (ABG) values, systemic inflammatory response syndrome (SIRS) criteria, acute physiological and chronic health evaluation (APACHE II) score, sequential organ failure assessment (SOFA) score, type of mechanical ventilation application, duration of invasive mechanical

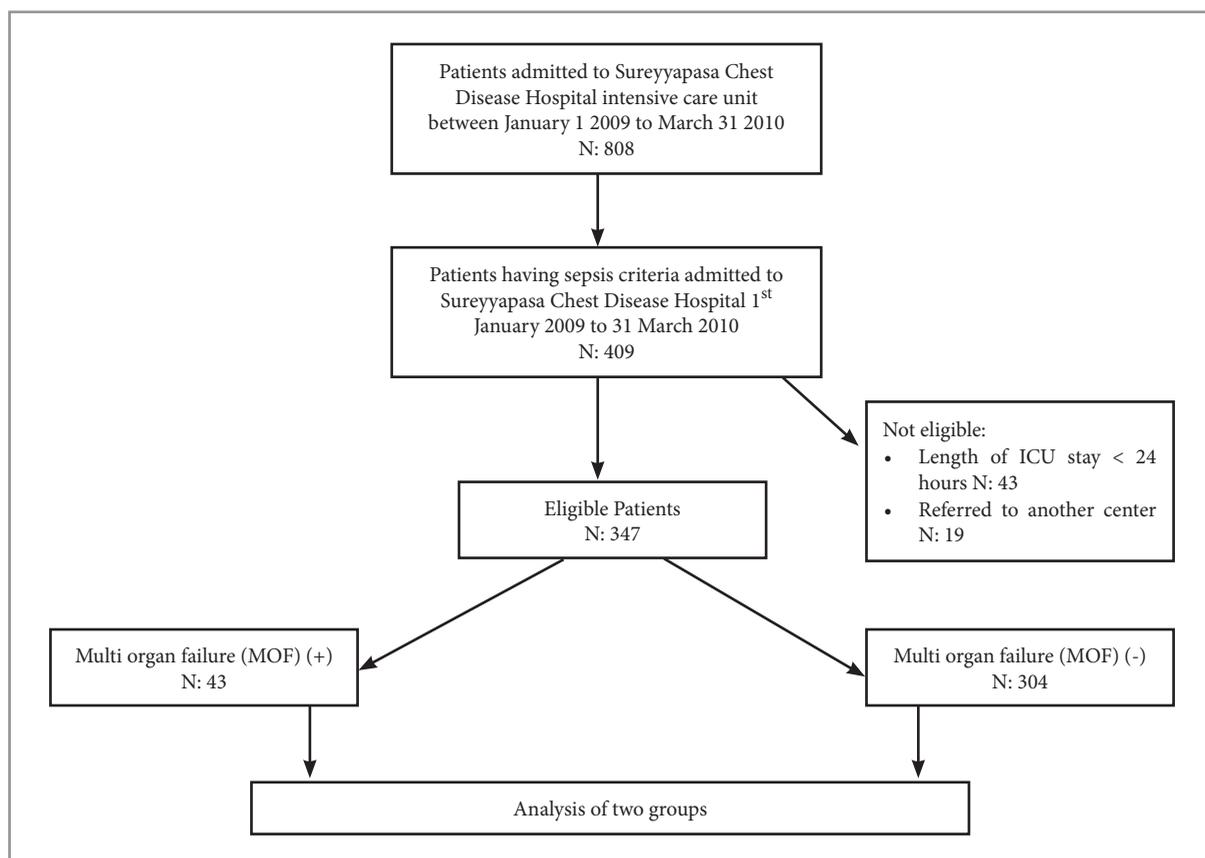


Figure 1. CONSORT diagram showing patient enrolment and stratification.

ventilation (IMV) or noninvasive mechanical ventilation (NIMV), length of ICU stay, the presence of septic shock, need of insulin or sedative agent infusion, presence of a central venous catheter, need for total parenteral nutrition (TPN), and co-morbidities of the groups were recorded from patient files (1,7,8).

Definitions

Sepsis was defined as SIRS with a proven or suspected source of infection. SIRS was defined as presence of two or more of the SIRS criteria (1). Patients who had organ dysfunction and/or hypoperfusion abnormalities were defined as severe sepsis. Shock was defined as the need for vasoactive drugs ($> 5 \mu\text{g}/\text{kg}/\text{min}$ of dopamine or dobutamine or norepinephrine at any dose) for at least 1 hour (1). Septic shock was diagnosed when shock was associated with documented or assumed infection with no other identifiable cause (1). MOF was defined as the presence of altered organ function in an acutely ill patient such that homeostasis could not be maintained without intervention (9). Any organ function meeting the conditions below was considered to have dysfunction.

- Cardiovascular system: systolic blood pressure < 90 mmHg, mean arterial pressure MAP < 70 mmHg, signs of shock, ventricular tachycardia, ventricular fibrillation, or myocardial infarction.
- Respiratory system: hypoxia requiring respirator-assisted ventilation for at least 3-5 days or $\text{PaO}_2/\text{FiO}_2 < 300$ mmHg.
- Nervous system: indifference, restlessness, lethargy, light coma, or deep coma, Glasgow score ≤ 14 without sedation.
- Hematological system: prothrombin time (PT) and activated partial thromboplastin time (APTT) increase $> 25\%$ or platelets $< 80.000 \times 10^9/\text{L}$.
- Hepatic system: serum bilirubin levels $\geq 2\text{-}3$ mg/dL, liver function tests \geq twofold normal, international normalized ratio (INR) > 1.5 .
- Renal system: creatinine levels > 1.4 mg/dL, urinary volume < 500 mL/24 h, or < 150 mL/8 h.

- Gastrointestinal system: intestinal ileus with intolerance to enteral feeding for > 5 days

Patients having more than one organ failure were considered to have MOF.

Modified Protocol for Surviving Sepsis

The “Early Goal-Directed Therapy” protocol was followed, which was based on fluid therapy to reach a MAP of 65 mmHg and appropriate antibiotic treatment (2,3).

Moderate tidal volume: providing a tidal volume not greater than 6 mL/kg per ideal body weight (10).

Moderate-dose steroids: stress-dose steroid therapy was applied in cases of septic shock after blood pressure was unresponsive to fluid and vasopressor therapy (basal cortisol or ACTH stimulation tests were not obtained as they were not available in our hospital) (11-13). Due to the absence of hydrocortisone in our country, methyl prednisolone was used at a dose of 20 mg tid for 7 days in patients without contraindications.

Glucose control protocol: when blood glucose level was > 150 mg/dL, continuous intravenous insulin infusion was applied to maintain blood glucose level between 110 and 140 mg/dL (< 150 mg/dL) (14,15).

Mechanical Ventilation

In our unit, noninvasive mechanical ventilation is the preferred method for ventilatory support of patients with acute respiratory failure if the patient has no contraindication (16). Invasive mechanical ventilation was applied with ICU ventilators (Prutan Bennett 760, Newport, Servo, Hamilton) if the patient had any of the intubation criteria, such as cardiac arrest, respiratory depression, loss of consciousness, hypercapnia unresponsive to NIMV, or shock. Assist control ventilation (A/C), with pressure or volume control, was preferred as the initial ventilation mode. In volume-control ventilation, inspiratory flow was set to provide an airway plateau pressure < 35 cmH₂O and a tidal volume of 6-8 mL/kg ideal body weight was applied. In pressure-control ventilation, inspiratory pressure was set to apply a pressure of 30-35 cmH₂O and titrated to reach a tidal volume of 6-8 mL/kg ideal bodyweight.

A weaning protocol was followed and patients meeting the weaning criteria were put on a t tube

trial (17). Patients who were successful during 30-min t-tube trial were extubated.

Sedation

The Richmond agitation sedation (RAS) scale was used to determine the need for sedation. Continuous infusion of a sedative agent was avoided (18).

Laboratory Records

The complete blood count (CBC), serum biochemistry, and CRP levels of patients were recorded on their first day in the ICU. CBC and blood electrolytes were checked every day and CRP was checked daily and on the third day in the ICU (control). The SOFA score was calculated on the first and third days in the ICU and APACHE II was calculated on the initial and the discharge day. Initial arterial blood gases (ABGs) were recorded.

Microbiology

Bronchial secretions of the intubated patients were collected by deep tracheal aspiration into the tracheal aspirate tube. In non-intubated patients, sputum was collected into a sputum Petri dish. In cases of low or high fever (< 36°C or > 38°C), a blood sample was collected into aerobic culture medium. Bronchial lavage samples were taken from the patients who underwent bronchoscopy. Resistant pathogens were defined as microorganisms that were resistant to one or more therapeutic classes of antimicrobial agents (19).

Possible risk factors for MOF and mortality such as presence of shock, resistant pathogen, total parenteral nutrition, application of invasive mechanical ventilation, presence of nosocomial infection, development of second sepsis during ICU stay, presence of a central venous catheter, and body mass index were recorded. Demographic data, departments where the patients were admitted, SIRS criteria, arterial blood gas values, number of days before ICU admission, first-day APACHE II, first- and third-day SOFA scores, sedative agents and insulin infusions, MV application, demographic data, and biochemical values of the both groups were compared.

Statistical Analysis

Continuous variables (age, biochemical values, body mass index, days on mechanical ventilation, APACHE II score, SOFA score, ICU days) with parametric and non-parametric values were analyzed by using Student's

t-test and the Mann-Whitney U-test, respectively. Categorical variables (gender, co-morbidity, NIMV and IMV application) of both groups were analyzed by using the χ^2 test. A risk analysis for MOF was performed by using logistic regression analysis. All parameters found significant in univariate analysis and that may affect the development of multiorgan failure (age, gender, presence of shock, co-morbidities, total parenteral nutrition, days on IMV and presence of resistant pathogen) were added to the logistic regression analysis. Non-parametric values were expressed as medians and parametric values were expressed as means \pm standard deviation. A p value < 0.05 was accepted as statistically significant.

RESULTS

Three hundred and forty seven patients having sepsis criteria were included. Forty three patients (12.4%) had the multiorgan failure criteria. Of the 347 patients, 52 (14.9%) died in the ICU. Demographic data, initial arterial blood gas values, SIRS criteria, APACHE II score, SOFA score, type of MV application, MV days, number of days in ICU, presence of septic shock, insulin infusion, sedative agent infusion,

presence of a central venous catheter, need for TPN, and co-morbidities of the groups were compared (Table 1). Leukocyte counts in patients with multiorgan failure were significantly higher than in patients without multiorgan failure ($p < 0.045$). pH ($p < 0.004$), $\text{PaO}_2/\text{FiO}_2$ ($p < 0.018$), HCO_3^- ($p < 0.002$), and base excess ($p < 0.001$) values in the first day arterial blood gas analysis of patients with multiorgan failure were significantly lower (Table 1).

In Table 2, APACHE II scores, length of hospital stay before admission to ICU, length of ICU stay, presence of a nosocomial infection, presence of septic shock, TPN need, presence of a central catheter, sedation or insulin infusion, type of MV application, days on IMV and NIMV, and mortalities of patients with and without multiorgan failure are summarized. First day APACHE II first and third-day SOFA scores of patients with MOF were significantly higher than scores of patients without MOF ($p = 0.001$ for each; Table 2). Length of hospital stay before admission to ICU and length of ICU stay in both groups were similar ($p > 0.05$). Percentage of patients on IMV was higher for the group with MOF and IMV was applied for a longer time in this group when compared with the group

Table 1. Characteristics and first day SIRS criteria of patients with and without multiorgan failure

Variables	Patients without MOF (n= 304)	Patients with MOF (n= 43)	P
Age, median (25% - 75%)	64 (51 - 72)	68 (52-72)	0.42
Female, %	34.8	20.9	0.069
Body mass index, kg/m^2 , median (25% - 75%)	25 (22 - 28)	25 (22-29)	0.76
Admitted from, n (%)			
Emergency	117 (38.5%)	16 (37.2%)	0.74
In-patient clinic	151 (49.7%)	24 (55.8%)	
Other ICU	36 (11.8%)	3 (7.0%)	
SIRS criteria			
Leucocyte $\times 10^3$ mL	13.2 (9.4 - 16.9)	14.9 (11.2 - 21.9)	0.045
Respiratory rate/m	27 (23 - 33)	26 (22 - 33)	0.39
Fever ($^{\circ}\text{C}$)	36.5 (36.1 - 37.0)	36.3 (36.0 - 37.2)	0.31
Pulse/min	110 (100 - 125)	121 (100 - 133)	0.08
ABG analysis			
pH	7.33 (7.26 - 7.42)	7.27 (7.17 - 7.41)	0.004
PaCO_2 mmHg	65.9 (45.0 - 79.8)	58.3 (45.0 - 84.4)	0.77
PaO_2 mmHg	70.0 (54.8 - 97.0)	68.0 (51.0 - 82.0)	0.31
$\text{PaO}_2/\text{FiO}_2$	172 (123 - 236)	131 (90 - 216)	0.018
SatO_2 , %	92.9 (86.5 - 96.7)	91.0 (81.7 - 96.0)	0.13
HCO_3^- mmol	31.0 (25.4 - 37.0)	27.0 (22.4 - 33.0)	0.002
Base excess, mmol	5.9 (1.2 - 11.5)	1.8 (-5.2 - 6.3)	0.001

MOF: Multiorgan failure, ICU: Intensive care unit, SIRS: Systemic Inflammatory Response Syndrome, ABG: Arterial blood gas analysis, PaCO_2 : Partial carbon dioxide pressure, PaO_2 : Partial oxygen pressure, FiO_2 : Fraction of inspired oxygen, SatO_2 : Oxygen saturation, HCO_3^- : Bicarbonate.

Table 2. Patient characteristics and ICU data

Variables	Patients without MOF (n= 304)	Patients with MOF (n= 43)	P
APACHE II score, median (25%-75%)	18 (15 - 23)	27 (22 - 30)	0.001
1 st day SOFA score, median (25%-75%)	4 (3 - 5)	8 (6 - 10)	0.001
3 rd day SOFA score, median (25%-75%)	3 (2 - 4)	7 (4 - 8)	0.001
Hospital stay length before ICU, median (25%-75%)	3 (2 - 8)	4 (2 - 8)	0.81
ICU stay length, median (25%-75%)	8 (5 - 12)	8 (5 - 17)	0.21
Presence of resistant pathogen, n (%)	55 (18.1)	16 (37.2)	0.004
Septic shock, n (%)	12 (4.0)	32 (74.4)	0.001
Sedative infusion, n (%)	34 (11.2)	15 (34.9)	0.001
Insulin infusion, n (%)	55 (18.1)	21 (48.8)	0.001
IMV days, median (25%-75%)	5 (3 - 10)	7 (5 - 15)	0.042
IMV, n (%)	90 (29.6)	34 (79.1)	0.001
NIMV, days, median (25%-75%)	6 (4 - 10)	5 (2 - 6)	0.004
NIMV, n (%), median (25%-75%)	259 (85.2)	26 (60.5)	0.001
Presence of central catheter, n (%)	22 (7.2)	13 (30.2)	0.001
TPN, n (%)	84 (27.6)	31 (72.1)	0.001
Mortality, n (%)	26 (8.6)	26 (60.5)	0.001

MOF: Multiorgan failure, APACHE II: Acute physiology and chronic health evaluation score, SOFA: Sequential organ failure assessment score, ICU: Intensive care unit, IMV: Invasive mechanical ventilation, NIMV: Non-invasive mechanical ventilation, TPN: Total parenteral nutrition.

without MOF ($p=0.001$ and $p=0.042$). The percentage of patients on NIMV was higher for the group without MOF and they were on NIMV for a longer time than the group with MOF ($p=0.001$ and $p=0.004$). Need for sedation ($p=0.001$), insulin infusion ($p=0.001$), presence of a central venous catheter ($p=0.001$), need for total parenteral nutrition ($p=0.001$), presence of shock ($p=0.001$) and presence of nosocomial sepsis ($p=0.004$) were significantly higher for patients with MOF versus patients without MOF (Table 2). The mortality rate was eightfold higher in the MOF group (Table 2).

For 174 (50.1%) patients, diagnostic procedures such as bronchial lavage, deep tracheal aspiration, blood and urine cultures were performed to identify the microorganism causing the sepsis. Resistant pathogen positivity was 55.8% ($n=24$) for patients with MOF and 17.4% ($n=53$) for patients without MOF ($p=0.001$). The first three etiologic agents were *Pseudomonas aeruginosa* ($n=22$, 28.5%), *Acinetobacter baumannii* ($n=20$, 25.9%), and methicillin-resistant *Staphylococcus aureus* (MRSA; $n=10$, 12.9%).

The incidences of renal disorders ($p=0.001$) and malignancies ($p=0.035$) were significantly higher in the MOF group. The presence of resistant pathogens, shock, sedation use, IMV application, insulin infusion, need for TPN, presence of nosocomial

infection, $\text{PaO}_2/\text{FiO}_2$, APACHE II, and presence of renal disorders and malignancies were studied using a logistic regression model. The presence of resistant pathogens, shock, TPN, and high APACHE II scores were found as risk factors for the development of MOF. Although APACHE II score was statistically significant, ($p=0.003$), its suggestibility was low due to the Odds ratio of 1.10 (Table 3).

Fifty two of the patients died and grouped as non-survivors. Demographic data and SIRS criteria were similar for survivors and non-survivors (Table 4). However, pH and $\text{PaO}_2/\text{FiO}_2$ values of non-survivors were significantly lower ($p=0.003$ and $p=0.023$, respectively).

APACHE II and SOFA scores, the presence of resistant pathogen, the application of mechanical ventilation, and the need for insulin, sedation and total parenteral nutrition for survivors and non-survivors are summarized in Table 5. APACHE II score, SOFA score and MV application were significantly higher in the non-survivor group (all $p=0.001$).

Presence of co-morbidities and type of organ failure of survivors and non-survivors were shown in Table 6.

Nosocomial sepsis ($p=0.005$), higher third-day SOFA score ($p=0.001$), presence of shock ($p=0.014$), sedation infusion ($p=0.003$), and need for TPN ($p=$

Table 3. Logistic regression analysis of risk factors for the development of multiorgan failure

Variables	P	Odds ratio	CI 95%
Resistant pathogen	0.015	3.47	1.27-9.47
Presence of shock	0.001	30.8	11.41-83.49
Total parenteral nutrition	0.028	3.08	1.13-8.39
APACHE II score	0.003	1.10	1.04-1.18

APACHE II: Acute physiology and chronic health evaluation score.

Table 4. Characteristics and first day SIRS criteria of survivors and non-survivors

	Survivors (n= 295)	Non-survivors (n= 52)	p
Age, median (25%-75%)	64 (52-73)	64 (49-72)	0.94
Female %	33.8	28.8	0.47
Body mass index kg/m ² , median (25% - 75%)	25 (22-28)	24 (21-28)	0.44
Admitted from, n (%)			
Emergency	116 (39.3)	17 (32.7)	
In-patient clinic	145 (49.2)	30 (57.7)	0.63
Other ICU	34 (11.5)	5 (9.6)	
SIRS criteria, median (25% - 75%)			
Leucocyte, cell/mL x10 ³	13.4 (9.4-16.8)	15.2 (11.2-20.3)	0.19
Pulse/min	110 (100-126)	116 (99-133)	0.26
Respiratory rate/min	27 (23-33)	26 (22-30)	0.34
Fever, C	36.5 (36.0 - 37.0)	36.4 (36.0-36.8)	0.51
Number of SIRS criteria	3 (2-3)	3(2-3)	0.21
First day arterial blood gas values, median (25%-75%)			
pH	7.33(7.27 - 7.42)	7.26 (7.19-7.40)	0.003
PaCO ₂ mmHg	65.5 (44.9 - 79.4)	66.0 (47.9-87.2)	0.63
PaO ₂ mmHg	70.6 (55.0 - 95.0)	65.2 (50.0-97.5)	0.39
PaO ₂ /FiO ₂	172 (122 - 236)	139 (90-226)	0.023
SatO ₂ %	93 (87 - 97)	90 (80-96)	0.070
HCO ₃ mmol	31.0 (25.5 - 36.6)	29.4 (23.0-33.6)	0.051
Base excess, mmol	5.8 (1.0 - 11.2)	3.6 (-1.3-8.9)	0.073

ICU: Intensive care unit, SIRS: Systemic Inflammatory Response Syndrome, PaCO₂: Partial carbondioxide pressure, PaO₂: Partial oxygen pressure, FiO₂: Fraction of inspired oxygen, SatO₂: Oxygen saturation, HCO₃: Bicarbonate.

0.003) were found to be related with mortality in logistic regression analysis (Table 7).

DISCUSSION

In this study, we determined that the presence of a resistant pathogen, shock, the need for TPN and a high APACHE II score could be used to predict the development of MOF in ICU patients with respiratory failure along with severe sepsis. Besides this the presence of a nosocomial infection, shock, need for sedative agent infusion, TPN and high third-day SOFA score were also found to be predictors of overall mortality in the ICU.

A sepsis protocol that aims to provide immediate intervention to decrease mortality has been used widely. It has been reported that applying this protocol decreases mortality (20,21). However, some recent studies suggested conflicting results unlike the former ones as "Early Goal-Directed Therapy", was not found efficient in reducing the mortality of patients presenting with septic shock (22). In our study, we did not analyze the treatments which had been applied in other departments (emergency, ward and other ICU) before the patient was admitted to the ICU, although departments from which patients were admitted to the ICU were similar for both groups.

Table 5. Characteristics and ICU severity scores of patients with sepsis

Variables	Survivors	Non-survivors	P
APACHE II score, median (25%-75%)	18 (15 - 23)	24 (20 - 30)	0.001
First day SOFA score, median (25%-75%)	4 (3 - 5)	7 (4 - 9)	0.001
Third day SOFA score, median (25%-75%)	3 (2 - 4)	6 (3 - 8)	0.001
Length of stay before ICU admission, median (25%-75%)	3 (1 - 7)	4 (2 - 9)	0.59
Length of ICU stay, median (25%-75%)	8 (5 - 12)	9 (5 - 15)	0.34
Patients with MOF, n (%)	17 (5.8)	26 (50)	0.001
Day on which MOF develops (25%-75%)	1 (1 - 1)	1 (1 - 6)	0.33
Presence of resistant pathogen n (%)	50 (16.9)	21 (40.4)	0.001
Presence of Septic shock, n (%)	18 (6.1)	26 (50)	0.001
IMV days, median (25%-75%)	6 (3 - 10)	7 (4 - 13)	0.09
IMV, n (%)	90 (30.5)	34 (65.4)	0.001
NIMV days, median (25%-75%)	6 (4 - 9)	5 (4 - 8)	0.19
NIMV, n (%)	252 (85.4)	33 (63.5)	0.001
Tracheostomy, n (%)	23 (7.8)	2 (3.8)	0.24
Insulin infusion, n (%)	54 (18.3)	22 (42.3)	0.001
Sedative infusion, n (%)	29 (9.8)	20 (38.5)	0.001
Central catheter, n (%)	14 (4.7)	21 (40.4)	0.001
Total parenteral nutrition, n (%)	78 (26.4)	37 (71.2)	0.001

APACHE II: Acute physiology and chronic health evaluation score, SOFA: Sequential organ failure assessment score, ICU: Intensive care unit, MOF: Multi organ failure, IMV: Invasive mechanical ventilation, NIMV: Non-invasive mechanical ventilation.

Table 6. Presence of Co-morbidities and organ failure of survivors and non-survivors

	Survivors (n= 295)	Non-survivors (n= 52)	P
Presence of comorbidity, n (%)	270 (91.5)	51 (98.1)	0.084
Cardiac disease	134 (45.4)	26 (50)	0.54
Pulmonary disease	229 (77.6)	41 (78.8)	0.84
Mechanical ventilator at home	56 (19)	7 (13.5)	0.34
Renal disease	5 (1.7)	6 (11.5)	0.002
Neurological disease	30 (10.2)	8 (15.4)	0.26
Cancer	19 (6.4)	9 (17.3)	0.008
Presence of organ failure, n (%)	17 (5.7)	26 (50)	
Cardiovascular system	15 (5)	26 (50)	0.41
Respiratory system	17 (5.7)	26 (50)	-
Renal system	9 (3)	21 (40)	0.05
Hematological system	1 (0.3)	7 (13.4)	0.08
Hepatic system	2 (0.6)	2 (3.8)	0.65
Nervous system	1 (0.3)	0	0.21
Gastrointestinal system	1 (0.3)	2 (3.8)	0.82

High blood glucose values and the need for insulin infusion indicated the severity of tissue injury which was caused by cytokines that play major role in the sepsis etiopathogenesis (6). However in a recent randomized controlled study there was no difference in the rate or severity of organ failure between the

two different intensity of glycemic controls (23). Also in this study it was stated that cohort differences may play a role in assessing the impact of glycemia on organ failure. In our study the ratio of patients who needed insulin infusions were found significantly higher in the MOF group. Although we had standard

Table 7. Intensive care unit mortality related risk factors of patients with sepsis

	p	Odds ratio	CI 95%
Presence of nosocomial infection	0.005	3.39	1.45-7.93
3 rd Day SOFA Score	0.001	1.51	1.27-1.81
Presence of shock	0.014	3.24	1.27-8.25
Sedative agent infusion	0.003	3.64	1.54-8.58
Total parenteral nutrition	0.001	3.38	1.51-7.57

target glucose level, there might be these kind of cohort differences in our study. Day in which insulin infusion started, frequency and amount of feeding, presence of insulin resistance, presence/dose of steroid therapy and comorbidities can affect the need for insulin infusion. It will be more accurate and externally valid to define effect of glycemic control on MOF in randomized clinical controlled studies.

IMV need is also already shown as a risk factor related with mortality. Significantly more patients were on IMV in the MOF group versus non MOF group. In contrast, the rate of NIMV application was significantly higher for patients without MOF. NIMV application is thought to decrease the need for IMV by protecting against the further problems that can be caused by IMV, so that it may prevent the development of MOF to some extent.

The first item of the sepsis protocol is "Early Goal-Directed Therapy", which must be applied in the first 4-6 h to prevent irreversible injury. In our study, first-day APACHE II and SOFA scores were markedly higher in MOF group patients versus than the non-MOF group (7,8). This may suggest that end organ damage had already begun and the opportunity to reverse the changes caused by sepsis had been missed, even the sepsis protocol was initiated without delay. Knox et al. stated that Glasgow Coma Scale scores dominated the association between admission SOFA score and 30-day mortality in a mixed ICU population (24). In our study, we did not analyze the contribution of every item of the SOFA score to mortality, but as our study included only patients treated in a respiratory ICU, the GCS part of the SOFA score may not be considered as a dominating item in SOFA scores of our patients.

Initiation of appropriate antibiotic treatment within 4-6 h after the sepsis process is considered essential (25-27). Tissue injury will be more severe in cases of resistant pathogens and inappropriate empirical treatment. A recent study showed that inappropriate

antibiotic treatment increased the hospital mortality rate of patients with severe sepsis and septic shock (28). In our study microbiological examination was performed in half of our patients and more patients were infected significantly with a resistant pathogen in the MOF group, comparing with the group without MOF (72.7% and 37.6%, respectively). The low culture positivity was assumed to be due to ongoing antibiotic therapy at the time of specimen collection and the initiation of empirical therapy before collection of the culture specimen. Culture results revealed infection with multiple pathogens in most of the patients. *P. aeruginosa*, *A. baumannii*, and MRSA were the most commonly encountered pathogens for nosocomial sepsis.

There are studies that show suboptimal offer-demand nutrition in critically ill patients, which is characterized by deterioration of nutritional status, higher rates of multiple organ dysfunction, complications, cachexia, loss of muscle strength, prolonged length of stay, and mortality (29). Therefore, intensivists tend to feed the patient at any cost and they are prone to start TPN earlier than recommended. However it was clearly shown that TPN causes the translocation of bacteria into the gastrointestinal tract and increases the resistant pathogen population by decreasing obligate anaerobes, particularly in elderly patients with SIRS/sepsis (30,31). All other nutrition guidelines for critically ill patients including ESPEN, ASPEN, SCCM, and CCCPG agree with the benefits of early enteral feeding, and enteral feeding is superior to parenteral nutrition. American Society for Parenteral and Enteral Nutrition (ASPEN) guideline recommends "If early enteral nutrition is not available in the first 7 days following admission to the ICU, no nutrition support therapy should be provided in the patient who was previously healthy prior to critical illness with no evidence of protein malnutrition; use of parenteral nutrition should be reserved and initiated only after the first 7 days of hospitalization (when enteral nutrition is not available) (32). In our center, we

prefer not to use TPN unless essential. In our study population, all patients on TPN were suffering from gastrointestinal system bleeding. This likely explains its identification as a risk factor for MOF development.

As presence of shock plays an important role in the development of MOF, the sepsis treatment protocol targets immediate treatment of shock and thus preventing end organ damage. In this study, logistic regression analysis showed that the presence of shock increased the probability of MOF development by thirtyfold. Additionally, the MOF rate was increased threefold by total parenteral nutrition usage and having resistant pathogens. In the analysis of overall mortality risk factors, the presence of shock, sedative infusion, and nosocomial infection increased the mortality risk 3-3.5-fold and third-day SOFA score increased the risk 1.5-fold. A recent study stated that additional prognostic factors, such as age and co-morbidities, might complement the predictive performance of SOFA scores (33). In a study by Oltean et al. it was also reported that using a co-morbidity index might be beneficial in assessing the risk of death in septic patients (34). In our study, we analyzed the presence of co-morbidity as an independent risk factor for mortality. As most of our patients were elder and had COPD, almost all of them were accepted having co-morbidities. Renal disorders and malignancies were found significantly more frequent in the non-survivor group at comparison of comorbidities.

This study had several limitations. First, it was a retrospective study performed at a single center. However, the follow-up and treatment of patients like data collection were performed by the same physician group using the same optimized computer software; therefore significant valid data were gathered. Second, the study was carried out in a respiratory ICU and included only severe sepsis patients with a respiratory system origin. The results may differ somewhat if the population was different; however, it should also be noted that sepsis with a pulmonary origin constitutes half of all patients in general ICUs. Finally, we did not perform a microbiological examination in half of our patients. In our respiratory ICU, we routinely take endotracheal aspirate culture specimens from intubated patients. However, taking sputum examples is not always possible in patients who are not intubated, and contamination of these specimens by the oropharynx flora is also a big issue in these patients.

CONCLUSION

Risk of MOF development in sepsis patients can be reduced by taking some precautions. Early detection and appropriate treatment of resistant pathogens, accurate management of shock therapy, and reducing the use of TPN can lessen MOF development. Initial high APACHE II score should be an alerting parameter for MOF development.

CONFLICT of INTEREST

None declared.

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