Turk J Intensive Care 2022;20(Suppl 1):1-6
DOI: 10.4274/tybd.galenos.2021.62533

ORIGINAL RESEARCH / *ÖZGÜN ARAŞTIRMA*

Fatma İrem Yeşiler,
Çağla Yazar,
İrem Ulutaş Ordu,
Helin Şahintürk,
Tuğba Yanık Yalçın,
Pınar Zeyneloğlu

Evaluation of Sepsis and Extensively Drug Resistant Infections in Deceased Critically Ill Patients

Mortal Seyreden Kritik Hastalarda Çoklu İlaç Dirençli Enfeksiyonların ve Sepsisin Değerlendirilmesi

Received/Geliş Tarihi : 31.08.2021
Accepted/Kabul Tarihi : 13.12.2021

Fatma İrem Yeşiler, Çağla Yazar, İrem Ulutaş Ordu, Helin Şahintürk, Pınar Zeyneloğlu
Başkent University Faculty of Medicine, Department of Anesthesiology and Critical Care, Ankara, Turkey

Tuğba Yanık Yalçın
Başkent University Faculty of Medicine, Department of Infectious Diseases and Clinical Microbiology, Ankara, Turkey

Fatma İrem Yeşiler MD (✉),
Başkent University Faculty of Medicine, Department of Anesthesiology and Critical Care, Ankara, Turkey

E-mail : fatmairem84@hotmail.com
Phone : +90 505 313 65 18
ORCID ID : orcid.org/0000-0002-0612-8481

ABSTRACT *Objective:* Sepsis due to the drug resistant infections is associated with the higher mortality rates in an intensive care unit (ICU). The aim of this study was to determine the demographic characteristics of the deceased critically ill patients, prevalence of the sepsis, and extensively drug resistant infectious-related (XDR) deaths within a year in the ICU.
Materials and Methods: The data of patients who died in the ICU between January 1, 2019 and 2020 was retrospectively analyzed.
Results: Out of 525 patients admitted to the ICU, 269 of them died. One hundred fifty-one of those deceased patients (56.1%) were in medical and 118 (43.9%) in the surgical ICU. Their mean age was 70.5±15 years and 126 (46.8%) of them were female. The mean Acute Physiology and Chronic Health Evaluation-II, Glasgow coma score, Sequential Organ Failure Assessment scores at ICU admission were 23.4±20.9, 9.8±4.4, and 8.2±3.6, respectively. A few reasons for the ICU admission were: respiratory failure (34.9%), neurologic dysfunction (19%), sepsis (17.8%), and cardiovascular failure (16%). Infection occurred in the 231 (85.9%) patients. Of the 109 (40.5%) deceased patients with the diagnosis of sepsis, 48 (40%) of them were admitted in the ICU with sepsis. The most common site of infection was the respiratory system (34.6%). Septic shock was seen in 170 patients (63.2%) and renal replacement therapy was needed in 61 (22.7%) of them. XDR developed in 34.6% of the deceased patients and was more frequent among those with an antibiotic usage before the ICU admission (p=0.02). The mean length of stay at hospital before the ICU admission and length of the ICU stay were 22±25.8 and 10.1±12.7 days, respectively. The number of the deceased medical patients were significantly higher than the surgical patients (p=0.018).
Conclusion: The deceased critically ill medical patients were higher than the surgical patients. A total of 40% of the deceased critically ill patients were diagnosed with a sepsis, and one third of them had XDR infection. XDR infections were more frequent among the patients with an antibiotic usage before the ICU admission.
Keywords: Extensively drug-resistant, sepsis, deceased critically ill patient, intensive care unit

ÖZ *Amaç:* İlaca dirençli enfeksiyonlara bağlı sepsis, yoğun bakım ünitesinde (YBÜ) yüksek mortalite oranları ile ilişkilidir. Bu çalışmanın amacı, YBÜ'de bir yıl içerinde ölen kritik hastaların demografik özelliklerinin, sepsis ve çoklu ilaç dirençli enfeksiyonlara bağlı (XDR) ölümlerin prevalansının belirlenmesidir.
Gereç ve Yöntem: 1 Ocak 2019-2020 tarihleri arasında YBÜ'de ölen hastaların verileri retrospektif olarak incelendi.
Bulgular: YBÜ'ye kabul edilen 525 hastadan 269'u öldü. Ölen hastaların 115'i (%56,1) dahili, 118'i (%43,9) cerrahi YBÜ'deydi. Yaş ortalamaları 70,5±15 yıl olup 126'sı (%46,8) kadındı. Yoğun bakıma yatışta ortalama Akut Fizyoloji ve Kronik Sağlık Değerlendirmesi-II, Glasgow koma skalası, Sıralı Organ Yetmezliği Değerlendirmesi skorları sırasıyla 23,4±20,9, 9,8±4,4 ve 8,2±3,6 idi. YBÜ'ye yatış nedenleri solunum yetmezliği (%34,9), nörolojik disfonksiyon (%19), sepsis (%17,8) ve kardiyovasküler yetmezlik (%16) idi. Enfeksiyon 231 (%85,9) hastada görüldü. Sepsis tanısı ile ölen 109 (%40,5) hastanın 48'i (%40) sepsis tanısı ile YBÜ'ye yatırıldı. En sık solunum sistemi enfeksiyonları saptandı (%34,6). Yüz yetmiş hastada (%63,2) septik şok görüldü ve bunların 61'inde (%22,7) renal replasman tedavisi gerekti. Ölen hastaların %34,6'sında XDR enfeksiyon gelişti ve YBÜ'ye yatmadan önce antibiyotik kullananlarda görülme sıklığı daha fazlaydı (p=0,02). YBÜ'ye

kabul edilmeden önceki ortalama hastanede kalış süresi ve YBÜ'de kalış süresi sırasıyla 22±25,8 ve 10,1±12,7 gün idi. Dahili YBÜ'de ölen hasta sayısı cerrahi YBÜ'de ölenlerden daha fazlaydı (p=0,018).
Sonuç: Dahili YBÜ'de ölen kritik hasta sayısı cerrahi YBÜ'de ölenlerden daha fazlaydı. Ölen kritik hastaların %40'ına sepsis teşhisi konuldu ve bunların 1/3'ünde XDR enfeksiyonu vardı. YBÜ'ye yatmadan önce antibiyotik kullanan hastalarda XDR enfeksiyonları daha sıktı.
Anahtar Kelimeler: Çoklu ilaç direnci, sepsis, ölen kritik hasta, yoğun bakım ünitesi

Introduction

Sepsis is a fatal syndrome that affects millions of people worldwide and life-threatening organ dysfunction due to a dysregulated host response to infection (1,2). The incidence of sepsis is increasing day by day and one of the most common causes of global mortality. Therefore, sepsis is an important public health problem with serious economic consequences. Its treatment is difficult and sepsis is one of the main causes of hospital and intensive care unit (ICU) deaths (3,4). Drug-resistant bacterial infections are one of the reasons that complicate the management of sepsis and increase mortality. There were many definitions of drug-resistant infections in the literature. Experts from the European Center for Disease and Control (ECDC) and the Centers for Disease Control and Prevention (CDC) have updated the definitions. Accordingly, multi-drug resistant defines the microorganism resistant to at least one of three or more antimicrobial agent categories; extensively drug-resistant (XDR); defines as nonsusceptibility to at least one agent in all but two or fewer antimicrobial categories. Pandrug resistant (PDR) defines as nonsusceptibility to all agents in all antimicrobial categories (5-7). Invasive procedures and usage of broad-spectrum antibiotics are associated with an increased incidence of sepsis and drug-resistant infections (6-8). The aim of this study was to determine the demographic and clinical characteristics of deceased critically ill patients, the prevalence of sepsis and XDR infectious-related deaths within 1 year in the ICU of Başkent University Medical Faculty Ankara Hospital.

Materials and Methods

The data of patients who died in the ICU of Başkent University Faculty of Medicine Ankara Hospital between January 1, 2019 and January 1, 2020 was retrospectively analyzed. Adult patients aged 18 years or more who died in ICU were included in the study. Patients younger than 18 years, who died within 24 hours of admission to ICU, who did not die in the ICU and whose data were not available were excluded. The following data were obtained from electronic medical and nursing records. The demographic characteristics and clinical characteristics (age, gender, comorbidities, transplantation, etc.), drugs used before ICU admission, reasons for ICU admission and severity scores [Acute Physiology and Chronic Health Evaluation (APACHE-II) score; Sequential Organ Failure Assessment (SOFA) score; Glasgow coma score (GCS)], incidence of infection, sepsis and XDR, focus of infection, septic shock, organ failures (change of consciousness, respiratory failure, cardiovascular failure and circulatory failure, acute kidney failure, acute liver failure), presence of vascular, urinary and drain catheters, intubation and mechanical ventilation characteristics, length of hospital and ICU stay of deceased critically ill patients were retrospectively analyzed. XDR strains were identified according to criteria defined by ECDC and CDC (5). Sepsis and septic shock were defined according to the 2020 surviving sepsis campaign (1). Acute kidney injury was identified on the basis to the Kidney Disease Improving Global Outcomes clinical practice guidelines (9).

Statistical Analysis

The statistical analysis was performed using The Statistical Package for Social Sciences 25.0 (version 25.0; SPSS Inc., Chicago, IL, USA). Frequencies were expressed as numbers (n) and percentages (%). Variables are expressed as mean values ± standard deviation. Categorical variables between the two groups were analyzed with the chi-square test. Values of $p<0.05$ were considered statistically significant. This study was approved by the Başkent University Institutional Review Board (project no: KA21/309).

Results

Of the 525 patients admitted to the ICU during the study period, of whom 269 died in the ICU. The mean age was 70.5±15.0 years (between 18 and 97 years) including 143 (53.2%) male and 126 (46.8%) female (Table 1). The mean APACHE-II score was 23.4±20.9, GCS was 9.8±4.4 and the SOFA score was 8.2±3.6 on ICU admission (Table 2). There were 151 patients (56.1%) in medical ICU and 118 patients (43.9%) in surgical ICU. Most of the patients were

admitted from other services (53.5%) within our hospital and emergency services (30.5%) (Table 1). Two hundred sixty (96.7%) of our patients had at least one comorbidity. Hypertension (130 patients, 48.3%) was the most common comorbidity and the others were malignancy (46.5%), cerebrovascular disease (35.7), immunosuppression (33.5%) and transplantation (2.6%). The reasons for ICU admission were respiratory failure (34.9%), neurologic dysfunction (19.0%), sepsis (17.8%), and cardiovascular failure (16.0%), respectively (Table 3). Two hundred forty two patients (90.0%) had central venous catheter, 55 patients (20.4%) had drain line, 238 patients (88.5%) had urinary catheterization. One hundred nine patients (40.5%) were followed up with a diagnosis of sepsis in the ICU. While 48 patients (44.0%) with sepsis were admitted to the ICU, 61 patients (55.9%) were diagnosed with sepsis during the follow-up in the ICU. Septic shock was seen in 170 patients (63.2%). The common focus of infection were the respiratory system (34.6%, n=93), genitourinary system (20.8%, n=56), blood stream infections (14.1%, n=38) and intraabdominal (10.0%, n=27), respectively. A total of 104 microorganisms were identified; 72 Gram-negative bacteria and 27 Gram-positive bacteria and 5 fungus. The infectious pathogens were *Klebsiella pneumoniae* (8.2%), *Enterococcus* spp. (5.6%), Extended-spectrum beta-lactamase *Escherichia coli* (5.2%), *Escherichia coli* (4.8%), *Pseudomonas aeruginosa* (4.5%), *Acinetobacter baumanii* (3.0%), respectively (Table 4). Nineteen percent of the patients had *Acinetobacter baumanii* colonization and 34.6% (n=93) had carbapenem resistance (XDR). Sixty-two (66.7%) patients with XDR infection used

Table 1. Demographic and clinical characteristics of patients

Variables	Total (n=269)
Age, years, mean ± SD, range, years	70.4±15.0 (18-97)
Sex	
Male	143 (53.2)
Female	126 (46.8)
Etiology	
Medical causes	151 (56.1)
Surgical causes	118 (43.9)
Admission from	
Emergency	82 (30.5)
Ward in hospital	144 (53.5)
From outer center	10 (3.8)
Others	33 (12.2)
Comorbidities	
Hypertension	130 (48.3)
Diabetes mellitus	87 (32.3)
Coronary artery disease	76 (28.3)
Obstructive pulmonary diseases	44 (16.4)
Malignancy	125 (46.5)
Cerebrovascular disease	96 (35.7)
Chronic kidney disease	48 (17.8)

SD: Standard deviation

Table 2. Severity scores on ICU admission of patients

Severtiy scores	Mean ± SD
APACHE-II score	23.4±20.9
SOFA score	8.2±3.6
GCS score	9.8±4.4

ICU: Intensive care unit, APACHE-II: Acute Physiology And Chronic Health Evaluation-II, SOFA: Sequential Organ Failure Assessment, GCS: Glasgow coma score, SD: Standard deviation

Table 3. The reasons to intensive care unit admission

Organ and system involvement	Number (%)
Respiratory system	94 (34.9)
Neurologic system	51 (19.0)
Cardiovascular system	43 (16.0)
Genitourinary system	10 (3.7)
Gastrointestinal system	6 (2.2)
Hematological system	3 (1.1)
Sepsis	48 (17.8)

Table 4. Types of infectious pathogens

Variables	Frequency (n)	Percent (%)
Patients with extensively drug resistant	93	34.6
Klebsiella pneumoniae	22	8.2
Pseudomonas aeruginosa	12	4.5
Acinetobacter baumanii	8	3.0
Proteus mirabilis	2	0.7
Extended-spectrum beta-lactamase-*Escherichia coli*	14	5.2
Escherichia coli	13	4.8
Enterococcus spp.	15	5.6
Staphylococcus aureus	11	4.1
Candida spp.	3	1.1
Aspergillus spp.	2	0.7

antibiotic before ICU admission. Presence of infection before ICU admission, central venous catheter, drain line and urinary catheter were associated with XDR infections (p=0.021, 0.001, 0.002, 0.044, respectively). While 37 (13.8 %) patients were isolated on ICU admission, 38 (14.1%) patients were isolated in the ICU. Fifty-one patients (19.0%) were not diagnosed with infection before ICU admission. There was an infection in 38.6% (n=104) of the patients while lying in the ward. Two hundred sixty four (98.1%) patients were intubated and 34 patients (12.6%) required tracheotomy. At the same time, mechanical ventilation were used in 226 patients (84.0%), and renal replacement therapy in 61 patients (22.7%) in the first 3 days.

The mean value of leukocyte, C-reactive protein and procalcitonin were 15.4±34.4 10^3/μL, 141.1±119.3 mg/dL and 9.1±15.7 ng/mL, respectively. There was no statistically significant difference between patients with and without XDR infection. The mean length of hospital stay was 12.3±21.6 days before ICU admission. The mean length of ICU and hospital stay were 10.1±12.7 and 22.0±25.8 days. Intubation was performed on the mean 2.2±3.8 day after ICU admission. The mean duration of intubation and mechanical ventilation were 4.8±4.2 and 7.1±10.0 days. The mean length of central venous catheter stay was 24.8±37.5 days. Patients with XDR infection had longer length of hospital stay before ICU admission, ICU-hospital stay. In this patient group, the number of days with intubation, mechanical ventilation and central venous catheter were higher than patients without XDR (p<0.05) (Table 5).

The 7 and 30 day mortality were 58.4% and 92.6%, respectively. The 30-day mortality rate of medical ICU (58.2%) was significantly higher than surgical ICU (41.8%) (p=0.018).

Discussion

In this study, we investigated the prevalence of sepsis and XDR infection in deceased critically ill patients for 1 year. Of the 525 patients admitted to the ICU during the study period, 269 deceased were evaluated. The deceased critically ill medical patients were higher than the surgical patients. Forty percent of deceased critically ill patients were diagnosed with sepsis and one third of them had XDR infection. XDR infections were more frequent among patients who used antibiotics, had infection and stayed in hospital before ICU admission, with central venous catheter, urinary catheter and drain line. The deceased patient with XDR infections had prolonged ICU-hospital stay and duration of intubation-mechanical ventilation. In our study, it was found that patients who died were mostly followed in the medical ICU. Orban et al. (10) presented that the mortality rate was higher in mixed (medical-surgical) ICU, most of the anticipited deaths were in the medical ICU. The number of organ failures was higher among anticipated death patients in Orban's study. This difference was thought to be related to the older age of our patients and the presence of more comorbidities in our study. At the same time, mortality rate was higher in medical ICU in the study of Ay et al. (11). Because, similar with our groups, they were older than 70 years and had more cardiopulmonary problems. Sepsis remain high-risk factor for mortality in critically ill patients. We presented that the the incidence of sepsis at ICU admission was 44%. Orban et al. (10) reported that the sepsis incidence was 28% and 63% of patients had central venous catheter. We thought that this high rate was related to the hospitalization, presence of infection and antibiotic usage of our patients before ICU admission. At the same time, our patients were older and had more comorbidities.

Table 5. Length of stay and outcomes of patients

	Mean ± SD			
	Total (n=269)	XDR (n=93)	Non-XDR (n=176)	p-value
Intubation time	4.8±4.2	5.2±0.5	3.2±0.2	<0.001
Duration of central venous catheter	24.8±37.5	37.5±2.8	36.2±3.7	0.006
Duration of MV	7.1±10.0	14.5±1.5	4.6±0.3	<0.001
LOS before ICU	12.3±21.6	27.5±2.8	17.5±1.3	0.038
LOS at ICU	10.1±12.7	17.6±1.8	6.1±0.4	<0.001
LOS at hospital	22.0±25.8	32.6±3.4	18.8±1.4	<0.001

SD: Standard deviation, XDR: extensively drug resistant, MV: mechanical ventilation, LOS: length of stay, ICU: intensive care unit

Invasive devices such as central venous or urinary catheters, or inadequate handwashing practices among healthcare workers, may cause the risk of infection in patients admitted to the hospital even for non-infectious reasons (4,10,12). A high number of our patients had central venous catheter and/or urinary catheterization. However, in our study, we did not investigate handwashing practices among healthcare workers. Further studies could meet this objective in the future. Antimicrobial resistance poses a major threat to patient's treatment as it leads to prolonged hospital-ICU stay, increased morbidity and mortality, and severe economic loss for patient and nation (13). We reported that 34.6% of deceased patients had XDR infection and infection before ICU admission, presence of central venous catheter, drain line and urinary catheter were associated with XDR infections. The patients with XDR infection had prolonged ICU and hospital stay. Longer duration of intubation and mechanical ventilation were required. Inappropriate and excessive usage of antibiotics and invasive procedures were common causes of drug-resistant infections have been presented (13,14). A clinical trial showed that receiving total parenteral nutrition, prior carbapenem use, and prior fluoroquinolone use were independently associated with XDR infections (8).

This study has some limitations. It was a retrospective study and had a small number of patients. It was conducted at a single center, which limits the generalizability of the results. Inclusion of only deceased patients is a limitation of the study for mortality rates. The data were collected from the digital patient records. There is a limitation for risk factors and a deficiency for identifying antibiotic types. Not all laboratory tests were done in all patients.

Conclusion

One of the most important causes of ICU death is sepsis and one of the causes of sepsis is drug-resistant infection. Forty percent of deceased critically ill patients were diagnosed with sepsis and one third of them had XDR infection. The deceased critically ill medical patients were higher than the surgical patients. XDR infections were associated antibiotic usage and hospital stay before ICU admission and invasive procedures (central venous catheter, drain line and urinary catheter, etc.). Preventing infections in ICU or hospital is most important than treatment. Determination and preventing risk factors for sepsis may reduce morbidity, mortality and economic losses.

Ethics

Ethics Committee Approval: This study was approved by the Başkent University Institutional Review Board (project no: KA21/309).

Informed Consent: Retrospective study.

Peer-review: Internally and externally peer-reviewed.

Authorship Contributions

Concept: H.Ş., P.Z., Design: H.Ş., P.Z., Data Collection and Process: F.İ.Y., Ç.Y., İ.U.O., T.Y.Y., Analysis or Interpretation: F.İ.Y., Ç.Y., İ.U.O., H.Ş., P.Z., Literature Search: F.İ.Y., Ç.Y., İ.U.O., T.Y.Y., Writing: F.İ.Y., H.Ş., T.Y.Y., P.Z.

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

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA 2016;315:801-10.
2. Cecconi M, Evans L, Levy M, Rhodes A. Sepsis and septic shock. Lancet 2018;392:75-87.
3. Fleischmann C, Scherag A, Adhikari NK, Hartog CS, Tsaganos T, Schlattmann P, et al. Assessment of Global Incidence and Mortality of Hospital-treated Sepsis. Current Estimates and Limitations. Am J Respir Crit Care Med 2016;193:259-72.
4. Rudd KE, Johnson SC, Agesa KM, Shackelford KA, Tsoi D, Kievlan DR, et al. Global, regional, and national sepsis incidence and mortality, 1990-2017: analysis for the Global Burden of Disease Study. Lancet 2020;395:200-11.
5. Magiorakos AP, Srinivasan A, Carey RB, Carmeli Y, Falagas ME, Giske CG, et al. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. Clin Microbiol Infect 2012;18:268-81.
6. Alexopoulou A, Vasilieva L, Agiasotelli D, Siranidi K, Pouriki S, Tsiriga A, et al. Extensively drug-resistant bacteria are an independent predictive factor of mortality in 130 patients with spontaneous bacterial peritonitis or spontaneous bacteremia. World J Gastroenterol 2016;22:4049-56.
7. Shi J, Sun T, Cui Y, Wang C, Wang F, Zhou Y, et al. Multidrug resistant and extensively drug resistant Acinetobacter baumannii hospital infection associated with high mortality: a retrospective study in the pediatric intensive care unit. BMC Infect Dis 2020;20:597.
8. Palavutitotai N, Jitmuang A, Tongsai S, Kiratisin P, Angkasekwinai N. Epidemiology and risk factors of extensively drug-resistant Pseudomonas aeruginosa infections. PLoS One 2018;13:e0193431.
9. Kidney disease: improving global outcomes (KDIGO) acute kidney injury work group. KDIGO clinical practice guideline for acute kidney injury. March 2012. https://kdigo.org/wp-content/uploads/2016/10/KDIGO-2012-AKI-GuidelineEnglish. pdf.
10. Orban JC, Walrave Y, Mongardon N, Allaouchiche B, Argaud L, Aubrun F, et al. Causes and Characteristics of Death in Intensive Care Units: A Prospective Multicenter Study. Anesthesiology 2017;126:882-9.
11. Ay E, Weigand MA, Röhrig R, Gruss M. Dying in the Intensive Care Unit (ICU): A Retrospective Descriptive Analysis of Deaths in the ICU in a Communal Tertiary Hospital in Germany. Anesthesiol Res Pract 2020;2020:2356019.
12. Mayr VD, Dünser MW, Greil V, Jochberger S, Luckner G, Ulmer H, et al. Causes of death and determinants of outcome in critically ill patients. Crit Care 2006;10:R154.
13. Trecarichi EM, Pagano L, Candoni A, Pastore D, Cattaneo C, Fanci R, et al. Current epidemiology and antimicrobial resistance data for bacterial bloodstream infections in patients with hematologic malignancies: an Italian multicentre prospective survey. Clin Microbiol Infect 2015;21:337-43.
14. Basak S, Singh P, Rajurkar M. Multidrug Resistant and Extensively Drug Resistant Bacteria: A Study. J Pathog 2016;2016:4065603.