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Determination of associated factors with death in *Staphylococcus aureus* bacteremia in hospitalized patients during the COVID-19 pandemic: A single-center, retrospective study

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The effect of COVID-19 on the outcomes of patients with Staphylococcus aureus bacteremia is still unknown. ***Aim:*** *In this study, we aimed to determine associated factors for mortality in patients with S. aureus bacteremia and to explore the impact of prior COVID-19. Design and setting: In this retrospective and single-center study, all adult patients (≥ 18 years old) with S. aureus bacteremia between March 2020 and February 2022 were included.* ***Methods:*** *The outcomes of our study were 14-day and 28-day hospital mortality after the first positive blood culture was obtained. Univariate and Cox regression analyses were performed.* ***Results:*** *A total of 140 patients with S. aureus bacteremia were included in the study. The median age was 64.5 (48.5-76) and 82 (58.5%) of the patients were male. 14-day and 28-day mortality rates were 28.6% and 37.1% respectively. Among patients with S. aureus bacteremia and previous COVID-19 history, 14-day and 28-day mortality rates were 33.9% (n = 21) and 41.9% (n = 26), respectively. Cox regression analysis revealed that Pitt bacteremia score, AST, urea, and previous antibiotic use were associated factors for 14-day mortality and 28-day mortality due to S. aureus bacteremia.* ***Conclusions:*** *This study justified the remarkable fatality of S. aureus bacteremia during the COVID-19 pandemic period and revealed that a high Pitt bacteremia score, increased levels of AST and urea, and previous antibiotic exposure were associated factors for mortality in patients with S. aureus bacteremia.*

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Key words: *Staphylococcus aureus; Mortality; Bacteremia; COVID-19; Pneumonia.*

Determinación de factores asociados con la muerte por bacteriemia por *Staphylococcus aureus* en pacientes hospitalizados durante la pandemia de COVID-19: estudio retrospectivo de un solo centro

El efecto de COVID-19 en los resultados de pacientes con bacteriemia por

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Author Contributions
GT, CGG, and SS proposed the concept, designed the study, wrote the protocol, and managed the study. GT, OFB, SS, KGG and YEO performed the statistics, interpreted the data, and wrote the manuscript. GT, CGG were involved in collecting the data. GT, CGG, SS, OFB, BC, YEO, FP, GS, and MY performed a critical review of the manuscript. KGG communicated with the journal and addressed comments from reviewers. All authors contributed to data acquisition, data analysis, or data interpretation, and reviewed and approved the final version.

Ethics Statement
All procedures performed in studies involving human participants were in accordance with the ethical standards of the Declaration of Helsinki and the National Research Committee. This study was approved by the Ethics Committee of XXX Hospital (approval number: 161-2022, date: 10/08/2022). Written informed consent was waived due to the retrospective nature of this study.

Staphylococcus aureus todavía es desconocido. ***Objetivo:*** *Determinar los factores asociados con la mortalidad en pacientes con bacteriemia por S. aureus y explorar el impacto del COVID-19 previo.* ***Métodos:*** *Estudio retrospectivo de un solo centro, que incluyó a todos los pacientes adultos (≥ 18 años) con bacteriemia por S. aureus entre marzo de 2020 y febrero de 2022. Estudiamos la mortalidad hospitalaria a los 14 y 28 días después de obtener el primer cultivo sanguíneo positivo, utilizando análisis univariados y de regresión de Cox.* ***Resultados:*** *Se incluyeron un total de 140 pacientes con bacteriemia por S. aureus en el estudio. La mediana de edad fue de 64,5 (48,5-76) años y 82 (58,5%) de los pacientes eran hombres. Las tasas de mortalidad a los 14 y 28 días fueron del 28,6% y 37,1%, respectivamente. Entre los pacientes con bacteriemia por S. aureus y antecedentes previos de COVID-19, las tasas de mortalidad a los 14 y 28 días fueron del 33,9% (n = 21) y 41,9% (n = 26), respectivamente. El análisis de regresión de Cox reveló que el puntaje de bacteriemia de Pitt, AST, urea y el uso previo de antibióticos fueron factores asociados con la mortalidad a los 14 y 28 días debido a la bacteriemia por S. aureus.* ***Conclusiones:*** *Este estudio justificó la notable letalidad de la bacteriemia por S. aureus durante el período de pandemia de COVID-19 y reveló que un puntaje de bacteriemia de Pitt elevado, niveles aumentados de AST y urea, y la exposición previa a antibióticos fueron factores asociados con la mortalidad en pacientes con bacteriemia por S. aureus.*

Palabras clave: *Staphylococcus aureus; Mortalidad; Bacteriemia; COVID-19; Neumonía.*

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S. aureus is one of the leading pathogens in both community acquired and hospital acquired infections. *S. aureus* causes dreadful complications including endocarditis, meningitis, and sepsis[1]. *S. aureus* bacteremia is a global concern for society and healthcare providers with high mortality[2]. It is known that bacterial co-infections or secondary bacterial infections in patients with viral pneumonia have associated with increased mortality[3-5]. Recently, some studies have been reported on the prevalence and outcomes of Staphylococcus aureus bacteremia in patients with COVID-19. Patients with COVID-19 have different clinical manifestations[6,7]. Complications of COVID-19 not only include severe respiratory problems, and multi-organ failure but also result in bacterial infections[8-9]. Bacteremia, which is the most severe and mortal complication among co-infection or seconder bacterial infections, is now arising concern in patients with COVID-19.

Many risk factors have been identified for the development of SAB. Foreign bodies placed in the body, such as intravascular catheters and orthopedic prostheses, constitute a potential source of SAB when infected[10-11]. Other factors that increase the risk of host-associated SAB include diabetes mellitus, cancer, dialysis, rheumatoid arthritis, human immunodeficiency virus (HIV) infection, intravenous drug use, and alcoholism[12].

Conducting surveillance and determining local risk factors are vital for mitigating poor outcomes in patients with S. aureus bacteremia[13]. The effect of COVID-19 on the outcomes of patients with S. aureus bacteremia is still unknown. In this study, we therefore aimed to determine associated factors for mortality in patients with *S. aureus* bacteremia and to explore the impact of prior COVID-19.

Patients and Methods

In this retrospective and single-center study, all adult patients (≥ 18 years old) with S. aureus bacteremia in XXX Hospital between March 2020 and February 2022 were included. The flow chart regarding the study design is as follows: The study cohort was obtained from the microbiology laboratory's database. Patients who developed SAB bacteremia between March 2020 and February 2022 were accessed from the database among all adult patients hospitalized. Whether these patients had COVID-19 before bacteremia was recorded (Figure 1).

The demographic characteristics, clinical features, laboratory parameters, microbiology culture results, radiological findings, treatments used, and clinical outcomes were collected from medical records evaluated. Vital signs including respiratory rate, heart rate, blood pressure, and body temperature before obtaining blood culture were recorded.

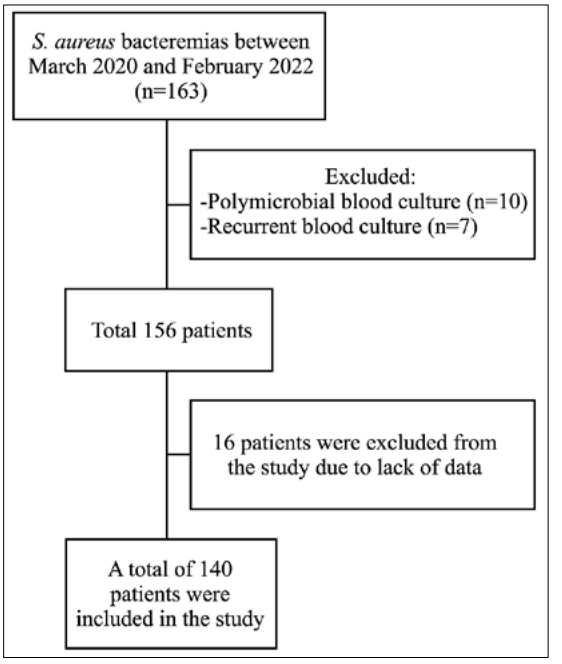

Figura 1.

Laboratory parameters including C-reactive protein (CRP), procalcitonin, neutrophil count, lymphocyte count, platelet count, hemoglobine, creatinine, urea, ferritin, albumin, fibrinojen, D-dimer, lactate dehydrogenase (LDH), total bilirubin, aspartate aminotransferase (AST), and alanin aminotransferase (ALT) on the day of blood culture was taken were evaluated.

qSOFA criteria, including state of consciousness, respiratory rate, and hypotension, were used for the diagnosis of sepsis. The relationship between mortality and conditions thought to be risk factors for bacteremia, such as the presence of a central venous catheter, mechanical ventilation, and hemodialysis, was evaluated. Again, the time to start empirical antibiotic treatment, the appropriateness of the empirical antimicrobial treatment started, the duration of hospital stay of the patients before bacteremia, and the relationship between admission to intensive care unit and mortality were examined.

S. aureus bacteremia was defined as the isolation of *S. aureus* from at least one blood culture in patients who have clinical findings for infection[14]. Repeated episodes were excluded and only a first bacteremic episode for each patient was included. Hospital-acquired infection was defined as a bacteremia with *S. aureus* more than 48 hours after hospital admission[15]. S. aureus bacteremia that developed in patients who did not receive healthcare recently were defined as community-acquired bacteremia[16]. Healthcare-associated *S. aureus* bacteremia was defined as a bacteremia that developed in outpatients or first 48 hours after hospitalization if the patient was hospitalized, with the following criteria; living in a nursing home, history of hospitalization in the last 6 months, receiving hemodialysis, immunosuppression (recently receiving chemotherapy or radiotherapy, receiving > 5mg/day prednisolone or its equivalent, HIV infection, primary or secondary immunodeficiency syndrome, bone marrow or solid organ transplantation history)[17,18]. Pitt bacteremia score was used to determine the

disease severity[19]. Comorbidity was evaluated with the Charlson Comorbidity Index[20]. Treatment failure was defined as death within 28 days after bacteremia episode or persistent bacteremia (> 10 days after initiation of appropriate therapy) or recurrent bacteremia (within 60 days after discontinuation of therapy).

According to our hospital overcrowding due to the dynamics of COVID-19 pandemic peaks, there were four peaks of COVID-19 in March 2020 and February 2022 in Türkiye, which coincided with the dominance of various variants of SARS-CoV-2. The first pandemic wave lasted from April to May 2020, the second wave lasted from October to December 2021, the third wave lasted from March to May 2021, and the fourth wave from August 2021 to February 2022.

A confirmed COVID-19 case was defined as a patient with symptoms consistent with COVID-19 and a positive nasopharyngeal swab sample by real time reverse transcriptase polimerase chain reaction. Acute COVID-19 period was up to 4 weeks following the onset of illness. Coinfection was defined as a bacteremia with S. aureus during the acute COVID-19 (within the last 4 weeks before the onset of illness).

For baseline chest CT evaluation for COVID-19 pneumonia, pulmonary findings on chest CT were scored to estimate the pulmonary involvement[21]. Time intervals for previous antibiotic use and previous hospitalization were 3 months after the first positive blood culture.

For identification and antimicrobial susceptibility, VITEK 2 (bioMérieux, USA) was used. All procedures were conducted according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST)[22]. An appropriate empirical treatment was defined as treatment with an antibiotic according to susceptibility results within the first 48 hours after obtaining blood culture[23].

The outcomes of our study were 14-day and 28-day all cause in-hospital mortality after the first blood culture was taken.

Statistical analysis

Continuous variables were described as median ±interquartile range (IQR), while categorical variables were described as numbers and percentages. Chi-square and Fisher's exact tests were used to compare categorical variables. The closeness of the median-mean values of the normal distribution was evaluated according to the box plot analysis, the result of the Kolmogrov-Smirnov Test and Kurtosis-Skewnes values. While Independent Sample T-test was used for variables with normal distribution, Mann-Whitney U test was used for variables with non-normal distribution. Power analysis was performed using G*Power Version 3.1.9.6 (University of Kiel, Kiel, Germany) program. In this power analysis, the power was 80%, the alpha error was 0.05, and the effect size was 0.3, and the required minimum sample size was 94. We performed univariate logistic regression analyses. Receiver operating charasteristic (ROC) curves were performed to obtain optimal cut-off values for variables which included Cox regression analysis.Then, Cox regression analysis was performed. Confounders with less than 10 events per variable were excluded from the multivariate model to mitigate overfitting. If there was a strong correlation between categorical and continuous variables, continuous variables were preferred to reduce the multicollinearity effect, which may cause bias errors. Odds ratio (OR) values with 95% confidence intervals (CI) at a p-value <0.05 were presented. IBM Statistical Package for Social Sciences (SPSS) 22.0 was used for statistical analyses.

Results

A total of 140 patients with *S. aureus* bacteremia were included in the study. The median age was 64.5 (48.5-76) and 82 (58.5%) of the patients were male. The most common comorbidities were diabetes mellitus (41.4%) and hypertension (54.3%), respectively. Sixty-two (44.3%) patients had previous COVID-19 within the last three months. 14-day and 28-day mortality rates were 28.6% and 37.1%, respectively. Among patients with *S. aureus* bacteremia and previous COVID-19 history, 14-day and 28-day mortality rates were 33.9% and 41.9%, respectively. Overall baseline characteristics including demographics, comorbidities, laboratory values, radiological findings, clinical outcomes, blood culture results, and therapies received were demonstrated in Table 1 and Supplementary table. Fifty-eight (42%) patients with COVID-19 had pulmonary

Table 1. Demographic characteristic of patients with *S. aureus* bacteremia

Parameters, (n %)		Total	Parameters, (n, %)		Total
Sex, female	Male	82 (58.5)	Cerebrovascular disease	Yes	16 (11.4)
	Female	58 (41.5)			
Age, years	< 50	39 (27.9)	Hematologic malignancy	Yes	3 (2.1)
	50-59	21 (15)	Solid tumor	Yes	17 (12.1)
	60-69	29 (20.7)	Chronic liver disease	Yes	8 (5.7)
	70-79	28 (20)	COPD	Yes	25 (17.9)
	> 80	23 (16.4)	Presence of central venous catheter	Yes	69 (49.3)
Comorbidity	Yes	123 (87.9)	Previous antibiotic use	Yes	43 (30.7)
Hypertension	Yes	76 (54.3)	Previous hospitalization	Yes	73 (52.1)
Chronic kidney failure	Yes	41 (29.3)	Dialysis	Yes	34 (24.3)
Cardiovascular diseases	Yes	41 (29.3)	Previous history of COVID-19 within the last 3 months	Yes	62 (44.3)
Diabetes mellitus	Non-diabetic or controlled	82 (58.6)	Acute COVID-19 in the last 4 weeks	Yes	17 (12.1)
	Uncomplicated	33 (23.6)	Dementia	Yes	5 (3.6)
	End organ damage	25 (17.9)			
14-day mortality	Yes	40 (28.6)	28-day mortality	Yes	52 (37.1)
Treatment failure	Yes	57 (40.7)	ICU admission	Yes	31 (22.1)

(COPD: Chronic obstructive pulmonary disease, ICU: Intensive care unit).

involvement. Pulmonary involvement was more common in deceased patients on the day-14 (55% vs. 36.7%, p = 0.049) and day-28 (55.8% vs. 33.7%, p = 0.01) than survivors.

There were no significant differences in 14-day (p = 0.262) or 28-day mortality (p = 0.162) between patients with SAB occurred in pandemic wave and in non- wave period. The median time between SARS-CoV-2 PCR results and positive bacterial culture was 13 (5-30) days. The median time from obtaining blood culture to time of positive signal was 11.5 (4-20) hours. The median time from blood culture to empiric antibiotic initiation (IQR) was 6 (3-12) hours. The median time from bacteremia onset to death (IQR) was 9.5 (5-25) days. The treatment started was appropriate, in 91 (70%) of 130 patients in whom empirical treatment was initiated. The most common focus of bacteremia were catheter (45.3%) and lung (28.3%). Methicilline resistance rate among S. aureus was 44.3% (n = 62) (Table 2).

In the univariate logistic regression analysis, associated factors for 14-day mortality due to *S. aureus* bacteremia were Pitt bacteremia score (p < 0.001), previous antibiotic use (p < 0.001), D-dimer (p = 0.01), neutrophil count (p = 0.01), urea (p = 0.005), AST (p = 0.02), and LDH (p < 0.001). Associated factors for 28-day mortality due to *Staphyloccocus aureus* bacteremia were age (p = 0.01), Pitt bacteremia score (p < 0.001), previous antibiotic use (p<0.001), D-dimer (p = 0.01), neutrophil count (p = 0.01), urea (p = 0.01), AST (p = 0.01), and LDH (p<0.001) (Table 3).

Cox regression analysis revealed that Pitt bacteremia score (HR: 5.66; 95% CI: 2.73-11.74, p <0.001), AST (HR: 3.08; 95% CI: 1.58-6.00, p = 0.001), urea (HR: 3.71; 95% CI: 1.87-7.32, p <0.001), and previous antibiotic use (HR: 2.01; 95% CI: 1.02-3.95, p = 0.041) were associated factors for 14-day mortality due to *S. aureus* bacteremia (Table 4). In addition, associated factors for 28-day mortality were Pitt bacteremia score (HR: 4.21; 95% CI: 2.24-7.90, p <0.001), AST (HR: 3.05; 95% CI: 1.70-5.47, p < 0.001), urea

Table 2. Univariate associations of continuous variables for 14-day and 28-day mortality in patients with *Staphylococcus aureus* bacteremia

		14-Day			28-Day		
Parameters, median (IQR)	**Total**	**Deceased**	**Survived**	**p value**	**Deceased**	**Survived**	**p value**
Age, years,	64.5 (48.5-76)	67 (55-76)	62.5 (46.5-76)	0.31	68 (58-78)	59 (44-72.5)	0.01
Body tempeture, (°C)	37.1 (36.8-38)	37 (37-37.5)	37.3 (36.8-38)	0.42	37 (36.9-37.5)	37.5 (36.8-38.1)	0.17
Blood pressure (mmHg)	110 (95-120)	97 (85-118)	110 (100-120)	< 0.001	105 (90-120)	110 (110-120)	< 0.001
Respiratory rate/minute	20 (20-25)	25 (20-35)	20 (18-24)	0.001	25.5 (20-32)	20 (18-23)	< 0.001
Time between positive bacterial culture and SARS-CoV-2 PCR results, days	13 (5-30)	11 (7-18)	17 (5-60)	0.19	12 (5-21)	14 (6-60)	0.33
Time from blood culture to time of positive signal, h	11.5 (4-20)	10 (3-18)	12 (4.5-20)	0.2	10 (3-18)	12 (4.5-20)	0.2
Time from blood culture to empiric antibiotic initiation, h	6 (3-12)	5 (3-8)	6 (3-16)	0.2	10 (3-18)	12 (4.5-20)	0.2
Treatment revision time (Escalation time)	72 (48-120)	48 (24-84)	72 (48-144)	0.03	48 (24-96)	72 (48-144)	0.17
Length of hospital stay before bacteremia, days	3.5 (1-9)	4 (1-9)	3 (1-9)	0.99	4 (1-9.5)	3 (1-8)	0.2
Length of hospital stay after bacteremia, days	12 (7-22)	5.5 (2-8.5)	18 (12-28)	<0.001	7 (3-12.5)	17 (11-30)	< 0.01
Charlson comorbidity index	4 (2-7)	4 (2.5-6.5)	5 (2-7)	0.87	4 (3-7)	4 (2-6.5)	0.49
Pitt bacteremia score	0 (0-2)	2.5 (0.5-7)	0 (0-1)	< 0.001	2 (0-6)	0 (0-1)	< 0.001
Quick sofa score	1 (0-2)	2 (1-3)	1 (0-1)	< 0.001	2 (1-3)	1 (0-1)	< 0.001
Leukocyte count/mm^3	10.800 (7415-15755)	13.415 (8.480-18.465)	10145 (7165-14075)	0.02	13.415 (8100-18.465)	10045 (7000-13.340)	0.01
Neutrophil count/mm^3	8840 (5790-13470)	12005 (7080-16740)	8170 (5010-12040)	0.01	11630 (6710-16680)	8005 (4800-11365)	< 0.001
Hemoglobin, mg/dL	9.8 (8.8-11.4)	10 (8.9-11.4)	9.6 (8.6-11.5)	0.38	10 (8.9-11.5)	9.6 (8.6-11.3)	0.25
Lymphocyte count/mm^3	750 (490-1080)	570 (375-945)	820 (540-1140)	0.02	570 (360-1050)	840 (580-1125)	0.01

Platelet count × 10^3/mm^3	171.5 (126.5-229.5)	173 (113.5-245.5)	171.5 (127.5-226.5)	0.89	183.5 (112.5-238)	169.5 (129-224)	0.007
Urea, mmol/L	30 (12-55)	42 (20-60)	22 (12-50)	< 0.001	40 (20-60)	21 (11-50)	<0.001
Creatinine, mg/dL	1.35 (0.75-3.09)	1.5 (0.91-2.91)	1.16 (0.72-3.15)	0.56	1.5 (0.83-2.55)	1.24 (0.72-3.39)	0.85
Alanine aminotransferase, UI/L	19 (12-37.5)	33.5 (18-54.5)	18 (11-31)	< 0.001	31 (17.5-52.5)	17 (11-30)	< 0.001
Aspartate aminotransferase, UI/L	25 (18-46)	43 (24-91)	22 (17-38)	<0.001	40 (22-73)	22 (17-36)	<0.001
Albumin	3.1 (2.5-3.5)	2.8 (2.4-3.4)	3.2 (2.6-3.5)	0.12	2.8 (2.5-3.4)	3.2 (2.6-3.5)	0.05
Lactate dehydrogenase, UI/L	295 (229-436)	417 (293-597)	271 (212-343)	< 0.001	413.5 (304-528)	253 (204-327)	< 0.001
Total bilirubin, mg/dL	0.6 (0.4-1.1)	1 (0.7-2)	0.5 (0.4-0.7)	< 0.001	0.8 (0.5-1.6)	0.6 (0.4-0.8)	0.01
D-dimer, μg/mL	1930 (946-4780)	3145 (1510-9500)	1656 (752-3730)	0.01	2639 (1100-8930)	1656 (761-3790)	0.02
Fibrinogen, g/L	450.5 (358-593)	480 (333-614)	434 (366-576)	0.84	480 (329-592)	434 (368-594)	0.93
C-reactive protein, mg/L	96 (43.5-191.5)	113 (79-229)	86 (38.5-178.5)	0.13	113 (66.5-235)	86 (37-170)	0.05
Procalsitonin, ng/mL	1 (0-7)	2 (0-4)	1 (0-7)	0.123	2 (0-4)	1 (0-7)	0.91

IQR: Interquartile range; h: hour.

Table 3. Univariate analysis of risk factors for mortality due to *Staphylococcus aureus* bacteremia at 14 days and 28 days

Logistic Regression	**14-day mortality**			**28-day mortality**		
	OR	**CI**	**p value**	**OR**	**CI**	**p value**
Age, years	-	-	-	2.724	1.338-5.555	< 0.001
Pitt bacteremia score	1.542	1.289-1.845	< 0.001	1.536	1.267-1.863	< 0.001
Previous antibiotic use	3.919	1.796-8.559	< 0.001	3.919	1.796-8.552	< 0.001
D-dimer, μg/Ml	1.000	1.000-1.000	0.014	1.000	1.000-1.000	0.01
Neutrophil count/mm3	1.000	1.000-1.000	0.01	1.000	1.000-1.000	0.01
Urea, mmol/L	1.017	1.005-1.029	0.05	1.017	1.005-1.029	0.005
Aspartate aminotransferase, UI/L	1.010	1.002-1.019	0.01	1.016	1.005-1.028	0.05
Lactate dehydrogenase, UI/L	1.004	1.002-1.007	< 0.001	1.005	1.003-1.008	< 0.001

(OR: Odd's ratio; CI: Confidence interval; CT: Computed tomography).

(HR: 2.74; 95% CI: 1.50-5.01, p = 0.02), and previous antibiotic use (HR: 2.06; 95% CI: 1.12-3.76, p = 0.019) (Table 4).

The Kaplan–Meier survival analysis revealed statistically significant differences in Pitt bacteremia score, urea, AST and previous antibiotic use for 14-day mortality and 28-day mortality (Table 5) (all log-rank p < 0.05).

Table 4. Cox regression analysis of risk factor mortality due to *Staphylococcus aureus* bacteremia at 14 days and 28 days

Cox regression analysis	14- day mortality			28- day mortality		
	HR	CI	p value	HR	CI	p value
Pitt bacteremia score	5.667	2.734-11.747	< 0.001	4.212	2.245-7.903	< 0.001
Urea, mmol/L	3.710	1.879-7.326	< 0.001	2.742	1.500-5.013	0.001
Aspartate aminotransferase, UI/L	3.082	1.584-6.000	0.001	3.052	1.701-5.477	< 0.001
Previous antibiotic use	2.016	1.028-3.953	0.041	2.061	1.129-3.763	0.019
Neutrophil count/mm3	-	-	-	-	-	-
Age, years				-	-	-

HR: Hazard ratio; CI: Confidence interval.

Table 5. Kaplan- Meier analysis for risk factor mortality due to *Staphylococcus aureus* bacteremia at 14 days and 28 days

Parameters		14- day mortality			28-day mortality		
		Mean survival time, days	Confidence interval	p value (log rank)	Mean survival time, days	Confidence interval	p value (log rank)
Pitt bacteremia score	< 2	24.880 ± 0.807	23.299-26.462	< 0.001	24.033 ± 0.830	22.405 ± 25.660	< 0.001
	≥ 2	15.438 ± 1.650	12.203-18.672		14.771 ± 1.581	11.672 ± 17.869	
Neutrophil count/mm^3	< 7000	23.756 ± 1.291	21.225- 26.286	0.099	23.022 ± 1.289	20.495-25.550	0.151
	≥ 7000	20.561 ± 1.109	18.387-22.736		19.851± 1.096	17.703- 22.000	
Urea, mmol/L	< 45	23.319 ± 0.942	21.471- 25.166	0.016	22.451 ± 0.941	20.606-24.295	0.049
	≥ 45	18.813 ± 1.657	15.565- 22.060		18.167 ± 1.632	14.967-21.366	
Aspartate amino-transferase, UI/L	< 30	23.928 ± 0.961	22.045-25.811	0.001	23.241 ± 0.968	21.345- 25.137	<0.001
	≥ 30	18.300 ± 1.487	15.387-21.214		17.386 ± 1.435	14.573- 20.199	
Previous antibiotic use	Yes	17.698 ± 1.642	14.479- 20.916	0.001	16.837 ± 1.564	13.771- 19.903	<0.001
	No	23.390 ± 0.959	21.511- 25.269		22.639 ± 0.966	20.747-24.532	

Discussion

In this study, we presented a detailed analysis of clinical characteristics, laboratory findings, and outcomes of 140 patients with *S. aureus* bacteremia. We found that Pitt bacteremia score, AST, urea and previous antibiotic use were associated factors for both 14-day and 28-day mortality in *S. aureus* bacteremia. However, previous history of COVID-19 was not associated with neither 14-day nor 28-day mortality.

Secondary infections and ventilator-associated pneumonia in patients with COVID-19 co-infections negatively affect patient prognosis and treatment process and result in long hospitalizations, morbidity, and mortality[24,25]. It is known that respiratory viral agents predispose to secondary bacterial infections by various immune mechanisms[26,27]. The relationship between the host and the pathogen is important in secondary infections occurring in severe and critical COVID-19. Viral virulence factors, immune

response dysregulation, and disruption of the microbiota during viral pneumonia play a role in the development of secondary infections. Changes in the microbiome, bacterial virulence factors, the immune response to SARS-CoV-2 cause an increase in virus titer, and cause mortality in severe and critically ill patients[28,29]. It is clear that invasive procedures (such as intubation, catheterization) in patients with COVID-19 pose a risk factor for the development of secondary bacterial infection[30-31].

In the study of Mormenea Bayo et al.[32], bacteremia was more frequent in patients with COVID-19 than patients without COVID-19. In addition, patients with COVID-19 had a higher proportion of nosocomial bacteremia than those without. In a recent study[33], Gram-positive microorganims among hospital acquired bloodstream infections were more frequent in COVID-19 patients than those without COVID-19 (39.7% vs. 32.1%, p = 0.033). In different studies in-hospital mortality rate was about 20%. The studies showed that older age, sepsis, transfer to ICU, hepatic failure presence of MRSA, presence of endocarditis and non-fatal underlying disease were independent predictors for mortality[12,33-36]. In a review[37], mortality rate in patients co-infected with COVID-19 and *S. aureus* was 61.7%. In our study, while 14-day and 28-day mortality rates in patients co-infected with COVID-19 and *S. aureus* were 33.9% and 41.9%, respectively. Espinoza Pérez et al.[38] reported that while 14-day and 28-day mortality rates in patients co-infected with COVID-19 and *S. aureus* were 30.8% and 46.2%, respectively. In the study of Arientová et al.[39] revealed that mortality due to S. aureus bacteremia increased in the first year of the COVID-19 pandemic (from 6% in 2019 to 23% in 2020, p = 0.085).

This study had some limitations. First, this was a retrospectively conducted single-center study. Second, our study had a relatively small sample size. These are limiting the generalizability of the results. Third, considerable number of COVID-19 patients were followed-up in different departments including surgical ones apart from infectious diseases clinical service especially during the COVID-19 waves. This may prevent a fully adequate evaluation, which is also one of the confounding factors for mortality, although infectious diseases specialist consultations were continued. In addition, the findings of this study show that the factors are associated with death, but do not indicate causality. Last, we included different definitions for *S. aureus* bacteremia such as community-acquired, healthcare associated, and hospital-acquired. However, we believe that this allowed us a representative study population for *S. aureus* bacteremia.

However, our study had some strengths. First, we could analyze different types of variables such as demographic characteristics, clinical features, vital signs, laboratory parameters, microbiology culture results, radiological findings, treatments. Therefore, we could perform univariate and multivariate analyses with a comprehensive evaluation. Second, our hospital was one of the pandemic epicenter in Istanbul, Türkiye. The first cases of the COVID-19 pandemic in our country were seen in Istanbul, and the highest number of patients were observed in Istanbul. The hospital where the study cohort was followed is one of the first hospitals in the country to be declared a pandemic hospital, and patients with COVID-19 has been monitored since the first day of the pandemic. This allowed us analyse patients co-infected with COVID-19 and *S. aureus*. To our knowledge, this was a first study to evaluate mortality and associated factors in patients with S. aureus bacteremia during the COVID-19 pandemic period in Türkiye. Last, although some patients were not followed-up after discharge, we could retrospectively obtained their survival status from the National Death Notification Service (https://obs.saglik.gov.tr). Therefore, we did not miss substantial number of deaths after discharge, especially for 28-day mortality.

Conclusion

This study justified the remarkable fatality of *S. aureus* bacteremia during the COVID-19 pandemic period and revealed that a high Pitt bacteremia score, increased levels of AST and urea, and previous antibiotic exposure were associated factors for mortality in patients with *S. aureus* bacteremia. Therefore, unnecessary antibiotic use should be strictly restricted and patients with the abovementioned predictors should be managed carefully.

Supplementary Table: Univariate associations of categorical variables for 14-day and 28-day mortality in patients with *S. aureus* bacteremia

Parameters, (n %)		**14-Day**			**28-Day**		
		Deceased (n = 40)	**Survived (n=100)**	**p value**	**Deceased (n = 52)**	**Survived (n = 88)**	**p value**
Sex, female	Male	23 (57.5)	59 (59)	0.871	29 (55.8)	53 (60.2)	0.605
	Female	17 (42.5)	41 (41)		23 (44.2)	35 (39.8)	
Age, years	< 50	7 (17.5)	32 (32)	0.158	8 (15.4)	31 (35.2)	0.039
	50-59	6 (15)	15 (15)		6 (11.5)	15 (17)	
	60-69	13 (32.5)	16 (16)		16 (30.8)	13 (14.8)	
	70-79	9 (22.5)	19 (19)		12 (23.1)	16 (18.2)	
	>80	5 (12.5)	18 (18)		10 (19.2)	13 (14.8)	
Comorbidity	Yes	36 (90)	87 (87)	0.623	48 (92.3)	75 (85.2)	0.215
Presence of central venous catheter	Yes	19 (47.5)	50 (50)	0.789	25 (48.1)	44 (50)	0.826
Mechanical ventilation	Yes	9 (22.5)	11 (11)	0.079	12 (23.1)	8 (9.1)	0.022
Previous antibiotic use	Yes	21 (52.5)	28 (22)	< 0.001	26 (50)	17 (19.3)	< 0.001
Previous hospitalization	Yes	25 (62.5)	48 (48)	0.121	32 (61.5)	41 (46.6)	0.087
Dialysis	Yes	4 (10)	30 (30)	0.013	6 (11.5)	28 (31.8)	0.007
Previous history of COVID-19 within the last 3 months	Yes	21 (52.5)	41 (41)	0.234	29 (56.9)	33 (37.5)	0.027
Acute COVID-19 in the last 4 weeks	Yes	2 (5)	15 (15)	0.024	5 (17.2)	12 (36.4)	0.092
Pulmonary involvement	Yes	22 (55)	36 (36)	0.049	29 (55.8)	29 (33.7)	0.01
Empiric antimicrobial therapy suitability	Yes	23 (57.5)	69 (69)	0.205	29 (60.4)	63 (75.9)	0.062
ICU admission	Yes	15 (37.5)	16 (16)	<0.001	21 (84)	10 (13)	<0.001
Identification of the source of bacteremia	Yes	24 (60)	53 (53)	0.452	28 (53.8)	49 (55.7)	0.833
Pneumonia	Yes	17 (42.5)	12 (12)	<0.001	21 (40.4)	8 (9.1)	<0.001
Catheter infection	Yes	5 (12.5)	34 (34)	0.01	6 (11.5)	33 (37.5)	<0.001
Infective endocarditis	Yes	4 (10)	4 (4)	0.167	4 (7.7)	4 (4.5)	0.438
Osteomyelitis	Yes	1 (2.5)	2 (2)	0.854	1 (1.9)	2 (2.3)	0.890
Soft tissue infection	Yes	1 (2.5)	6 (6)	0.391	1 (1.9)	6 (6.8)	0.199
Other	Yes	1 (2.5)	3 (3)	0.873	1 (1.9)	3 (3.4)	0.61
Bacteremia definition	Community acquired	11 (27.5)	15 (15)	0.104	13 (25)	13 (14.8)	0.107
	Healthcare associated	8 (20)	35 (35)		11 (21.2)	32 (36.4)	
	Hospital acquired	21 (52.5)	50 (50)		28 (53.8)	43 (48.9)	
Causative agent	MSSA	19 (47.5)	59 (59)	0.216	24 (46.2)	54 (61.4)	0.08
	MRSA	21 (52.5)	41 (41)		28 (53.8)	34 (38.6)	

Treatment failure	Yes	38 (95)	19 (19)	< 0.001	49 (94.2)	8 (9.1)	< 0.001
Diabetes mellitus	Non-diabetic or controlled	22 (55)	60 (60)	0.782	27 (51.9)	55 (62.5)	0.148
	Uncomplicated	11 (27.5)	22 (22)		17 (32.7)	16 (18.2)	
	End organ damage	7 (17.5)	18 (18)		8 (15.4)	17 (19.3)	
Hypertension	Yes	24 (60)	52 (52)	0.391	31 (59.6)	45 (51.1)	0.331
Chronic kidney failure	Yes	11 (27.5)	30 (30)	0.769	13 (25)	28 (31.8)	0.392
Cardiovascular diseases	Yes	15 (37.5)	26 (26)	0.177	19 (36.5)	22 (25)	0.147
Pandemic wave period	Yes	23 (57.5)	47 (47)	0.262	30 (57.7)	40 (45.5)	0.162

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