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Coronavirus Pandemic

Differences between COVID-19 and non-COVID-19 patients' bloodstream infections: a single-center retrospective study

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Abstract

Introduction: This study aimed to examine the differences between coronavirus disease 2019 (COVID-19) and non-COVID-19 patients with intensive care unit (ICU)-associated bloodstream infections (BSIs), in terms of epidemiological, clinical, microbiological, and outcome data.
Methodology: All patients who were followed up in the ICU of a university hospital between 18 March 2020 and 18 April 2022, and who had developed ICU-acquired BSI, based on the study criteria, were selected and divided into 2 groups: COVID-19 and non-COVID-19. Descriptive statistics were used to analyze differences between the groups. Logistic regression analysis was applied to determine mortality risk factors in BSI patients.
Results: 234 patients were treated for ICU-acquired BSI, 127 COVID-19 and 107 non-COVID-19. Respiratory sources were significantly more common in COVID-19 patients compared to non-COVID-19 patients (43.3% vs. 26%, $p = < 0.01$). Among the causative pathogens, *Acinetobacter baumannii* (24.4% vs. 5.6%, $p \leq 0.01$) and Gram-negative multidrug-resistant (MDR) bacteria (81.7% vs. 61.7%, $p = 0.020$) were detected more frequently in COVID-19 patients than in non-COVID-19 patients. The duration of antibiotic use in the hospital before BSI was longer in COVID-19 patients than in non-COVID-19 patients, and this was also associated with BSI in which Gram-negative MDR bacteria were active ($p = < 0.01$). Survival times after BSI were shorter in COVID-19 patients than in non-COVID-19 patients ($p = 0.032$).
Conclusions: We demonstrated that MDR microorganisms were prevalent in COVID-19 patients with ICU-acquired BSI, and this was partly due to antibiotic use in the hospital prior to BSI.

Key words: COVID-19; nosocomial infection; associated; BSI.

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Introduction

During the coronavirus disease 2019 (COVID-19) pandemic, the healthcare system developed due to severe patients requiring follow-up in the intensive care unit (ICU) following respiratory failure requiring mechanical fan support, shock, disseminated coagulopathy, and organ failure [1,2]. Bacterial infections were significantly more common in patients followed in the ICU than in patients in the ward [3], and this was found to increase the morbidity rate and mortality [4]. Although bloodstream infections (BSI) in patients with COVID-19 have been studied in recent years [5–7], few studies have focused on characteristics of BSI in COVID19 patients compared with those in non-COVID-19 patients [8,9].

It has been suggested that the abundance of Gram-positive cocci (especially coagulase-negative staphylococci (CNS) and enterococci) is greater in COVID-19 patients than in non-COVID-19 patients [8,10]. Reports have shown that Gram-negative bacteria originating from hospitals are more common [7,11]. It has also been shown that candidemia is more common in pregnant patients than in the general population [12].

It was noted that the incidence of infections caused by multidrug-resistant (MDR) bacteria increased during the pandemic period, and the risks associated with taking inadequate measures to control infections and unnecessary use of antibiotics was emphasized [9,13,14].

Our study was conducted over a longer period of time than previous studies in the literature, and planned to examine the basic features of BSI in COVID-19 and non-COVID-19 patients; including differences in the distribution of microorganisms, source of infection, and mortality, over a 2-year pandemic period.

Methodology

Patients aged > 18 years, who were hospitalized in

the ICU of a tertiary university hospital between 18 March 2020 and 18 April 2022, and who developed BSI > 48 hours after admission to the ICU were examined. The patients were divided into two groups: the COVID-19 group, in which the patients were severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) polymerase chain reaction (PCR) positive or compatible with typical radiological findings for COVID-19; and the non-COVID-19 group, in which the patients were PCR negative with radiological findings that were not compatible with COVID-19. Patient information was obtained retrospectively from the hospital database system. The patients who were transferred from another center, those with missing data, and those whose hospitalization date exceeded 90 days were not included.

Microbiology

Biochemical tests, disk diffusion tests, or the BD Phoenix automated system (Becton Dickinson, Sparks, NV, USA) were used to identify the microorganisms grown in blood culture, and their sensitivity to antibiotics. The sensitivity of the bacteria to antibiotics was determined according to the recommendations of the European Committee on Antimicrobial Susceptibility Testing (EUCAST) by means of a disc diffusion test based on the zone diameter or minimum inhibitory concentration (MIC) levels in an automated system.

Colistin sensitivity was assessed by an automated system or broth microdilution method. Gram-negative bacteria (*Klebsiella pneumoniae*, *Acinetobacter baumannii*, and *Pseudomonas aeruginosa)*, which were resistant to carbapenem; and Gram-positive bacteria vancomycin-resistant enterococci (VRE) and methicillin-resistant *S. aureus* (MRSA), were considered MDR [15].

Definitions

Occurrence of ICU-acquired BSI was determined based on the reproduction of a bacterium, that was considered to be a pathogen in the patient's blood culture, on the third day of BSI adjustment and thereafter. Typical skin contaminants (e.g., coagulase-negative staphylococci (CNS), *Corynebacterium* spp., etc.) were considered to be the cause of bacteremia if growth was observed in two or more vials out of four vials of blood cultures taken at different times, signs of infection were present, and antibiotic therapy was initiated by the clinician. The Gram-negative bacteria *S. aureus* and fungi were also considered pathogens when reproduced in a single vial. If enterococci and streptococci were not identified at the species level, and if they were reproduced in 2 or more vials, the pathogen was accepted by the clinic, and treatment was initiated. Streptococci other than viridans were considered pathogenic if clinically compatible.

In patients with multiple bacteremia periods, only the initial period was recorded, but the active fungus was also included in the subsequent period.

The diagnosis of BSI (primary or secondary), and other infections that cause BSI, were based on the guidelines of the Centers for Disease Control and Prevention (CDC) criteria [16–19].

Statistical analysis

IBM SPSS version 22 (IBM Corp., Armonk, NY, US) was used for statistical analysis. Student's t test and Mann–Whitney U test were used for the quantitative data; and the χ^2 test, Fisher's definitive test, Fisher–Freeman–Halton test, and Yates's continuity correction were used for the qualitative data. Logistic regression analysis was applied for the analysis of multivariable variance. The Kaplan–Meier method and the log-rank test were used for right-wing analysis.

Table 1. General characteristics of the patients.

Variables	COVID-19 (n = 127)	Non-COVID-19 (n = 107)	All (n = 234)	*p* value
Age, mean (std)	64.54 ± 12,02	65.95 ± 15.37	65.19 ± 13.64	0.442
Charlson comorbidity index, median (IQR)	3 (2–4)	4 (2–6)	3 (2–5)	**0.024***
SAPS II, mean ± std	6.51 ± 1,31	6.04 ± 1.25	6.29 ± 1.30	**< 0.01***
Length of stay in ICU (days), median (IQR)	16 (10–24)	19 (12–27)	16 (10.8–26)	0.120
Duration of invasive mechanical ventilation (days), median (IQR); n = 213	13 (8–18)	12 (6–22.5)	13 (8–21)	0.872
Time from hospital admission to ICU admission, median (IQR)	3 (0–6)	2 (0–5.75)	3 (0–6)	0.794
Gender				
Male, n (%)	76 (59.8%)	66 (61.7%)	142 (60.7%)	0.774
Female, n (%)	51 (40.2%)	41 (38.3%)	92 (39.3%)	
SVC use, n (%)	124 (97.6%)	104 (97.2%)	228 (97.4%)	0.574
HFNC/NIMV use, n (%)	20 (15.7%)	15 (14%)	35 (15%)	0.853
Antibiotic use in the last 3 months, n (%)	39 (30.7%)	48 (44.9%)	87 (37.1%)	**0.026***

Std: standard deviation; IQR: interquartile range; SAPS: simplified acute physiology score; ICU: intensive care unit; SVC: santral venous catheter; HFNC: high-flow nasal cannula; NIMV: noninvasive mechanical ventilation; COVID-19: coronavirus disease 2019. **Bold font** indicates significant *p* values.

Results

Our study included 234 patients, of whom 127 were COVID-19 and 107 were non-COVID-19 patients. The differences in the general characteristics of the patients in the two groups are summarized in Table 1. The simplified acute physiology score II (SAPS-II) score ($p = 0.06$) at the time of admission to the ICU was higher for those who did not have COVID-19.

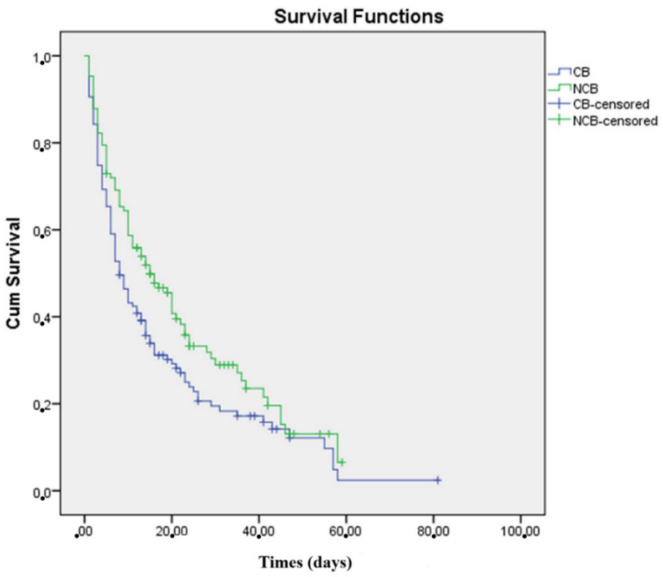
A total of 83.5% of COVID-19 patients and 60.7% of non-COVID-19 patients received invasive mechanical ventilation at the onset of BSI. 94.5% patients in the COVID-19 group and 86.9% patients in the non-COVID-19 group ($p = 0.074$) required invasive mechanical ventilation for at least 2 days during the duration of stay in the ICU.

Desaturation at the time of BSI was significantly more common in non-COVID-19 patients ($p = 0.022$). C-reactive protein (CRP) ($p = 0.019$) and procalcitonin ($p \leq 0.01$) were lower in COVID-19 patients than in non-COVID-19 patients. COVID-19 patients were more likely to have lower respiratory tract infections as a source of BSI than non-COVID-19 patients (26% vs 43.3%; $p \leq 0.01$).

The sequential organ failure assessment (SOFA) score ($p = 0.000$) and Pitt bacteremia score ($p \leq 0.01$) at the time of BSI, the number of days on which antibiotics were used before BSI ($p = 0.045$), and the proportion of patients requiring invasive mechanical ventilation at the time of BSI ($p \leq 0.01$) were greater in the COVID-19 group than in the non-COVID-19 group.

Compared to non-COVID-19 patients, empirical treatment was significantly less appropriate for COVID-19 patients ($p = 0.031$), and an increased antibiotic therapy spectrum ($p \leq 0.01$) was needed (Table 2). COVID-19 patients died earlier after the onset of BSI ($p = 0.045$) than non-COVID-19 patients. There was no significant difference in mortality between the two groups ($p = 0.071$), but there was a significant difference in survival ($p = 0.032$; Figure 1).

Figure 1. Kaplan–Meier analysis of the length of hospital stay due to bacteremia in COVID–19 patients and non-COVID–19 patients.



T_0 indicates the first day of bacteremia. CB: COVID-19 patient with bacteremia; NCB: non-COVID-19 patient with bacteremia; cum survival: cumulative survival.

Table 2. Comparison of BSI-related data in COVID-19 and non-COVID 19 patients.

Variables	COVID-19 (n = 127)	Non-COVID-19 (n = 107)	All (n = 234)	*p* value
Time from ICU admission to BSI (days)	10 (7–15)	8 (5–14)	9 (6–14)	0.071
Spent use of antibiotics before BSI (days)	10 (8–17)	9 (3–18)	10 (6–17)	**0.045***
Source of BSI				
Lower respiratory tract	55 (43.3%)	22 (20.6%)	77 (32.9)	**< 0.01***
Primary BSI	40 (31.5%)	28 (26.2%)	68 (29%)	0.371
Clinical and laboratory findings specific to BSI				
Desaturation	76 (59.8%)	48 (44.9%)	124 (53%)	**0.022***
Requirement of invasive mechanical ventilation at the time of BSI	106 (83.5%)	65 (60.7%)	171 (71.1%)	**< 0.01***
Requirement for inotropes/increased amount in the patient receiving inotropes	69 (54.3%)	61 (57%)	130 (55.5%)	0.681
SOFA score	11 (8–13)	8 (5–11)	10 (7–12)	**< 0.01***
Pitt bacteriemia score	8 (5–8)	6 (1–8)	6 (4–8)	**< 0.01***
CRP (mg/dl)	113.3 (59.8–204.4)	159.1 (76.5–233.2)	127.7 (68.9–207.01)	**0.019***
Procalcitonin (ng/ml)	0.9 (0.35–2.4)	1.85 (0.63–7.5)	1.21 (0.38–3.45)	**< 0.01***
Treatment				
Appropriateness of empirical treatment	58 (45.7%)	64 (59.8%)	122 (52.1%)	**0.031***
Decreased antibiotic therapy spectrum	0 (0%)	4 (3.7%)	4 (1.7%)	-
İncreased antibiotic therapy spectrum	68 (53.5%)	39 (36.4%)	107 (45.7%)	**< 0.01***
Mortality				
Time from BSI to death (days)	6 (3–13,3)	10 (4–20)	7 (3–16)	**0.045***
30-day mortality (time from BSI)	106 (83.5%)	79 (73.8%)	185 (79%)	0.071

The results are reported as n (%) for categorical variables and as median (IQR) for continuous variables. BSI: bloodstream infection; COVID-19: coronavirus disease 2019; ICU: intensive care unit; SOFA: sequential organ failure assessment scale; CRP: C-reactive protein. **Bold font** indicates significant *p* values.

Table 3. Distribution of microorganisms causing BSI in COVID-19 and non-COVID-19 patients.

Microorganism	COVID-19 (n = 127)	Non-COVID-19 (n = 107)	*p* value
Gram-negative bacteria	81 (63.8%)	59 (55.1%)	0.179
Enterobacteriaceae spp.	49 (38.6%)	44 (41.1%)	0.693
Klebsiella pneumoniae	46 (36.2%)	36 (33.6%)	0.681
Non-fermentative Gram-negative bacilli	33 (26%)	18 (16.8%)	0.125
Acinetobacter baumannii	31 (24.4%)	6 (5.6%)	**< 0.01***
Gram-positive bacteria	48 (37.8%)	40 (37.4%)	0.948
Enterococcus spp	26 (20.5%)	15 (14%)	0.262
Staphylococcus aureus	12 (9.4%)	13 (12.1%)	0.650
CNS	11 (8.7%)	12 (11.2%)	0.665
Fungi	9 (7.1%)	12 (11.2%)	0.384

BSI: bloodstream infection; COVID-19: coronavirus disease 2019; CNS: coagulase negative staphylococci. **Bold font** indicates significant *p* values.

Among the microorganisms that caused BSI in COVID-19 patients, 63.8% were Gram-negative bacteria, 37.8% were Gram-positive bacteria, and 7.1% were fungi (Table 3).

The occurrence of *Acinetobacter baumannii* as the pathogen causing BSI was much higher in COVID-19 patients than in non-COVID-19 patients (56% vs. 24.4%, $p \leq 0.01$). Enterococci were relatively more abundant in COVID-19 patients, but the difference was not statistically significant (20.5% vs 14%, $p = 0.262$).

An increase in the rate of MDR bacteria was observed in the COVID-19 group (Table 4). MDR bacteria were significantly more common in patients with COVID-19 (48.5% vs. 69.5%, $p = 0.02$). This difference was more pronounced in the case of Gram-negative bacteria. The incidence of MDR among Gram-negative bacteria was significantly greater in non-COVID-19 patients than in COVID-19 patients (81.7% vs. 61.7%, $p = 0.020$). The main reason for the difference in the occurrence of Gram-negative bacteria was the greater number of carbapenem-resistant *Acinetobacter baumannii* in those with COVID-19.

Table 4. Distribution of MDR bacteria in COVID-19 patients and non-COVID-19 patients.

Microorganism	COVID-19 (n = 127)	Non-COVID-19 (n = 107)	*p* value
Klebsiella pneumoniae (n = 82)			
Carbapenem-resistant	32 (69.6%)	22 (61.1%)	0.571
Acinetobacter baumannii (n = 37)			
Carbapenem-resistant and colistin-sensitive	28 (90.3)	6 (100)	0.579
Carbapenem and colistin-resistant	2 (6.5)	0	-
Pseudomonas aeruginosa (n = 8)			
Carbapenem-resistant	0	4 (50)	-
Enterococcus spp (n = 41)			
Vancomycin-resistant	3 (11.6)	1 (6.6)	-
Staphylococcus aureus (n = 25)			
Methicillin-resistant	12 (100)	9 (69.2)	0.096
Gram-negative bacteria (n = 141)			
Gram-negative MDR	67 (81.7%)	37 (62.7%)	**0.020***
Gram-positive bacteria (n = 88)			
Gram-positive MDR	15 (31.3%)	10 (25%)	0.682
All bacteria (n = 215)			
MDR	82 (69.5%)	47 (48.5%)	**< 0.01***

MDR: multidrug-resistance; COVID-19: coronavirus disease 2019. **Bold font** indicates significant *p* values.

Table 5. Evaluation of correlational statistics between MDR bacteria and the use of antibiotics.

	MDR (+) (n = 129)	MDR (-) (n = 86)	*p* value
Use of antibiotics in the last 3 months	48 (37.2%)	29 (33.7%)	0.601
Spent use of antibiotics before BSI (days)	11 (8–19)	7 (3–13.3)	**< 0.01***
	Gram-negative MDR (+) (n = 104)	**Gram-negative MDR (-) (n = 37)**	
Use of antibiotics in the last 3 months, %	40 (38.5%)	19 (27.9%)	0.209
Spent use of antibiotics before BSI (days)	12 (9–19)	8,5 (4.3–14)	**< 0.01***
	Gram-positive MDR (+) (n = 25)	**Gram-positive MDR (-) (n = 63)**	
Use of antibiotics in the last 3 months, %	8 (32%)	19 (30.2%)	1.000
Spent use of antibiotics before BSI (days)	7 (5–19)	9 (5–14)	0.978

The results are reported as n (%) for categorical variables and as the median [IQR] for continuous variables. MDR: multidrug resistant; BSI: bloodstream infection; IQR: interquartile range. **Bold font** indicates significant *p* values.

No correlation was found between the use of antibiotics in the last 3 months and the number of days antibiotics were used before BSI, but there was a correlation between the presence of Gram-negative MDR bacteria and the number of days antibiotics were used before BSI (p = 0,009; Table 5).

Based on multivariate analysis, the Pitt bacteremia score was a risk factor for mortality in patients with BSI [OR: 1.548 (95% CI: 1.235–1.939)]. The diagnosis of COVID-19 was not a risk factor for mortality (Table 6).

Discussion

The need for mechanical ventilation before BSI was significantly greater in patients without COVID-19 than in patients with COVID-19. Nevertheless, desaturation occurred more frequently in those with COVID-19 than in those without COVID-19. One reason for this is that the most common source of BSI in the COVID-19 group was respiratory infection. In addition, the diagnosis of ventilator associated pneumonia (VAP) requires that there be an increase in positive end-expiratory pressures (PEEPs) [18]. Since COVID-19 patients have acute respiratory distress syndrome (ARDS) in the foreground, BSI may have worsened the situation. The increased need for mechanical ventilation in COVID-19 patients is one of the major causes of respiratory infection. Studies have also shown that the incidence of VAP in COVID-19 patients in the ICU is 40% [3]. It is thought that the higher rate of mechanical ventilation requirement and more severe ARDS findings in COVID-19 patients before BSI may facilitate the development of VAP. The widespread use of the prone position may also have increased the incidence of VAP-causing microaspirations [20], and this treatment may have been more common in COVID-19 patients for the reasons mentioned earlier. Moreover, in patients with COVID-19, pulmonary infarction, which is more common due to coagulopathy, may increase the risk of secondary infection [21].

Studies conducted on microorganisms that cause BSI in COVID-19 patients have reported conflicting results regarding the distribution of the microorganism. The bacterial distribution in our study was similar to that in Italy, Hungary, Serbia, Romania, Bulgaria, Greece, Croatia, and India; where carbapenem resistance exceeded 50% and Gram-negative bacteria were endemic [7–9,14]. A retrospective study in India revealed that Gram-negative bacteria caused 82.8% of bloodstream infections in COVID-19 patients, with *Acinetobacter baumannii* accounting for 32.8% and *Klebsiella pneumoniae* accounting for 21.9%. All Gram-positive bacteria were enterococci [7].

Moreover, bacteremia of unknown cause was also found to be common in COVID-19 patients. In Buetti *et al*.'s study comparing COVID-19 and non-COVID-19 patients with ICU-acquired BSI, the source of bacteremia was not identified in 47.4% of COVID-19 patients and 25% of non-COVID-19 patients. This condition has been associated with bacteria, especially enterococci [8]. In our study, the source of bacteremia was unknown in 73% of the patients who had COVID-19 with enterococcal bacteremia. In the non-COVID-19 group of patients with enterococcal bacteremia, the predominant sources of bacteremia were catheter-related infections and intra-abdominal infections, with an unknown bacteremia rate of 26%. In addition, 77% of the polymicrobial bacteria in the COVID-19 group were enterococci. *Enterococcus* spp. and *Klebsiella pneumoniae* together accounted for 46% of polymicrobial bacteremia cases, but the source of this type of bacteremia is unknown. In non-COVID-19 patients, the association of two Gram-negative bacteria

Table 6. Evaluation of mortality risk factors in patients with BSI.

	Univariate analysis			Multivariate analysis	
	Non-survivors (n = 185)	**Survivors (n = 49)**	***p* value**	**OR (95% CI)**	***p* value**
Age, mean (std)	66.32 ± 12.76	60.9 ± 15.99	**0.013***		
Charlson comorbidity index, (median) [IQR]	3 (2–5)	2 (0.5–3.5)	**< 0.01***		
..SAPS II, mean (std)	6.47 ± 1.28	5.6 ± 1.13	**< 0.01***		
Duration of invasive mechanical ventilation (days), median (IQR)	13 (8–22)	9 (4–16.8)	**0.013***		
SOFA, (median) [IQR]	11 (8–13)	5 (3.5–8)	**< 0.01***		
Pitt bacteriemia score, median (IQR)	8 (6–8)	1 (0–4.5)	**< 0.01***	**1.548** (1.235–1.939)	**< 0.01***
	n (%)	**n (%)**			
Requiring invasive mechanical ventilation at the time of BSI, %	157 (84.9%)	14 (28.6%)	**< 0.01***		
Lower respiratory tract infection, %	67 (36.2%)	10 (20.4%)	0.055		
COVID-19 diagnosis, %	106 (57.3%)	21 (42.9%)	0.071		
Appropriateness of empirical treatment, %	98 (53%)	24 (49%)	0.619		
Acinetobacter baumannii, %	30 (16.2%)	7 (14.3%)	0.913		
Gram-negative MDR, %	90 (77.6%)	14 (56%)	**0.048***		

The results are reported as n (%) for categorical variables and as the median (IQR) for continuous variables. BSI: bloodstream infection; CI: confidence interval; OR: odds ratio; IQR: interquartile range; SAPS: simplified acute physiology score; SOFA; sequential organ failure assessment; COVID-19: coronavirus disease 2019; MDR: multidrug resistant. **Bold font** indicates significant *p* values.

with polymicrobial bacteria, which are generally proven intra-abdominal infections, was common. It has been previously noted that bacteria belonging to the intestinal microbiota, most commonly enterococci, are commonly found as the causative agent of BSI in COVID-19 patients in the ICU [8,22–24]. This has been associated with SARS-CoV-2-associated coagulopathy affecting micro- and macrocirculation, thus likely increasing the risk of bacterial translocation (e.g., in the gastrointestinal tract), the frequent occurrence of endothelial dysfunctions of the digestive system in patients with COVID-19, and the increased incidence of mesenteric infarction [8,25].

Acinetobacter baumannii was isolated significantly more often in the COVID-19 group than in the non-COVID-19 group. In the COVID-19 group, VAP was the source of infection in 77.5% of patients with *Acinetobacter baumannii* bacteremia. Fan *et al*. studied the microbiota of lung tissue in 20 patients who died from mechanical ventilation and COVID-19; and found that the microbiome was enriched with species of *Acinetobacter*, including carbapenem-resistant *Acinetobacter baumannii* [26]. Russo *et al.* studied *Acinetobacter baumannii* infections in non-COVID-19 patients between 2019 and 2021, and reported that the prevalence of bacteremia was significantly greater in those with COVID-19 than in non-COVID-19 patients (56% vs. 8%). Nearly 60% of all bacteremia are caused by VAP, and bacteremia has been identified as a risk factor for mortality [27]. In European countries, the first 2 years of the pandemic showed a significant increase in the rate of circulatory infections caused by *Acinetobacter baumannii* compared to the previous 3 years. This was especially the case in countries where carbapenem resistance exceeded 50%, and statistically significant increases were observed, mostly in the US [28]. In our country, the rates of resistance to carbapenem in *Acinetobacter baumannii* were similar during the pandemic period, as they were 90% resistant even prior to the pandemic.

The prominence of *Acinetobacter baumannii*, which is known to be able to spread epidemics easily through contamination of the hands of health workers, medical instruments, and hospital surfaces; suggests a lack of measures to control infections. It could be argued that the healthcare workers were not paying enough attention to infection control measures, especially hand hygiene, due to their workload. Behaviors such as continuing to use the same gloves after disinfecting them with alcohol, using double gloves, and using the same contact apron or gloves due to the lack of supplies or the intensity of workload during the pandemic period have been observed in our hospital.

Many publications have indicated that MDR bacteria rates increased during the pandemic. A single-center retrospective study was performed on ICU-associated BSI in COVID-19 patients in a university hospital in Croatia during the pandemic. All of *Acinetobacter baumannii* strains and 87.5% of *Klebsiella pneumoniae* strains were resistant to carbapenems, and 20.5% of enterococcal strains were resistant to vancomycin [14]. This finding is similar to the data in our study. Poor implementation of infection control measures and the fact that 93.4% of patients received antibiotics before BSI were shown as causes of MDR bacteremia [29]. In a retrospective study of MDR Gram-negative bacterial infections among ICU patients at a single center in Italy, the incidence of carbapenem-resistant *Acinetobacter baumannii* was significantly greater in those with COVID-19 than in those without COVID-19 (78.9% vs 38.6%), and *Pseudomonas aeruginosa* was never identified in the COVID-19 group, similar to our study. [14]. During the COVID-19 pandemic, many hospitals experienced outbreaks in the ICU that were often caused by Gram-negative MDR bacteria. Among the Gram-negative bacteria, carbapenem-resistant *Acinetobacter baumannii* is the most frequently occurring pathogen [30], and has been found to be associated with high mortality [27].

Since the study was conducted over a period of 2 years, the distribution of COVID-19 and non-COVID-19 patients over time was variable. COVID-19 cases were very concentrated during the peak periods, and non-COVID-19 patients decreased simultaneously during this period. Conversely, when COVID-19 cases decreased, the areas allocated for non-COVID-19 patient follow-up increased. The incidence of BSI in patients with COVID-19 was very high in the 4-month period between September and December 2020, when the number of COVID-19 cases increased significantly. One of the most important reasons for the increase in MDR in COVID-19 patients was the high patient load in some periods, and the provision of service above the patient capacity for that period. Such a situation was not observed in the non-COVID-19 group.

In a study by Buetti *et al*. [9], antibiotic use in the week before BSI was more common in patients with COVID-19 than in patients without COVID-19, suggesting that this was associated with the development of BSI with more MDR bacteria. A systematic review of MDR bacterial outbreaks in COVID-19 patients revealed increased antibiotic use as

a significant contributing factor to outbreaks in 7 studies [30]. In our study, COVID-19 patients had used fewer antibiotics in the previous 3 months, and there was no correlation between this and the development of BSI with MDR bacteria. The duration of antibiotic use before BSI was longer in COVID-19 patients, and there was a significant association between the duration of antibiotic use before BSI in the hospital and the development of BSI with Gram-negative MDR bacteria. Accordingly, the findings indicate that prolonged antibiotic use in the hospital before BSI, rather than antibiotic use before hospitalization, played a more significant role in the development of BSI with MDR bacteria in patients with severe COVID-19 admitted to the ICU.

During BSI, SOFA and Pitt bacteremia scores were significantly greater in those with COVID-19 than in the non-COVID-19 patients. In a single-center retrospective study in a university hospital in Italy where the incidence of MDR Gram-negative bacteria in COVID-19 patients in the ICU was compared with that in non-COVID-19 patients, the rate of septic shock during bacteremia and the Pitt bacteremia score were significantly greater in those with COVID-19 [14].

In a study comparing COVID-19 patients with non-COVID-19 patients [8], there was no significant difference between the 60-day mortality rates. Another study [9] showed that the 28-day mortality rate was significantly greater for those with COVID-19 than for those without COVID-19, and there was a significant difference in survival. In our study, there was no difference in 60-day mortality rates between COVID-19 and non-COVID-19 patients, but when evaluated with the log rank test for survival time, survival times were lower in COVID-19 patients than in non-COVID-19 patients, with statistically significant differences between the two groups ($p = 0.032$, $p < 0.05$, respectively). This may be associated with a heavier organ failure chart during BSI in the COVID-19 group and a higher SAPS-II score during admission to the ICU. In a study by Buetti *et al*. [9], the SOFA score at the time of BSI was found to be an independent risk factor for mortality. In our study, Pitt bacteremia scores were found to be an independent risk factor for mortality in patients with BSIs. Several studies have shown that a diagnosis of COVID-19 in patients with BSIs is a risk factor for mortality, but our study did not find this association [9,14].

This study had several limitations. First, the study was retrospective. Furthermore, our findings cannot be generalized to the entire population because they were obtained from a single center. We did not have data on the antibiotics administered to the patients. Furthermore, due to the constraints of the pandemic period, we were unable to identify certain bacteria at the species level.

Conclusions

Our study found a higher rate of MDR in COVID-19 patients, and it is important to organize empirical treatment considering this situation. The rate of antibiotic use in the last 3 months was lower in COVID-19 patients compared to non-COVID-19 patients, while the number of days of antibiotic use in the hospital before BSI was longer, which may be related to the development of MDR. However, infection control measures such as hand hygiene and contact isolation may have also caused an increase in MDR bacteria, and our study could not examine the effect of this. More studies are needed on this subject.

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This work was conducted at the Istanbul University Faculty of Medicine, Istanbul, Turkey.

Ethics approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Istanbul University Clinical Research Ethics Committee (1523523) in 2022. Informed consent was obtained from all participants.

Authors' contributions

HÖ, organization and coordination of the trial; ÇKS, chief investigator, and was responsible for the data analysis; ÇKS, HÖ, SB, AB, trial development, management and administration of the trial, writing the final manuscript.

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Conflict of interests

No conflict of interests is declared.

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