Research Article / Araştırma Makalesi
doi: 10.18678/dtfd.1069393

Duzce Med J, 2022;24(2):187-192
Düzce Tıp Fak Derg, 2022;24(2):187-192

The Effect of Antibiotic Resistance and Inappropriate Empirical Antibiotic Therapy on 3-Day and 28-Day Mortality in Bacteremic Patients in the Intensive Care Unit: 5-Year Retrospective Analysis

Yoğun Bakım Ünitesindeki Bakteriyemik Hastalarda Antibiyotik Direncinin ve Uygunsuz Ampirik Antibiyotik Tedavisinin 3 Günlük ve 28 Günlük Mortalite Üzerine Etkisi: 5 Yıllık Retrospektif Analiz

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Received / Geliş Tarihi : 07.02.2022
Accepted / Kabul Tarihi : 08.08.2022
Available Online / Çevrimiçi Yayın Tarihi : 15.08.2022

ABSTRACT

Aim: The aim of this study was to examine the effects of antibiotic resistance, empirical antibiotic therapy, and comorbid diseases on 3-day and 28-day mortality in patients with bloodstream infections.

Material and Methods: Files of the patients with positive blood cultures results, between January 1st, 2015, and January 1st, 2020 were analyzed retrospectively. The primary outcome was 3-day mortality and the secondary outcome was 28-day mortality.

Results: A total of 515 patients, 208 (40.4%) female and 307 (59.6%) male, were included in the study. The median age of the patients was 73 (range, 18-95) years. Vancomycin resistance was detected in 8 (3.4%) of 233 gram-positive bacteria. Third-generation cephalosporin, meropenem, and colistin resistance rates of the 282 gram-negative bacteria were found to be 72.7% (n=205), 53.2% (n=150), and 9.9% (n=28), respectively. The 3-day and 28-day mortality rates were 14.4% (n=74) and 64.3% (n=331), respectively. Charlson comorbidity index score (CCIS) (p=0.001) and acute physiology and chronic health evaluation (APACHE) II score (p=0.019) were found to be risk factors for 3-day mortality. Risk factors for 28-day mortality were; age (p<0.001), CCIS (p<0.001), APACHE II score (p=0.001), chronic obstructive pulmonary disease (p=0.007), hospital-acquired infection (p=0.033), and inappropriate antibiotic therapy (p<0.001).

Conclusion: There was no association between antibiotic resistance and mortality, but inappropriate antibiotic treatment was found to increase the risk of 28-day mortality. In addition, since high CCIS and APACHE II scores increase the risk of both 3-day and 28-day mortality, we think that considering these scoring systems will reduce the risk of mortality.

Keywords: Mortality; sepsis; critical care; bacteremia; antibiotic; resistance.

ÖZ

Amaç: Bu çalışmanın amacı, kan dolaşımı enfeksiyonu tanılı hastalarda antibiyotik dirençi, ampirik antibiyotik tedavisi ve komorbid hastalıkların 3 günlük ve 28 günlük mortalite üzerine etkisinin incelenmesidir.

Gereç ve Yöntemler: 1 Ocak 2015 ile 1 Ocak 2020 tarihleri arasında pozitif kan kültürü sonucu olan hastaların dosyaları geriye dönük olarak analiz edildi. Birincil sonlanım noktası 3 günlük mortalite ve ikincil sonlanım noktası 28 günlük mortalite idi.

Bulgular: Çalışmaya, 208 (%40,4) kadın ve 307 (%59,6) erkek, toplam 515 hasta dahil edildi. Hastaların ortanca yaşı 73 (aralık, 18-95) yıl idi. 233 gram pozitif bakterinin 8'inde (%3,4) vankomisin direnci saptandı. 282 gram negatif bakterinin üçüncü kuşak sefalosporin, meropenem ve kolistin direnç oranları sırasıyla %72,7 (n=205), %53,2 (n=150) ve %9,9 (n=28) bulundu. 3 günlük ve 28 günlük mortalite oranları sırasıyla %14,4 (n=74) ve %64,3 (n=331) idi. Charlson komorbidite indeks skoru (Charlson comorbidity index score, CCIS) (p=0.001) ve akut fizyoloji ve kronik sağlık değerlendirmesi (acute physiology and chronic health evaluation, APACHE) skoru (p=0,019) 3 günlük mortalite için risk faktörleri olarak saptandı. 28 günlük mortalite için yaş (p<0,001), CCIS (p<0,001), APACHE II skoru (p=0,001), kronik obstrüktif akciğer hastalığı (p=0,007), hastane kaynaklı enfeksiyon (p=0,033) ve uygunsuz antibiyotik tedavisi (p<0,001) risk faktörleri idi.

Sonuç: Antibiyotik direnci ile mortalite arasında bir ilişki yoktu, ancak uygunsuz antibiyotik tedavisinin 28 günlük mortalite riskini artırdığı saptandı. Ayrıca yüksek CCIS ve APACHE II skorları hem 3 günlük hem de 28 günlük mortalite riskini arttırdığı için, bu skorlama sistemlerinin dikkate alınmasının mortalite riskini azaltacağını düşünüyoruz.

Anahtar kelimeler: Mortalite; sepsis; yoğun bakım; bakteriyemi; antibiyotik; direnç.

INTRODUCTION

Bloodstream infection (BSI) is a serious problem that causes an estimated five million deaths per year worldwide (1). Comorbid disease, antibiotic-resistant microorganisms, and inappropriate antibiotic therapy are thought to be risk factors for mortality in BSI (2-5). Infections due to bacterial resistance to antibiotics are a growing global problem. Unfortunately, our country has the greatest antibiotic use and antibiotic resistance (6,7). Increasing antibiotic resistance negatively affects the success of empirical antibiotic therapy. As a general opinion, it is thought that appropriate empirical therapy reduces mortality rates in patients with bacteremia (5,8). The majority of studies supporting this view were conducted on 28, 30, or 60-day mortality (3,5,9). Studies in England and Japan determined that a significant portion of mortality (6.7-11%) due to BSI occurred in the first 7 days (2,3). The clinical condition of patients who are admitted to the intensive care unit (ICU) with a pre-diagnosis of BSI or patients who develop BSI while being monitored in the ICU rapidly worsens within 3 days and results in mortality. The fact that the risk factors of 3-day mortality have not been investigated until now gives rise to a serious lack of information in the literature. Physicians need new strategies to identify risk factors affecting 3-day mortality from BSI to decrease mortality.

We aimed to examine the effects of antibiotic resistance, empirical antibiotic therapy, and comorbid diseases on 3-day and 28-day mortality in patients with BSI.

MATERIAL AND METHODS

This single-center case-control study was conducted at Niğde Ömer Halisdemir University Training and Research Hospital, a tertiary health care center with 47 beds in the ICU. Data were collected through the hospital's electronic system. Samples for blood cultures were obtained when patients had a body temperature of ≥38.3℃ or when a diagnosis of sepsis was made. Cultures with positive results were examined. Data belonging to the day when the patient's positive blood culture was taken were included in the study. Patients with bacteremia aged 18 years and over who were in the ICU between January 1st, 2015, and January 1st, 2020, were included in the study (Figure 1).

Exclusion criteria:

1. Single blood cultures positive for coagulase-negative staphylococci, *Corynebacterium* spp., *Bacillus* spp., and other potential skin contaminants,
2. Repeated positive culture results with the same bacteria after a first positive blood culture,
3. Two or more different bacteria are identified in the same blood culture.

The primary endpoint was mortality within the first 3 days of admission, while the secondary endpoint was mortality in 28 days. The study was approved by the Niğde Ömer Halisdemir University ethics committee (Date: 04.10.2019, no: 2019/36). The study was performed in accordance with the ethical standards of the 1975 Declaration of Helsinki.

Inappropriate antibiotic therapy was defined as the microorganism being resistant to the antimicrobial agent used. Intermediate susceptibility was classified as resistant. Combination therapy was considered to be appropriate if it contained at least one appropriate antibiotic. Patients who did not take antibiotics on the day of blood culture were considered as having inappropriate antimicrobial therapy. After culture and antibiotic resistance results were obtained, antibiotic therapy was adjusted according to the sensitivity pattern of the microorganism (de-escalation or escalation).

3-day mortality was defined as mortality that occurred within the first 72 hours after a blood culture sample was taken. 28-day mortality was defined as mortality that occurred within the first 28 days after a blood culture sample was taken. Hospital-acquired infection (HAI) was defined as infections that developed 48 hours or more after admission and did not appear to be incubating at the time of admission. The diagnoses of sepsis and septic shock were based on sepsis-1 criteria (10). In determining the sources of bacteremia, the physician's diagnosis in the patient records was taken into consideration. For mortality risk assessment, leukocyte count above 12 000 /mm^3, age of 75 years and over, C-reactive protein (CRP) above 100 mg/L, Charlson comorbidity index score (CCIS) of 4 points and above, and acute physiology and chronic health evaluation (APACHE) II score of 20 points and above were accepted as cut-off value. A white blood cell count (WBC) of 4000 to 10000 cells/mm^3 was considered normal and a CRP level between 0 and 5 mg/L was considered normal.

Bacterial identification and susceptibility were assessed using the VITEK 2 system (bioMérieux, France). Antibiotic susceptibility results were interpreted according to the European committee on antimicrobial susceptibility testing (EUCAST) criteria (11).

Statistical Analysis

All statistical analyses were performed using the IBM SPSS v.23. Normality assumption was assessed through the Kolmogorov-Smirnov test. Categorical variables were summarized as numbers and percentages, and continuous variables as median (interquartile range) [min-max]. The Pearson chi-square test or Fisher's exact test were used for comparisons of categorical variables. For the comparison of continuous measurements between the groups, the Mann-Whitney U test was used. All binary categorical and

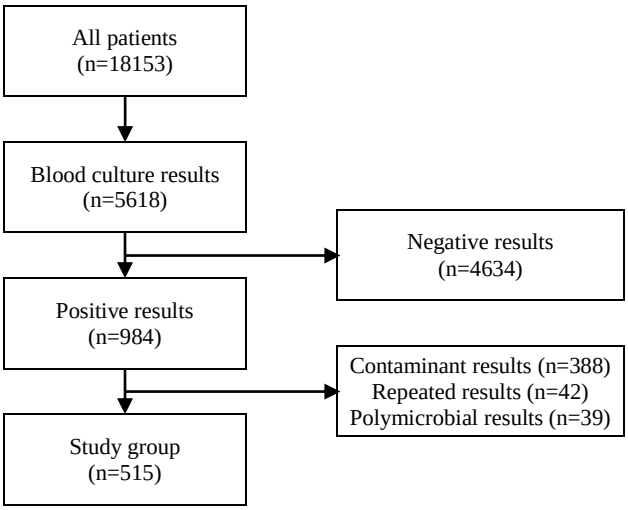

Figure 1. Flowchart of the study

continuous variables were compared to the variable patient survival using univariate binary logistic regression analysis. Variables found to be associated with mortality in univariate analyzes were included in the multivariate binary logistic regression (Backward: Wald method) model used to build a prediction model for BSI mortality. Variables found associated with BSI mortality were expressed with odds ratio (OR) and 95% confidence interval (CI). In all tests, $p<0.05$ was considered statistically significant.

RESULTS

After examining the files of 18 153 patients according to the inclusion and exclusion criteria, a total of 515 patients, of whom 208 (40.4%) were female and 307 (59.6%) were male, were included in the study. The median age of the patients was 73 (range, 18-95) years. The 3-day mortality rate was 14.4% (n=74), while the 28-day mortality rate was 64.3% (n=331). 414 (80.4%) patients had HAI. Of the 74 patients with 3-day mortality, 14 (18.9%) had HAI and of the 331 patients with 28-day mortality, 41 (12.4%) had HAI. 146 (28.3%) patients were in septic shock. Of those with 3-day mortality, 31 (41.9%) were in septic shock, and 104 (31.4%) of those with 28-day mortality were in septic shock. The baseline characteristics of the study group and the comparison of baseline characteristics for 3-day and 28-day mortality were shown in Table 1.

Antibiotic treatment of 332 (64.5%) patients was not found appropriate. While 49 (66.2%) patients in the 3-day mortality group were receiving inappropriate antibiotic treatment, 230 (69.5%) patients in the 28-day mortality group were receiving inappropriate antibiotic treatment. In the 3-day mortality group, empirical antibiotics were not started in 5 (6.8%) patients in the first 24 hours, 47 (63.5%) had monotherapy and 22 (29.7%) had combined empirical antibiotic therapy. Of the patients with 28-day mortality, empirical antibiotics were not started in 23 (6.9%) patients in the first 24 hours, 227 (68.6%) had monotherapy and 81 (24.5%) had combined empirical antibiotic therapy. We found no significant difference in 3-day mortality between those whose empirical antibiotics were not started in the first 24 hours, and those who started monotherapy and combined empirical antibiotic therapy (p=0.148). The most common bacteria was *Acinetobacter baumannii* (Table 2).

In the univariate analyses, CCIS (p<0.001), APACHE II score (p=0.007), septic shock (p=0.005), diabetes mellitus (DM) (p=0.020), malignancy (p=0.029), and *A. baumannii* bacteremia (p=0.030) were found to be risk factors for 3-day mortality. Age (p<0.001), CCIS (p<0.001), APACHE II score (p<0.001), prolonged ICU stay (p=0.004), septic shock (p=0.038), HAI (p<0.001), DM (p=0.032), chronic obstructive pulmonary disease (COPD) (p=0.021), mechanical ventilation (MV) (p<0.001), central venous catheter (p=0.010), history of antibiotic use (p=0.001), source of lung infection (p=0.016), urinary tract infection (UTI) (p=0.031), *A. baumannii* bacteremia (p=0.027), *E. coli* bacteremia (p=0.002), combined empirical antibiotic therapy (p=0.048), and inappropriate empirical antibiotic therapy (p=0.002) were found to be risk factors for 28-day mortality.

Risk factors for 3-day mortality in multivariate analysis were CCIS (p=0.001) and APACHE II score (p=0.019). Age (p<0.001), CCIS (p<0.001), APACHE II score (p=0.001), COPD (p=0.007), HAI (p=0.033), and inappropriate antibiotic therapy (p<0.001) were found to be risk factors for 28-day mortality (Table 3).

Table 1. Baseline characteristics of the 3-day and 28-day survivors and non-survivors

	3-day Mortality			28-day Mortality			Total (n=515)
	Non-Survivors (n=74)	Survivors (n=441)	p	Non-Survivors (n=331)	Survivors (n=184)	p	
Age (years)*	73 (19) [26-95]	73 (20) [18-95]	0.979	75 (19) [22-95]	68 (24) [18-95]	**<0.001**	73 (20) [18-95]
Age ≥75 years, n (%)	32 (43.2)	213 (48.3)	0.420	177 (53.5)	68 (37)	**<0.001**	245 (47.6)
Female, n (%)	35 (47.3)	173 (39.2)	0.191	140 (42.3)	68 (37.0)	0.237	208 (40.4)
DM, n (%)	28 (37.8)	110 (24.9)	**0.020**	99 (29.9)	39 (21.2)	**0.032**	138 (26.8)
COPD, n (%)	21 (28.4)	155 (35.1)	0.256	125 (37.8)	51 (27.7)	**0.021**	176 (34.2)
Malignancy, n (%)	10 (13.5)	28 (6.3)	**0.029**	28 (8.5)	10 (5.4)	0.208	38 (7.4)
MV, n (%)	47 (63.5)	266 (60.3)	0.602	232 (70.1)	81 (44.0)	**<0.001**	313 (60.8)
CVC, n (%)	17 (23.0)	109 (24.7)	0.747	93 (28.1)	33 (17.9)	**0.010**	126 (24.5)
Antibiotic used, n (%)	35 (47.3)	196 (44.4)	0.648	167 (50.5)	64 (34.8)	**0.001**	231 (44.9)
Lung infection, n (%)	28 (37.8)	123 (27.9)	0.082	109 (32.9)	42 (22.8)	**0.016**	151 (29.3)
UTI, n (%)	18 (24.3)	100 (22.7)	0.755	66 (19.9)	52 (28.3)	**0.031**	118 (22.9)
CCIS ≥4, n (%)	38 (51.4)	143 (32.4)	**0.002**	146 (44.1)	35 (19)	**<0.001**	181 (35.1)
CCIS*	4 (3) [0-11]	2 (3) [0-10]	**<0.001**	3 (2) [0-11]	2 (2) [0-9]	**<0.001**	2 (3) [0-11]
APACHE II ≥20, n (%)	34 (45.9)	225 (51.0)	0.240	188 (56.8)	71 (38.6)	**<0.001**	259 (50.3)
APACHE II*	26 (10) [14-36]	23 (10) [6-38]	**0.007**	25 (9) [7-38]	21 (11) [6-34]	**<0.001**	24 (10) [6-38]
DBA-BC*	9 (15) [1-85]	10 (20) [1-170]	0.293	12 (19) [1-170]	5 (14) [1-104]	**0.004**	10 (20) [1-170]
WBC (/mm^3)*	12 (10) [1-30]	12 (8) [1-125]	0.843	12 (9) [1-48]	12 (8) [1-125]	0.370	12 (8) [1-125]
CRP (mg/L)*	152 (146) [24-554]	155 (127) [8-547]	0.225	155 (136) [11-554]	155 (139) [8-470]	0.504	155 (133) [8-554]

DM: diabetes mellitus, COPD: chronic obstructive pulmonary disease, MV: mechanical ventilation, CVC: central venous catheter, UTI: urinary tract infection, CCIS: Charlson comorbidity index score, APACHE: acute physiology and chronic health evaluation, DBA-BC: days between admission to blood culture, WBC: white blood cell count, CRP: C-reactive protein, *: median (interquartile range) [minimum-maximum]

Table 2. Distribution of microorganisms, and antibiotics resistance in 3-day and 28-day mortality groups

	3-day Mortality			28-day Mortality			Total (n=515)
	Non-Survivors (n=74)	Survivors (n=441)	p	Non-Survivors (n=331)	Survivors (n=184)	p	
Empirical antibiotic							
3. gen. CPH	16 (21.6)	87 (19.7)	0.706	62 (18.7)	41 (22.3)	0.334	103 (20.0)
PIP-TAZO	17 (23.0)	109 (24.7)	0.747	72 (21.8)	54 (29.3)	0.055	126 (24.5)
Carbapenem	29 (39.2)	169 (38.3)	0.887	135 (40.8)	63 (34.2)	0.143	198 (38.4)
Aminoglycoside	2 (2.7)	8 (1.8)	0.642	8 (2.4)	2 (1.1)	0.507	10 (1.9)
Glycopeptide	11 (14.9)	44 (10.0)	0.208	38 (11.5)	17 (9.2)	0.430	55 (10.7)
Colistin	11 (14.9)	36 (8.2)	0.064	33 (10.0)	14 (7.6)	0.373	47 (9.1)
Quinolones	9 (12.2)	35 (7.9)	0.229	34 (10.3)	10 (5.4)	0.060	44 (8.5)
GNB	45 (60.8)	237 (53.7)	0.258	181 (54.7)	101 (54.9)	0.964	282 (54.8)
A. baumannii	20 (27.0)	73 (16.6)	**0.030**	69 (20.8)	24 (13.0)	**0.027**	93 (18.1)
Klebsiella spp.	11 (14.9)	64 (14.5)	0.937	48 (14.5)	27 (14.7)	0.958	75 (14.6)
E. coli	6 (8.1)	54 (12.2)	0.305	28 (8.5)	32 (17.4)	0.002	60 (11.7)
P. aeruginosa	6 (8.1)	34 (7.7)	0.906	27 (8.2)	13 (7.1)	0.657	40 (7.8)
Others	2 (2.7)	12 (2.7)	1.000	9 (2.7)	5 (2.7)	0.999	14 (2.7)
Antibiotic resistance for GNB (n=282)							
Ampicillin	42 (93.3)	222 (93.7)	1.000	168 (92.8)	96 (95.0)	0.462	264 (93.6)
3. gen. CPH	32 (71.1)	173 (73.0)	0.795	135 (74.6)	70 (69.3)	0.340	205 (72.7)
PIP-TAZO	26 (57.8)	146 (61.6)	0.630	109 (60.2)	63 (62.4)	0.722	172 (61.0)
Meropenem	24 (53.3)	126 (53.2)	0.983	94 (51.6)	56 (55.4)	0.571	150 (53.2)
Colistin	6 (13.3)	22 (9.3)	0.416	20 (11.0)	8 (7.9)	0.400	28 (9.9)
Ciprofloxacin	32 (71.1)	165 (69.6)	0.842	127 (70.2)	70 (69.3)	0.880	197 (69.9)
Gentamycin	24 (53.3)	117 (49.4)	0.626	93 (51.4)	48 (47.5)	0.535	141 (50.0)
GPB	29 (39.2)	204 (46.3)	0.258	150 (45.3)	83 (45.1)	0.964	233 (45.2)
CoNS	9 (12.2)	97 (22)	0.053	65 (19.6)	41 (22.3)	0.477	106 (20.5)
E. faecalis	7 (9.5)	44 (10.0)	0.890	35 (10.6)	16 (8.7)	0.494	51 (9.9)
S. aureus	9 (12.2)	36 (8.1)	0.260	26 (7.8)	19 (10.3)	0.341	45 (8.7)
E. faecium	4 (5.4)	23 (5.2)	1.000	22 (6.6)	5 (2.7)	0.055	27 (5.2)
Streptococcus spp.	0 (0)	4 (0.9)	1.000	2 (0.6)	2 (1.1)	0.620	4 (0.7)
Antibiotic resistance for GPB (n=233)							
Ampicillin	14 (48.3)	128 (62.7)	0.135	91 (60.7)	51 (61.4)	0.907	142 (60.9)
Clindamycin	16 (55.2)	144 (70.6)	0.094	106 (70.7)	54 (65.1)	0.377	160 (68.7)
Ciprofloxacin	17 (58.6)	131 (64.2)	0.558	102 (68.0)	46 (55.4)	0.056	148 (63.5)
Vancomycin	0 (0)	8 (3.9)	0.600	6 (4.0)	2 (2.4)	0.715	8 (3.4)

CPH: cephalosporin, PIP-TAZO: piperacillin-tazobactam, GNB: gram-negative bacteria, GPB: gram-positive bacteria, CoNS: coagulase-negative Staphylococci

DISCUSSION

The mortality of BSI in ICU patients is high worldwide. Many variables such as the patient's underlying diseases, the genus of bacteria, antibiotic resistance, and appropriate treatment are effective on mortality. In the current study, factors affecting the risk of early and late mortality in BSI were examined. Malignancy, DM, chronic renal failure, heart disease, and age were reported as risk factors for mortality (8,12-14). In this study, COPD, DM, and age were associated with increased 28-day mortality risk. We think that the reason why COPD significantly increased the mortality risk in this study was that the source of infection was the lung, the percentage of patients on MV was high, and the frequency of *A. baumannii* was higher. Dysfunction in adaptive and innate immune responses due

Table 3. Multivariate analysis of risk factors for mortality

	B	OR (95% Cl)	p
3-day mortality			
CCIS	0.227	1.255 (1.095-1.438)	**0.001**
APACHE II	0.063	1.065 (1.010-1.122)	**0.019**
28-day mortality			
Age	0.028	1.028 (1.012-1.044)	**<0.001**
CCIS	0.301	1.351 (1.170-1.559)	**<0.001**
APACHE II	0.066	1.068 (1.025-1.112)	**0.001**
COPD	0.811	2.250 (1.242-4.077)	**0.007**
HAI	0.811	2.249 (1.066-4.745)	**0.033**
IAT	0.998	2.712 (1.599-4.599)	**<0.001**

HAI: Hospital-acquired infections, IAT: Inappropriate antimicrobial therapy

to DM reduces survival in sepsis. DM was the only chronic disease affecting both 3-day and 28-day mortality in univariate analysis. We anticipate that the mortality rate in patients with diabetes will decrease with the changes we plan to make in routine practice by monitoring blood glucose levels hourly in critically ill patients, and with early surgical intervention in diabetic foot infections.

It has been stated in many publications that CCIS and APACHE II scores were useful in 28-day mortality estimations in BSI (3,8,9,12,15,16). We found that both high APACHE II scores and CCIS were risk factors for 3-day and 28-day mortality. This was a new result for the literature and was important in the sense that it demonstrated benefits in predicting mortality in both 3-day and 28-day periods in both scoring systems.

Bloodstream infections caused by UTIs have a lower risk of mortality (3,12). In this study, mortality was lower in UTIs, which is consistent with the literature. It is noteworthy that we determined that lung-borne BSI increased 28-day mortality. The first reason why this result was not found in other studies may be the lower rates of MV use and the second reason may be the low prevalence of *A. baumannii* pneumonia (4,12). In this study, the source of infection was not a risk factor for 3-day mortality. According to this result, it can be interpreted that in the treatment of infections caused by the lung or urinary system, similar benefits are provided in the first 3 days, but it is more difficult to control pneumonia in 28 days; UTIs are more easily controlled in the following days. Lower respiratory tract infection frequency can be reduced by following infection control measures, shortening the duration of intubation, and head-of-bed elevation, thus reducing mortality. In studies conducted in Japan, England, and Switzerland, *E. coli* and *S. aureus* were the most frequently detected pathogens in BSI (3,5,12,17). In the study of Ergönül et al. (15) covering gram-negative bacteria, the most frequently seen were *A. baumannii* and *K. pneumoniae*, and in the study of Delle Rose et al. (13) and in this study, the most frequently observed pathogens were *A. baumannii*, *Klebsiella* spp., and coagulase-negative staphylococci. In these studies, where the frequency of *A. baumannii* and *Klebsiella* spp. was high, it is striking that the mortality rate and history of antibiotic use were higher than in other studies. The history of antibiotic use is an important risk factor for the emergence of such resistant microorganisms. We believe that mortality can be reduced by increasing compliance with antibiotic management programs, avoiding prolonged MV, and paying attention to isolation measures and hand hygiene.

In the treatment of BSI, it is essential to start antibiotic therapy quickly, at the right dose, and in accordance with epidemiological data. Inappropriate empirical antibiotic therapy is thought to increase mortality in BSI (5,8,9,12,18). We found that inappropriate antibiotic treatment increased 28-day mortality 2.7 times. However, Lim et al. (4) and Schuttevaer et al. (19) concluded that appropriate empirical antibiotic therapy did not reduce mortality. We think the fact that Lim et al. (4) only included ICU-acquired infections in their study and the frequency of *A. baumannii* was low caused them to reach this conclusion. The difference in patient selection criteria and methodology in the study of Schuttevaer et al. (19) may have led to this result. We believe that regulating empirical antibiotic therapy, taking into account risk factors such as colonization with resistant microorganisms, antibiotic use, and local antibiotic resistance will reduce inappropriate antibiotic use and 28-day mortality.

The irrational use of antibiotics is a serious problem in Türkiye, and the Republic of Türkiye Ministry of Health published a national action plan in 2014 (20). In the article published by Ergönül et al. (15) before this plan, it was determined that 68% of patients with BSI who died had used antibiotics before admission to the hospital. This study was conducted in Türkiye and antibiotic resistance rates of third-generation cephalosporin, quinolone, and carbapenem for gram-negative bacteria were found as 89%, 78%, and 62%, respectively (15). Antibiotic resistance of Türkiye is still higher than that of Japan and Switzerland (3,12). However, the decrease in antibiotic resistance and antibiotic use before hospitalization seen in this study, which was conducted 4 years after the study of Ergönül et al. (15), is promising. It can be predicted that methods to reduce unnecessary antibiotic use, such as the implementation of rational antibiotic management programs and national planning to restrict antibiotic use, will contribute to decreasing antibiotic resistance and the reduction of the mortality rates of BSI in the ICU in the future.

The 28-day mortality rate in this study was consistent with other studies (2-4,9,16,17). No studies in the literature show the 3-day mortality rate, but Evans et al. (2), and Hattori et al. (3) reported 7-day mortality rates of 6.7% and 11%, respectively. It is striking that we had a higher mortality rate in a shorter period. This result can be explained by the high frequency of HAI, the *A. baumannii* rate being much higher than in other studies, and the high rate of inappropriate antibiotic therapy.

The limitations of this study are that because it is a retrospective study, there may be minor errors in the patient records. Other limitations are the absence of Pitt bacteremia scores, sequential organ failure assessment scores, ceftazidime-avibactam treatment results, and intravenous fosfomycin treatment results. The study may be insufficient to reflect global practice because it is a single-center study.

CONCLUSION

In conclusion, the relationship between mortality and empirical antibiotic treatment, bacterial species, antibiotic resistance, CCIS, APACHE II score, and comorbid diseases in BSI were examined. This study indicated that both a high CCIS and a high APACHE II score were associated with increased 3-day and 28-day mortality. In addition, a correlation between 28-day mortality and advanced age, COPD, HAI, and inappropriate antibiotic therapy were found. Reducing HAI by following infection control measures, correct management of comorbid diseases, and appropriate empirical antibiotic use may be beneficial in reducing mortality. We think that this study will contribute to the literature in terms of showing that high APACHE II score and CCIS are important risk factors for both 3-day and 28-day mortality.

Ethics Committee Approval: The study was approved by the Ethics Committee of Niğde Ömer Halisdemir University (04.10.2019, 36).

Conflict of Interest: None declared by the authors.

Financial Disclosure: None declared by the authors.

Acknowledgments: The authors would like to thank Çağla Sarıtürk (Department of Statistics, Başkent University) for her assistance in statistical methods.

Author Contributions: Idea/Concept: İÖ, TAG; Design: İÖ, TAG; Data Collection/Processing: İÖ, Analysis/Interpretation: İÖ, TAG; Literature Review: İÖ; Drafting/Writing: İÖ, TAG; Critical Review: İÖ, TAG.

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