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Differences in the Epidemiology, Clinical Characteristics, Distribution of Microorganisms and Outcomes between COVID-19 Patients and Non-COVID-19 Patients with ICU-Associated BSIs: A One-Center Retrospective Study

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Abstract

Background: We aimed to study the differences between patients with COVID-19 and non-COVID-19 ICU-associated BSIs in terms of epidemiological, clinical, microbiological and outcome data.

Methods: All patients who were followed up in the intensive care unit of a university hospital between 18th March, 2020 and 18th April, 2022 and the ICU-acquired BSI definition according to the study criteria were selected and divided into two groups: COVID-19 and non-COVID-19. In patients with multiple bacteriemia periods, only the initial period was recorded, but the active fungus was also included in the subsequent period. Descriptive statistics were used to analyze differences between patients with COVID-19 and those without COVID-19. Logistic regression analysis was applied to determine mortality risk factors in BSI patients.

Results: 234 patients were treated for ICU-acquired BSI, 127 with COVID-19 and 107 without COVID-19. Respiratory sources were significantly more common in COVID-19 patients compared to non-COVID-19 patients (43.3% *vs.* 26%, $p \leq 0.01$). 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 ($p \leq 0.01$). Survival times after BSI were shorter in COVID-19 patients than in non-COVID-19 patients (p=0.032).

Conclusion: We showed that MDR microorganisms were prevalent in COVID-19 patients with ICU-acquired BSI and this was partly due to the length of antibiotic use in the hospital prior to BSI. Survival was lower in COVID-19 patients with BSI.

Keywords: COVID-19; Bloodstream infection; ICU-acquired infections; Multidrug resistant bacteria

Abbreviations: MDR: Multidrug-Resistant; ICU: Intensive Care Unit; CNS: Coagulase-Negative *Staphylococci*; PCR: Polymerase Chain Reaction; CT: Computed Tomography; VRE: Vancomycin-Resistant *Enterococci*; MRSA: Methicillin-Resistant *S. aureus*; EUCAST: European Committee on Antimicrobial Susceptibility Testing; SOFA: Sequential Organ Failure Assessment.

Introduction

During the COVID-19 (Coronavirus disease 2019) pandemic, the healthcare system has developed a density due to severe patients requiring follow-up in the Intensive Care Unit (ICU) due to respiratory failure requiring mechanical ventilator support, shock, dyseminate coagulopathy and organ failure [1,2]. In addition to various problems, bacterial infections were found to be significantly more common in patients followed in the ICU than in patients in service and this has been found to increase the morbidity rate of mortality [3,4]. Although bloodstream infections in patients with COVID-19 have been studied in various studies, few studies have examined their differences compared with those in non-COVID-19 patients [5-9].

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 also shown that gram-negative bacteria originating from hospitals are more common [7,11]. It has also been shown that candidaemia is more common in pregnant patients than in the general population [12].

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

Our study included a longer period of time than 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, during a two-year pandemic period.

Materials and Methods

Patients aged >18 years who were hospitalized in the intensive care unit of a tertiary university hospital between 18th 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 SARS-CoV-2-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 system. Patients who were transferred from another center, those with missing data, and those whose hospitalization date exceeded 90 days were not included.

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Microbiology

1. Biochemical tests, disk diffusion tests or BD Phoenix automated system (Becton Dickinson, USA) were used to identify microorganisms grown in blood culture and their sensitivity to antibiotics.
2. Recommendations of the European Committee on Antimicrobial Susceptibility Testing (EUCAST) have determined the sensitivity of bacteria to antibiotics by means of a disc diffusion test based on the zone diameter or MIC levels in an automated system.
3. Colistine sensitivity assessed by an automated system or broth microdilution method.
4. *Klebsiella pneumoniae*, *Acinetobacter baumannii* and *Pseudomonas aeruginosa*, which are resistant to carbapenem from gram-negative bacteria, and Vancomycin-Resistant *Enterococci* (VRE) and Methicillin-Resistant *S. aureus* (MRSA), which are from gram-positive bacteria, are considered Multidrug Resistant (MDR) [15].

Definitions

1. ICU-acquired BSI was defined as the reproduction of a bacterium considered to be a pathogen in the patient's blood culture on the third day of BSI adjustment and thereafter. Bacteriemia is caused by typical skin contaminants (e.g., Coagulase-Negative *Staphylococcus* (CNS), *Corynebacterium* spp., etc.), reproduction in two or more vials of four vials of blood cultures taken at different times, clinical signs of infection and initiation of antibiotic therapy, as validated by the clinic. The gram-negative bacteria *S. aureus* and fungus were also considered pathogens when reproduced in a single vial. If *Enterococci* and *Streptococci* were not identified at the species level, if they were reproduced in two or more vials, the pathogen was accepted by the clinic and treatment was initiated. *Streptococci* other than viridans were considered pathogenic if clinically compatible.
2. In patients with multiple bacteriemia periods, only the initial period was recorded, but the active fungus was also included in the subsequent period.
3. Diagnosis of bloodstream infection (primary or secondary) and other infections that cause BSI, based on Centers for Disease Control and Prevention (CDC) criteria [16-19].

Statistical analysis

IBM SPSS statistics 22 was used. For the quantitative data, student's t test and the Mann-Whitney U test were used; for the qualitative data, the χ^2 test, Fisher's definitive test, Fisher-Freeman-Halton test and Yates's continuity correction were used. Logistic regression analysis was applied to the analysis of multivariable variance. The Kaplan-Meier method and the log-rank test were used for right-wing analysis.

Results

Our study included 234 patients, including 127 with COVID-19 and 107 non-COVID-19. The differences between the general characteristics of the patients are shown in Table 1. The SAPS-2 score (p=0.06) at the time of admission to the ICU was greater for those who did not have COVID-19.

Variables	COVID-19 (n=127)	Non-COVID-19 (n=107)	All (n=234)	p
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 ICU (days), median (IQR)	16 (10-24)	19 (12-27)	16 (10,8-26)	0.12
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

Table 1: General characteristics of the patients.

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

Desaturation at the time of BSI (p=0.022) was significantly more common in non-COVID-19 patients. 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 were (%26 *vs.* 43.3; $p \leq 0.01$).

The Sequential Organ Failure Assessment (SOFA) score (p=0,000) and Pitt bacteraemia 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 HABSI ($p \leq 0.01$) 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).

Variables	COVID-19 (n=127)	Non-COVID-19 (n=107)	All (n=234)	p
SOFA	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
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
CRP (mg/dl)	113, 3 (59, 8-204, 4)	159, 1 (76, 5-233, 2)	127, 7 (68, 9-207, 01)	0.019
Procalsitonin (ng/ml)	0, 9 (0, 35-2, 4)	1, 85 (0, 63-7, 5)	1, 21 (0, 38-3, 45)	<0.01
Time from BSI to death (days)	6 (3-13, 3)	10 (4-20)	7 (3-16)	0.045
Source of BSI				
Lower respiratory tract, %	55 (43.3%)	22 (20.6%)		<0.01
Primary BSI, %	40 (31.5%)	28 (26.2%)		0.371

Requiring invasive mechanical ventilation at the time of BSI, %	106 (83.5%)	65 (60.7%)		<0.01
Clinical findings at BSI time				
Desaturation	76 (59.8%)	48 (%44.9)	124 (53%)	0.022
Requirement for inotropes/increased amount in the patient receiving inotropes	69 (54.3%)	61 (%57)	130 (55.5%)	0.681
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
30-day mortality (time from BSI)	106 (83.5%)	79 (73.8%)	185 (79%)	0.071

Note: The results are reported as the n (%) for categorical variables and as the median (IQR) for continuous variables. Sequential Organ Failure Assessment Scale (SOFA), C-reactive protein (CRP).

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

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).

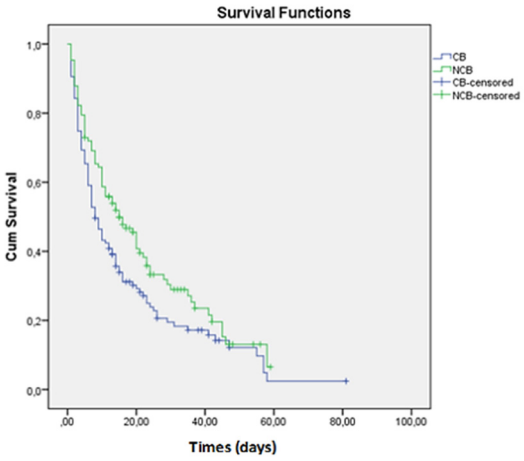

Figure 1: Kaplan-Meier analysis of the length of hospital stay from bacteremia in COVID-19 patients and non-COVID-19 patients. T0 was the first day of bacteremia.

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

Microorganism	**COVID-19**	**Non-COVID-19**	**p**
	(n=127)	**(n=107)**	
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
Nonfermentative 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
S. aureus	12 (9.4%)	13 (12.1%)	0.65
Coagulase Negative *Staphylococci* (CNS)	11 (8.7%)	12 (11.2%)	0.665
Fungi	9 (7.1%)	12 (11.2%)	0.384

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

The rate 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 ≤ 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 MDR bacteria was observed in the COVID-19 group (Table 4). MDR bacteria were significantly more common in those COVID-19 (48.5% *vs.* 69.5%, p=0.02). This difference was more pronounced in gram-negative bacteria. The incidence of MDR bacteria 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 between the gram-negative bacteria was the greater number of carbapenem-resistant *Acinetobacter baumannii* in those with COVID-19.

Microorganism	**COVID-19**	**Non-COVID-19**
	(n=127)	**(n=107)**
Klebsiella pneumoniae (n=82)		
Carbapenem-resistant	32 (69.6%)	22 (61.1%)
Acinetobacter baumannii (n=37)		
Carbapenem-resistant and colistin-sensitive	28 (90.3)	6 (100)
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)
S. aureus (n=25)		
Methicillin-resistant	12 (100)	9 (69.2)
Gram-negative bacteria (n=141)		
Gram-negative MDR	67 (81.7%)	37 (62.7%)
Gram-positive bacteria (n=88)		

Gram-positive MDR	15 (31.3%)	10 (25%)
All bacteria (n=215)		
MDR	82 (69.5%)	47 (48.5%)

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

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 correlational statistics between the presence of gram-negative MDR bacteria and the number of days antibiotics were used before BSI (p=0,009) (Table 5).

	MDR (+)	**MDR (-)**	**p**
	(n=129)	**(n=86)**	
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 (+)	**Gram-negative MDR (-)**	**p**
	(n=104)	**(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 (+)	**Gram-positive MDR (-)**	**p**
	(n=25)	**(n=63)**	
Use of antibiotics in the last 3 months, %	8 (32%)	19 (30.2%)	1
Spent use of antibiotics before BSI (days)	7 (5-19)	9 (5-14)	0.978
Note: The results are reported as n (%) for categorical variables and as the median (IQR) for continuous variables.			

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

According to the multivariate analysis, the Pitt bacteraemia score was found to be a risk factor for mortality in patients with BSIs (OR: 1,548 (95% CI: 1,235-1,939)). The diagnosis of COVID-19 was not a risk factor for mortality (Table 6).

	Univariate analysis		**p**	**Multivariate analysis**	
	Nonsurvivors (n=185)	**Survivors (n=49)**		**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 (%)**	**p**		
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, %	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		
Note: The results are reported as n (%) for categorical variables and as the median (IQR) for continuous variables.					

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

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 VIP requires that there be an increase in PEEPs [18]. Since COVID-19 patients have ARDS in the foreground, KDI 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 VİP in COVID-19 patients in the ICU is 40% [3]. This finding also suggested that COVID-19 patients need more mechanical ventilation before receiving an ICD and that they have more severe symptoms of ARDS, which could facilitate the development of VIP in particular. The widespread use of the prone position may also have increased the incidence of VİP-causing microaspirations and this treatment may have been more common in COVID-19 patients for the reasons mentioned earlier [20]. Moreover, in patients with COVID-19, pulmonary infarction, which is more common due to coagulopathy, may increase the risk of secondary infection [21].

In studies conducted on microorganisms that cause of BSI in COVID-19 patients, there are 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 exceeds 50% and gram-negative bacteria are endemic. 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 are *Enterococci* [7].

Moreover, bacteraemia of unknown cause was also found to be common in COVID-19 patients. In Buetti et al., 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 with COVID-19 with enterococcal bacteraemia. In the non-COVID-19 group of patients with enterococcal bacteraemia, the predominant sources of bacteraemia were catheter-related infections and intra-abdominal infections, with an unknown bacteraemia rate of 26%. In addition, 77% of the polymicrobial bacteria in the COVID-19 group were *Enterococci*. *Enterococcus* spp. and *Klebsiella pneumoniae* together account for 46% of polymicrobial bacteraemia cases, but the source of this type of bacteraemia is unknown. In non-COVID-19 patients, the association of two gram-negative bacteria in 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 causes such as SARS-CoV-2-associated coagulopathy affecting microcirculation 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, in 77.5% of patients with *Acinetobacter baumannii* bacteraemia, the source of infection was ventilator-associated pneumonia. 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]. In a study in which Russo et al., studied *Acinetobacter baumannii* infections in non-COVID-19 patients between 2019 and 2021, the prevalence of bacteraemia was significantly greater in those with COVID-19 than in non-COVID-19 patients (56% *vs.* 8%). Nearly 60% of bacteremias are caused by VAP and bacteremia has been identified as a risk factor for mortality [27].

In European countries, the first two years of the pandemic showed a significant increase in the rate of circulatory infections caused by *Acinetobacter baumannii* compared to the previous three years. Especially in countries where carbapenem resistance exceeds 50%, statistically significant increases have been observed, most of which are in the U.S. [28]. In our country, the rates of resistance to carbapenem in *Acinetobacter baumannii* are similar during pandemic periods, as they were 90% prior to pandemics.

The prominence of *Acinetobacter baumannii*, which is known to be able to spread epidemics easily through contamination of health workers' hands, medical instruments and hospital surfaces, suggests a lack of measures to control infections. It could be argued that particularly effective in healthcare workers not paying enough attention to infection control measures, especially hand hygiene, due to their workload. It has been observed behaviours 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 in our hospital.

Many publications have indicated that MDR bacteria rates increased during the pandemic. A single-center retrospective study was performed in a university hospital in Croatia on ICU-associated BSI in COVID-19 patients during the pandemic. Among Acineobacter baumannii strains, 87.5% of *Klebsiella pneumoniae* strains and 20.5% of *Enterococci* strains are resistant to vancomycin [14]. This finding was 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 have been 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 (78.9% *vs.* 38.6%) in those with COVID-19 than in those without COVID-19 and has never been identified as a factor in the COVID-19 group, similar to our study on *Pseudomonas aeruginosa* [14]. During the COVID-19 pandemic, many hospitals have experienced outbreaks in the ICU often caused by gram-negative MDR bacteria. Among the gram-negative bacteria, carbapenem-resistant *Acinetobacter baumannii* is the most frequently occurring and has been found to be associated with high mortality [27,30].

In a study by Buetti et al., 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 [9]. A systematic review of MDR bacterial outbreaks in COVID-19 patients revealed increased antibiotic use as a significant contributing factor to outbreaks in seven studies [30].

In our study, COVID-19 patients had used fewer antibiotics in the past 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 bacteraemia scores were significantly greater in those with COVID-19 than in those non-COVID-19. In a single-center retrospective study in a university hospital in Italy where the incidence of MDR gram-negative bacteria in the ICU was compared with that in non-COVID-19 patients, the rate of septic shock during bacteraemia and the Pitt bacteraemia score were significantly greater in those with COVID-19 [14].

In a study comparing COVID-19 patients with non-COVID-19 patients, there was no significant difference between the 60 days mortality rates [8]. Another study showed that the 28 days mortality rate was significantly greater for those with COVID-19 than for those without COVID-19 and there was a significant difference in survival [9]. In our study, there was no difference in 60-day mortality rates between patients with COVID-19 and without COVID-19, 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 ($p=0.032$; $p<0.05$). 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., the SOFA score at the time of BSI was found to be an independent risk factor for mortality [9].

In our study, Pitt bacteraemia 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 has several limitations. The first is that the study was retrospective. Furthermore, it is not possible that our findings can be generalized to the entire population because they were obtained from

a single center. We did not have data on what antibiotics patients used. Furthermore, due to the constraints of the pandemic period, we were unable to identify certain bacteria at the species level.

Conclusion

We found a higher rate of MDR in COVID-19 patients and it is important to organize empirical treatment considering this situation. In our study, it was shown that 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 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.

Ethics Approval and Consent to Participate

This study was reviewed and approved by the Istanbul University Clinical Research Ethics Committee (1523529-23). Informed consent was obtained from all participants. All procedures were performed in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants and legally authorized representative of minor participants involved in the study.

Availability of Data and Materials

The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

Authors' Contribution

Halit Özsüt was responsible for the organization and coordination of the trial. Çağla Keskin Sarıtaş was the chief investigator and was responsible for the data analysis. Çağla Keskin Sarıtaş, Halit Özsüt, Seniha Başaran and Aysun Benli developed the trial. All authors contributed to the writing of the final manuscript. All members of the study team contributed to the management or administration of the trial.

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