Original Article

Associated Risk Factors and Clinical Outcomes of Bloodstream Infections among COVID-19 Intensive Care Unit Patients in a Tertiary Care Hospital

Mahalakshmamma Dasarahalli Shivalingappa, Supriya Gachinmath, Shiva Kumar Narayan[1]

Departments of Microbiology, [1]Critical Care Medicine, St. John's Medical College and Hospital, Bengaluru, Karnataka, India

Abstract

Introduction: The COVID-19 infection is an ongoing public health crisis causing millions of deaths worldwide. COVID-19 patients admitted to the intensive care unit (ICU) are more vulnerable to acquire secondary bloodstream infections (sBSIs) which cause a significant morbidity and mortality. Thus, we aim to assess the risk factors of sBSIs and outcomes in COVID-19 ICU patients. **Methods:** One hundred blood culture samples with growth (cases) and other 100 blood culture with no growth(controls) were collected.. All the demographic data, laboratory data and antimicrobial resistance pattern were analysed . Blood culture bottle received in the Microbiology laboratory were loaded into Automated blood culture system. Flagged bottles were processed for final identification by MALDI TOF and automated antibiotic susceptibility testing. Flagged bottles were processed for final identification by MALDI TOF and automated antibiotic susceptibility testing. **Results:** Raised C-reactive protein (CRP) (P = 0.0035), interleukin-6 (P = 0.0404), mechanical ventilation (MV) (P = 0.024), prior antimicrobial exposure (P = 0.002), longer ICU stay with median 11 days (P = 0.022), and higher mortality rate (P = 0.001) were significantly associated with the BSI. A significant proportion of BSIs were Gram-negative bacteria (n = 115) such as *Acinetobacter baumannii* 38 (33%) and *Klebsiella pneumoniae* 30 (26%). Monomicrobial organisms in blood yielded a higher proportion in our study 72 (72%). The highest resistance for *Acinetobacter* species (50) was observed with ceftazidime 29 (96.6%) amikacin 48 (96%), meropenem 48 (96%), cefotaxime 47 (94%), ciprofloxacin 46 (92%), and netilmicin 46 (92%). *K. pneumoniae* was highly resistant to cefotaxime 29 (96.6%), ceftazidime 29 (96.6%), ciprofloxacin 22 (73.3%), and cefuroxime 21 (70%). Among Gram-positive organisms, *Enterococcus* species showed that a resistance for high-level gentamicin and penicillin was 66.6%. **Conclusions:** Raised CRP, need of MV, prior antimicrobial exposure, and longer ICU stay should alarm clinicians for BSI. Hence, our study highlights the associated risk factors for BSI and emphasizes adherence to hospital infection control policies and antibiotic stewardship program.

Keywords: Antimicrobial resistance, COVID-19, intensive care unit, secondary bloodstream infections

Introduction

Severe acute respiratory syndrome coronavirus 2, a virus which causes coronavirus disease COVID-19, originated in Wuhan City, China, in December 2019.[1] COVID-19 has become a global pandemic affecting millions of people in the world. There are complications from mild symptoms to hypoxic respiratory failure, acute respiratory distress syndrome (ARDS), thromboembolic disease, cytokine release syndrome, multiorgan failure, and bacterial/fungal secondary infections.[2]

Bloodstream infections (BSIs) are well described in patients with influenza or other viral respiratory illnesses, which occur due to alteration in the epithelial cell surface and immune response resulting in severe inflammation and acquisition of secondary bacterial infections.[1]

COVID patients are vulnerable to BSI probably due to anti-inflammatory drugs like tocilizumab, steroids, comorbid conditions like diabetes, catheter related blood stream infection

Access this article online

Quick Response Code:

Website: www.jgid.org

DOI: 10.4103/jgid.jgid_108_23

Address for correspondence: Dr. Supriya Gachinmath, Department of Microbiology, St. John's Medical College and Hospital, Bengaluru, Karnataka, India.
E-mail: supriya.bg@stjohns.in

How to cite this article: Shivalingappa MD, Gachinmath S, Narayan SK. Associated risk factors and clinical outcomes of bloodstream infections among COVID-19 intensive care unit patients in a tertiary care hospital. J Global Infect Dis 2024;16:60-7.

Received: 14 June 2023 **Revised:** 08 January 2024
Accepted: 29 January 2024 **Published:** 26 June 2024

(CRBSI) and longer ICU stay. ICU admission is required for 20% of patients with COVID-19 due to ARDS. ICU patients are susceptible to hospital-acquired infections, and BSIs are associated with an increased morbidity and mortality.[3]

Patients in ICUs are at high risk for health-care-acquired infections (HAIs) due to the high prevalence of invasive procedures and devices, induced immunosuppression, comorbidity, frailty, and increased age. Over the past decade, we have seen a successful reduction in the incidence of HAIs related to invasive procedures and devices. However, the rate of ICU-acquired infections remains high. Within this context, the ongoing emergence of new pathogens further complicates treatment and threatens patient outcomes. Additionally, the SARS-CoV-2 (COVID-19) pandemic highlighted the challenge that an emerging pathogen provides in adapting preventive measures regarding the risk of exposure to caregivers and to maintain quality of care.[4]

There are limited data regarding risk factors associated with BSI in COVID-19 ICU patients. Hence, there is a need to look for the risk factors of BSI among COVID-19 ICU patients, as an aid to treat the patients.

Methods

We conducted a retrospective cohort study, wherein a total of 100 blood culture samples with growth and 100 samples with no growth were collected and considered as case and control respectively. All the demographic data, clinical data and microbiological data were collected for both blood culture growth and no growth from January 2021 to January 2022. All the patients ≥18 years hospitalized in COVID-19 ICU with a positive result of ICMR-approved COVID-19 test and blood culture drawn during ICU hospitalization with mean oxygen <90% of saturation on room air with clinically suspected BSIs were included in the study. BSI is a bacterial or fungal infection identified in blood culture using an automated blood culture system (Bact T alert system) among clinically suspected patients with fever >100°F or raised total blood counts. All confirmed positive patients admitted to COVID-19 ICU with blood culture investigation from clinical suspected cases were received in microbiology diagnostics.

Blood cultures were sent from the ICU when a hospital acquired infection is suspected- when patient is febrile with fever > 101-degree F, new onset hypotension requiring vasopressors, worsening other organ functions like worsening of acute kidney injury.

Blood cultures were considered as skin contaminant if there was coagulase–negative Staphylococcus species (CONS) in only 1 blood without clinical evidence of a true bacteraemia and blood culture growing environmental contaminants like aerobic spore bearing gram positive bacilli were excluded from the study. This study was approved by the Institutional Ethics Committee, Bangalore (IEC 245/2021).

Methodology

The blood samples were loaded in the automated blood culture system and positively flagged samples were processed for complete identification and antibiotic susceptibility testing. The method for identification was MALDI-TOF method, and antibiotic susceptibility testing was done by automated method or conventional method as per the standard protocol. The clinical data were collected from the medical records for cases and controls. The data were compared and further analyzed [Figure 1].

Statistical analysis

Risks and outcomes were compared between cases (BSI) and controls (no BSI).

Proportions of parameter differences were compared using a Chi-square test. Mann–Whitney *U*-test used for nonnormally distributed continuous variables. Logistic regression was used to calculate odds ratios and 95% confidence intervals (CIs) for C-reactive protein (CRP), procalcitonin, ICU, mechanical ventilator, and prior antimicrobial exposure to see the clinical outcome of BSI.

Results

A total of 200 blood culture samples were collected in St John's hospital from January 2021 to January 2022, in which 100 samples were blood culture with growth (Case with BSI) and 100 were blood culture with no growth (Control with no BSI). mean value of age distribution among cases 53.7 and controls 54.5, almost comparable with similar pattern between the two groups towards blood stream infections (BSI). However, age from 40 to 60 followed by 61 to 81 years were at high risks for COVID-19. Among cases 63 were males and 37 were female p value of 0.174, there was no statistical differences [Table 1]. Blood culture with growth (cases) were having symptoms like fever 74%, cough 70% and shortness of breath 51 % and blood culture with no growth (control) patients were with fever 65 %, cough 68% and shortness of breath 57 %. These symptoms were commonly seen in COVID-19 patients .Association of comorbidities among case and control (70% and 66%), which was not significant with *P* value 0.544. So different comorbidity was associated

Table 1: Sociodemographic data of case (bloodstream infection) and control (no bloodstream infection) patients in COVID-19 intensive care unit

Characteristics	Case (*n*=100)	Control (*n*=100)	*P*
Sex (%)*			
Male	63	72	0.174
Symptoms (%)*			
Fever	74	65	0.167
Cough	71	68	0.76
Shortness of breath	54	51	0.395
Comorbidities (%)*	70	66	0.544

*By Pearson Chi-square method

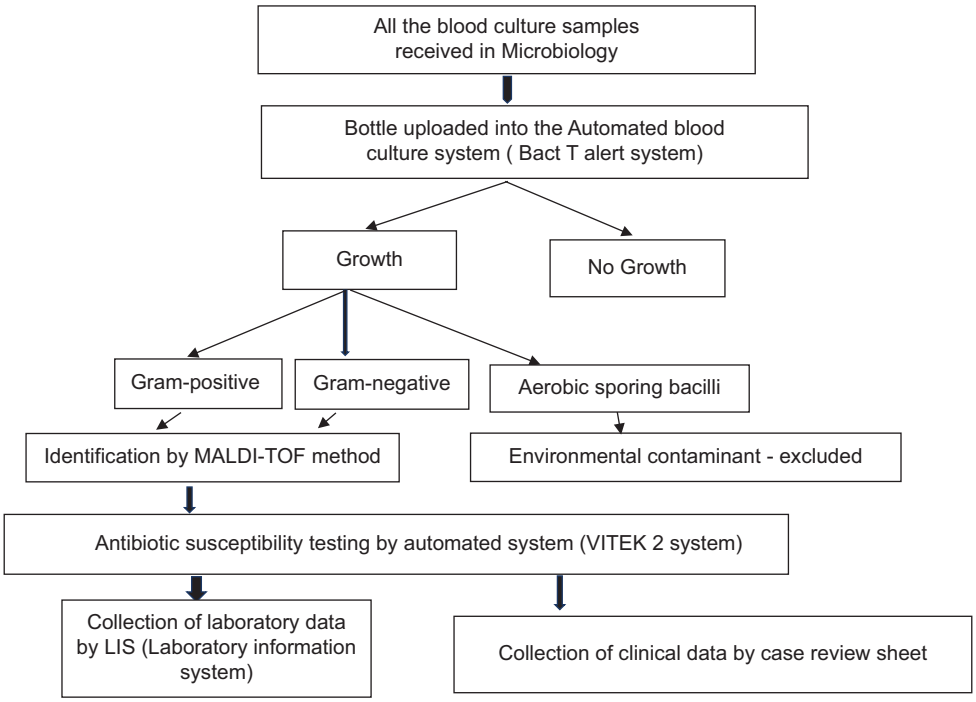

Figure 1: Methodology used for blood sample collection and processing of sample from case (BSI) and control (no BSI) patients admitted to COVID-19 intensive care unit

with increase in the association of COVID-19 infection but not with blood stream infections.

The median (interquartile range [IQR]) ICU stay was 11 (6.0–14.5) days for cases and 8 (5.0–12.0) days for controls and was found to be significant with $P = 0.022$ by Mann–Whitney *U* test [Table 2]. This indicates that secondary BSI (sBSIs) adds to the prolonged ICU stay which will add to the morbidity.

Patients who were on mechanical ventilation (MV) yielded a higher percentage of blood culture with growth 92 (54.74%) when compared to other patients who yielded no growth 76 (45.24%) The association of patients with blood culture growth on mechanical ventilation was found to be significant among secondary blood stream infections with p value of 0.002 by Chi square test. A total of 100 patients, 97 (53.59%) patients were prior antimicrobial exposure in case and in control group it was 84 (46.41%) of 100 patients. (*p* value 0.002 by Chi-Square Tests). This suggests that the strict adherence to the antibiotic policy and rationale use of antibiotics among ICU patients. The mortality was high among case with 64 (64%) which was found to be statistically significant with *p* value (<0.001) by Chi square test.

We collected the other laboratory data for hematology and biochemical laboratory parameters [Table 3]. Our study witnessed statistically significant values in CRP and IL6, The median CRP value among cases were 11.655 mg/l (4.75-24.19) and controls had 6.82 mg/dl (1.93-15.89) with p value 0.0035 which was significant. The median IL6 value among cases were 164.2 pg/ml (143.4-276.6) and controls had 10.435 pg/ml (4.475-43.335) with p value 0.0404 which was significant.

Table 2: Clinical data of cases (bloodstream infection) and controls (no bloodstream infection) admitted to COVID-19 intensive care unit

	Case (*n*=100)	Control (*n*=100)	*P*
ICU stay (days)**	11 (6.0–14.5)	8 (5.0–12.0)	0.022
Mechanical ventilation, *n* (%)*	92 (54.74)	76 (45.24)	0.002
Prior antimicrobial exposure, *n* (%)	97 (53.59)	84 (46.41)	0.002
Mortality rate (%)*	64	29	<0.001

**ICU stay expressed in median and IQR (Q1–Q2) by Mann–Whitney *U*-test others by Chi-square test. ICU: Intensive care unit, IQR: Interquartile range

In logistic regression (Table 4) BSI showed significant association among cases for CRP (*p* value - 0.003), procalcitonin (*p* value - 0.045), ICU stay (*p* value - 0.005), mechanical ventilation (*p* value - 0.024) and prior antimicrobial exposure (p value - 0.005) by univariate analysis. However, after adjusting to other variable for multivariable analysis, they were not significant but odds ratio of CRP (1.022), procalcitonin (1.652), mechanical ventilator (2.410) and ICU stay (1.019) showed strong association among cases when compared to controls.

Positive procalcitonin in the case group was 34 (62.96%) and the control group was 20 (37%) with $P = 0.057$ by Chi-square test, which was not found to be significant. The most common Gram-positive cocci [Figure 2] were *Enterococcus* species, which were *Enterococcus faecium* 10 (33%), *Enterococcus faecalis* 4 (13%), and other *Enterococcus* species 6 (20%).

Table 3: Laboratory data of case (bloodstream infections) and control (no bloodstream infections) patients in COVID-19 intensive care unit patients

Parameters	Case	Control	*P*
Hemoglobin (g/dL), *n*, mean	94, 11.75	99, 11.7 (3.012)	0.959
Platelet (lakhs/mm^3), *n*, mean	91, 197.4	95, 226.1 (107.1)	0.066
WBC (cells/mm^3), *n*, median (IQR)	91, 14.0 (9.93–18.79)	98, 13.7 (9.52–21.26)	0.9131
Creatinine (mg/dL), *n*, median (IQR)	91, 0.82 (0.64–2.58)	92, 0.87 (0.72–2.03)	0.4783
CRP (mg/L), *n*, median (IQR)	82, 11.6 (4.75–24.19)	78, 6.82 (1.93–15.89)	0.0035
D-dimer (ng/mL), *n*, median (IQR)	77, 966 (548–2255)	82, 1392 (574–3388)	0.1027
Ferritin (ng/mL), *n*, median (IQR)	68, 917.35 (446.2–2291.65)	75, 839.6 (311–1741.5)	0.4449
LDH (U/L), *n*, median (IQR)	45, 525 (434–832)	68, 616 (423.5–835.5)	0.7315
Troponin (ng/mL), *n*, median (IQR)	29, 0.048 (0.013–0.146)	50, 0.065 (0.015–0.422)	0.3956
IL-6 (pg/mL), *n*, median (IQR)	5, 164.2 (143.4–276.6)	8, 10.43 (4.47–43.33)	0.0404
Procalcitonin, *n*, mean	68, 62.96	60, 37.4	0.057

Hemoglobin, platelet, and procalcitonin by Chi-square test, others expressed in median and IQR (Q1–Q2) by Mann–Whitney *U*-test. WBC: white blood cells, CRP: C-reactive protein, IL-6: Interleukin-6, LDH: Lactate dehydrogenase, IQR: Interquartile range, *n*: Total number of cases and controls

Table 4: Univariate and multivariate logistic regression analysis of biochemical parameters and clinical parameters

Variables	Univariate logistic regression analysis		Multivariate logistic regression analysis	
	P	OR (95% CI)	*P*	OR (95% CI)
CRP	0.003	1.04 (1.01–1.08)	0.308	1.02 (0.98–1.06)
Procalcitonin	0.045	1.95 (1.01–3.7)	0.270	1.65 (0.67–4.03)
Mechanical ventilators	0.003	3.63 (1.54–54)	0.227	2.41 (0.57–10.0)
ICU stay	0.024	1.06 (1.0–1.11)	0.574	1.01 (0.95–1.08)
Prior antibiotic exposure	0.005	6.15 (1.73–21.8)	0.319	3.29 (0.31–34.0)

OR: Odds ratio, CI: Confidence interval, CRP: C-reactive protein, ICU: Intensive care unit

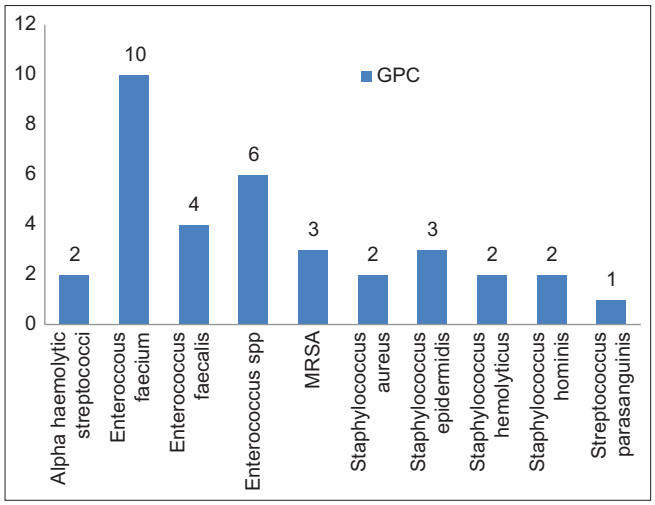

Figure 2: Distribution of Gram-positive bacteria isolated from blood with COVID-19 intensive care unit patients (*n* = 32). MRSA: Methicillin-resistance *Staphylococcus aureus*

Staphylococcus species most commonly isolated were methicillin-resistant *Staphylococcus aureus* (MRSA) and *Staphylococcus epidermidis* each being 3 (10%), followed by *S. aureus* 2 (6%), *Staphylococcus haemolyticus* 2 (6%), and *Staphylococcus hominis 2 (*6%). However, CONS were considered to be the skin commensals and reported only if clinically significant.

Acinetobacter baumannii was the most common organism to be identified in blood culture 38 (33%) followed by *Klebsiella pneumoniae* 30 (26%) [Figure 3].

Acinetobacter species, *Escherichia coli*, and *Pseudomonas aeruginosa* were 12 (10%), 9 (7%), and 5 (4%), respectively. *A. baumannii* was the most common organism to be isolated in both samples which was about 19 (63.3%) followed by *K. pneumoniae* 7 (23.3%), *P. aeruginosa* 3 (10%), and *E. coli* 1 (3%).

Antibiotic resistance pattern of predominant Gram-negative blood stream isolates [Table 5] in COVID -19 patients, *Acinetobacter baumanni* and *Klebsiella pneumoniae* were the most common organisms to show resistance in blood stream infections followed by *Escherichia.* Many nonfermenters which are very common and inherently multidrug resistant were *Chryseobacterium indologenes* and *Myroides* species. Among Gram-positive bacteria [Table 6], *Enterococcus* species (6) showed the highest resistance to gentamicin and penicillin which was 4 (66%) and MRSA (3) resistance to ciprofloxacin, erythromycin, and methicillin 3 (100%).

Discussion

COVID-19 is a newly emerging life-threatening infectious disease, and we are still trying to enhance our comprehensive knowledge to deal with the disease. We indulged in this study

to know deeply about the risk factors and outcomes of sBSIs in COVID-19 ICU. Age distribution among case and control groups and other demographic data were comparable as there was no significant differences found between two groups Table 1.

Comorbidities among growth and no growth (70% and 66%) did not have any correlations to BSIs between the two groups ($P = 0.544$). Palanisamy *et al*. reported that comorbidities were significant in COVID-19 patients ($P = 0.01$).[5] This suggests the association of comorbidities found in COVID-19 infection but not with BSIs.

There was no significant difference in symptoms between the case and control groups; however, in COVID-19 patients, fever, cough, and breathlessness were more commonly observed in both the groups. As per our observation, clinical data among [Table 2] COVID-19 patients who were admitted to ICU for a longer time had more chances of acquiring BSI. Their median days were 11 among 85 cases and 8 among 84 controls, which was statistically significant ($P = 0.022$).

Another study Buetti *et al*. observed that Among the total ICU-BSI, 8 (3.4%) were in the non-COVID-19 group and 35 (14.9%) in the COVID-19 group (p value ≤ 0.0001) respectively. ICU-BSI among COVID-19 patients occurred in median 12 (IQR 9-16) days after ICU admission versus 6.5 days [IQR 5–12.5] for non-COVID-19 patients with p value of 0.086. So , according to this study the risk of BSI started to significantly increase in critically ill COVID-19 patients after 7 days in ICU.[3]

Another study done by Giacobbe etc, they reported that the cumulative risk of developing blood stream infections increased with ICU stay, in this study overall 78 critically ill patients with COVID-19 were included, 45 episodes of ICU-acquired blood stream infections were registered in 31 patients, with an incidence rate of 47 episodes (95% confidence interval [CI] 35-63) per 1000 patient-days at risk. They estimated cumulative risk of developing at least one blood stream infection episode was of almost 25% after 15 days at risk, and possibly surpassing 50% after 30 days at risk.[6]

According to our study, patients who were on MV yielded higher blood culture growth 92 (54.74%) than patients who

Table 5: Antibiotic resistance pattern of Gram-negative bacteria in bloodstream infection among COVID-19 patients

Antibiotics	*Acinetobacter* spp. ($n=50$)	*Klebsiella pneumoniae* ($n=30$)	*Escherichia coli* ($n=9$)	*Pseudomonas* spp. ($n=7$)	*Citrobacter* spp. ($n=3$)
Amikacin	48	15	4	-	1
Cefuroxime	34	21	5	-	1
Cefotaxime	47	29	8	1	1
Ceftazidime	49	29	8	2	1
Cotrimoxazole	3	-	-	-	-
Ciprofloxacin	46	22	7	1	-
Colistin	1	2	-	-	-
Gentamicin	44	18	6	2	-
Meropenem	48	15	6	2	-
Netilmicin	46	16	4	1	-
Piperacillin/ tazobactam	42	17	6	2	-

Table 6: Antibiotic resistance pattern of predominant Gram-positive isolates as bloodstream infection among COVID-19 patients

Antibiotics	*Enterococcus faecium* (10)	*Enterococcus* faecalis (4)	*Enterococcus* spp. (6)	MRSA (3)	*Staphylococcus aureus* (2)	*Staphylococcus epidermidis* (3)	*Staphylococcus hominis* (3)
Amikacin	-	-	1	-	-	-	-
Chloramphenicol	-	-	-	-	-	-	-
Cotrimoxazole	-	-	-	1	-	1	-
Ciprofloxacin	-	-	1	3	-	1	-
Erythromycin	-	-	-	3	2	2	1
Gentamicin	-	2	4	2	-	-	-
Netilmicin	-	-	-	-	-	-	-
Penicillin	-	1	4	3	2	2	2
Teicoplanin	-	-	-	-	-	-	-
Tetracycline	-	-	-	-	-	-	1
Vancomycin	-	-	-	-	-	-	-
Methicillin	-	-	-	3	-	1	1

MRSA: Methicillin-resistant *Staphylococcus aureus*

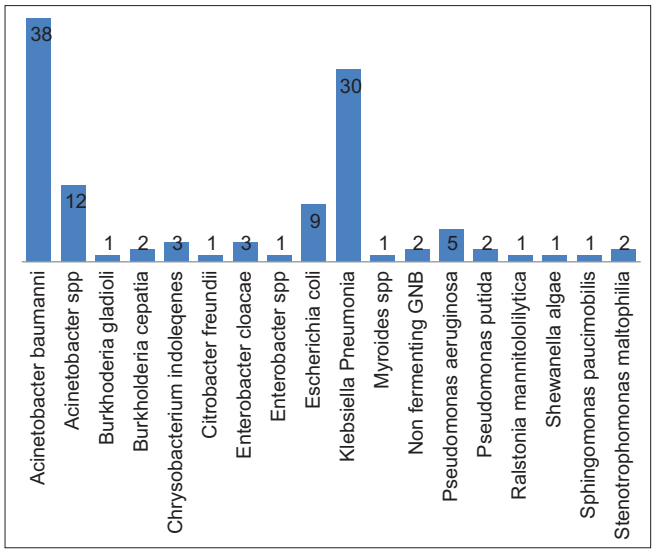

Figure 3: Distribution of Gram-negative bacteria isolated from blood among COVID-19 intensive care unit patients (n = 115)

were not on MV 8 (25.0%). This was found to be statistically significant with P = 0. 002. This suggests that mechanically ventilated patients are at high risk toward BSIs. According to Fu *et al*.'s study, the secondary bacterial infection in COVID-19 was associated with MV, which disturbed airway barriers and facilitated the invasion of opportunistic pathogen.[7]

In this study, COVID-19 ICU patients who had (53.59%) prior antimicrobial exposure in BSI were high when compared to patients with no BSI (46.41%) and with P = 0.002. In general, prior antimicrobial exposure is not recommended to initiate routinely in patients admitted to the emergency department or ICU with proven COVID-19. However, in view of the emerging literature on the predominance of Gram-negative pathogens in ventilator-associated pneumonia among COVID-19 patients including multidrug resistance (MDR) pathogens, and Gram-positive bacteremia with CONS, *E. faecalis* empirical coverage may be recommended in certain clinical condition.[8] We could conclude that we found more MDR pathogens and antimicrobials were initiated for these patients.

Furthermore, we witnessed a higher mortality rate in COVID-19 patients with BSIs (64%) compared to patients with no BSIs (34.52%) with P < 0.001. It may be due to prolonged ICU stay and comorbidities. Bhatt *et al*. reported a higher mortality rate with a BSI versus controls (53.1% vs. 32.8%, P = 0.0001) among COVID-19 patients.[1]

Raised CRP levels in COVID-19 patients could be because of liver syntheses of an acute-phase protein (CRP). This acute inflammatory protein is a highly sensitive biomarker for inflammation, tissue damage, and infection. CRP levels also correlated with the levels of inflammation and can promote phagocytosis, activate the complement system . The same was seen in our study, there was a significant difference of CRP levels with p value of 0.003 among cases and controls. This is because of COVID 19 infection along with BSI which has led to significant increase in CRP levels among cases.

Sadeghi Haddad Zavareh *et al*.'s study revealed significantly higher levels in severe cases than in nonsevere cases; thus, it could be suggested that the CRP level may be a biomarker of disease severity and progression in patients with COVID-19.[9,10]

In our study, IL6 was also significantly raised among cases when compared to control groups. The values were 5 (164.2) and 8 (10 .435) respectively among two groups which was found to statistically significant (p value - 0.0404). Other studies have revealed that levels of IL-6, the most common type of cytokine released by activated macrophages, rise sharply in severe manifestations of COVID-19.[11]

One meta-analysis reviewing six studies showed a mean IL-6 concentrations of 2.9-fold higher in patients with complicated COVID-19 compared to those with noncomplicated diseases (n = 1302; 95% CI 1.17–7.19).[12]

Hence, there could be a relation between raised IL-6 toward BSI in COVID-19 ICU patients. Apart from CRP and IL-6, other biochemical parameters such as creatinine, D-dimer, ferritin, troponin, and lactate dehydrogenase have not shown statistical significance to BSI.

Procalcitonin in our study did not show a greater significance among cases and controls. It was found to be 34 (62.96%) in cases and 20 (37.04%) in controls with P = 0.057. According to Palanisamy *et al*., procalcitonin showed an elevated level in patients with BSIs.[5]

In logistic regression [Table 4], we witnessed a significant association among CRP, procalcitonin, MV, prior antimicrobial exposure, and ICU stay in univariate analysis. However, after adjusting to other variables in the model for multivariable analysis, they were not significant, but the odds ratio of CRP (1.022), procalcitonin (1.652), mechanical ventilator (2.410), ICU stay (1.019), and prior antimicrobial exposure (0.319) was high indicative of strong association for these variables. This analysis supports that these variables can be the predisposing factors resulting in BSIs among COVID-19 patients.

In this study [Figure 2], we observed a relatively high proportion of *Enterococcus* isolates as BSIs, which were 10, 6, and 4 of *E. faecium*, *Enterococcus* species, and *E. faecalis*, respectively. Bonazzetti *et al*. proposed a theory that SARS-CoV-2-mediated disruption of the gut barrier and bacterial translocation could trigger increased BSI, especially *Enterococcus* spp.[13]

Gram-negative organisms [Figure 3] were more predominant BSI in this report. Similar observations were described in Palanisamy *et al*. (cohort study) and Vijay *et al*.[5,14] Conversely, another study reported the increased prevalence of Gram-positive organisms, particularly *S. aureus* in COVID-19 ICU patients.[15] In this study, we also observed the

high predominance of *A. baumannii* (*n* = 38), *Acinetobacter* species (*n* = 12), and *K. pneumoniae* (*n* = 30). This is in contrast to a previous report described with *A. baumannii* in <1% of the cases.[13] This increase in the prevalence and resistance could be explained by prolonged ICU stay, MV, and inadvertent use of carbapenem with antimicrobial selection pressure, which are the usual triggers.[16.17] In our study, a greater percentage of isolates were monomicrobial (72%), whereas just 28% were polymicrobial as co-pathogens. Among monomicrobial pathogens, we observed that Gram-negative bacteria yielded a higher growth of organisms than that of Gram-positive bacteria.

In our study, we compared organisms which yielded in blood to other samples like BAL. BAL samples received were 76, in which 30 (39.4%) same organisms yielded in both blood and BAL and the most common organism was *A. baumannii* 19 (63.3%) followed by *K. pneumoniae* 7 (23.3%). This can be explained by the fact that probably these might be primary pathogens causing respiratory infection which invade the bloodstream and can cause BSI.

Antibiotic susceptibility pattern [Table 5] showed, highest resistance to ceftazidime 49 (96%), amikacin 48 (96%), meropenem 48 (96%), cefotaxime 47 (94%), ciprofloxacin 46 (92%), netilmicin 46 (92%) for Acinetobacter species (*n* – 50). *A. baumannii* has emerged as a worldwide problem as a nosocomial pathogen in hospitalized patients. *Acinetobacter* spp. can cause a multitude of infections including pneumonia, bacteremia, meningitis, urinary tract infections, and skin and soft = 9tissue infections, and the mortality associated with these infections is high. There is no simple answer to the treatment of *Acinetobacter* infections. Eradication of *Acinetobacter* spp. requires adherence to good infection control practices and prudent antibiotic use, as well as effective antimicrobial therapy. Alternative therapies such as colistin, ampicillin/sulbactam, and tetracycline are potential options, but prospective, randomized, controlled trials are still lacking.[18]

The second most resistant organism was *K. pneumoniae* (*n* = 30) which was resistant to ceftazidime 29 (96.6%) ciprofloxacin 22 (73.3%), and cefuroxime 21 (70%). According to the study by Wu *et al*., the prevalence of colonization/infection with carbapenem-resistant Enterobacterales in ICUs is of great concern and should be monitored systematically. Surveillance of colonization/infection with carbapenem-resistant Enterobacterales at admission and during the patient's stay represents an early identification tool to prevent further transmission of carbapenem-resistant Enterobacterales.[19]

These two organisms showed the highest resistance to antibiotics compared to *E. coli* and *P. aeruginosa.* An observational multicenter (*n* = 24) study was done by Vogelaers *et al*. who investigated relationships between antimicrobial choices and rates of empiric appropriate or adequate therapy and subsequent adaptation of therapy in 171 ICU patients with severe nosocomial infections. Empiric schemes were classified according to coverage of (i) ESBL-producing Enterobacteriaceae and nonfermenting Gram-negative bacteria ("meropenem based"), (ii) nonfermenting Gram-negative bacteria (schemes with an antipseudomonal agent), and (iii) first-line agents not covering ESBL-Enterobacteriaceae nor nonfermenting Gram-negative bacteria.In this study Meropenem-based schemes showed significantly (p<0.001), higher rates of appropriate/adequate therapy. This benefit remained when only patients without risk factors for MDR were considered (P = 0.021). In this study reflecting real-life practice, first-line use of meropenem provided significantly higher rates of the appropriate/adequate therapy, irrespective of the presence of risk factors for MDR.[20]

Among Gram- positive bacteria [Table 6] Enterococcus species (6) showed the highest resistance to high level gentamicin and penicillin which were 4 (66%) each and MRSA (3) were resistant to ciprofloxacin and erythromycin.

Routinely, hospital infection control practices are followed in the management of central line catheters. A daily central line checklist is filled for each patient with central line in the ICU. A daily review of the need of central line is done by infection control nurse and consultant of the ICU and the same is documented in the patient file. An infection control policy is followed during each central line handling by the ICU nurse and being monitored by HICC team on a regular basis. However, our study limitations are that blood culture could not be correlated with median days of ICU stay when blood cultures were sampled and also APACHE score or SOFA score could not be collected from ICU patients.

Conclusions

There have been limited studies regarding sBSIs in COVID-19 ICU patients. In our study, we report the raised CRP levels and measuring this biomarker at the admission and during the course of COVID-19 diseases would help to identify BSI. Furthermore, measuring biomarkers such as CRP, procalcitonin, and IL-6 in COVID-19 patients on admission period could help to mitigate BSI and provide early treatment. MV, prior antimicrobial exposure, and longer ICU stay patients are higher risks toward BSI. Moreover, we report a greater proportion of *A. baumannii* and *K. pneumoniae* in BSI. Mortality cases are high in patients with BSI among COVID-19 ICU patients. Hence, we suggest to maintain the ICU infection control practices and implement the antimicrobial stewardship to prevent secondary infections and emergence of drug resistance.

Acknowledgment

We would like to thank the Department of Critical Care Medicine, SJMCH, Bengaluru 560068.

Research quality and ethics statement

This study was approved by the Institutional Ethics Committee (ID: 245/2021). The authors followed the applicable EQUATOR Network guidelines during the conduct of this research project.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Bhatt PJ, Shiau S, Brunetti L, Xie Y, Solanki K, Khalid S, *et al*. Risk factors and outcomes of hospitalized patients with severe coronavirus disease 2019 (COVID-19) and secondary bloodstream infections: A multicenter case-control study. Clin Infect Dis 2021;72:e995-1003.
2. Sepulveda J, Westblade LF, Whittier S, Satlin MJ, Greendyke WG, Aaron JG, *et al*. Bacteremia and blood culture utilization during COVID-19 surge in New York City. J Clin Microbiol 2020;58:e00875-20.
3. Buetti N, Ruckly S, de Montmollin E, Reignier J, Terzi N, Cohen Y, *et al*. COVID-19 increased the risk of ICU-acquired bloodstream infections: A case-cohort study from the multicentric OUTCOMEREA network. Intensive Care Med 2021;47:180-7.
4. Blot S, Ruppé E, Harbarth S, Asehnoune K, Poulakou G, Luyt CE, *et al*. Healthcare-associated infections in adult intensive care unit patients: Changes in epidemiology, diagnosis, prevention and contributions of new technologies. Intensive Crit Care Nurs 2022;70:103227.
5. Palanisamy N, Vihari N, Meena DS, Kumar D, Midha N, Tak V, *et al*. Clinical profile of bloodstream infections in COVID-19 patients: A retrospective cohort study. BMC Infect Dis 2021;21:933.
6. Giacobbe DR, Battaglini D, Ball L, Brunetti I, Bruzzone B, Codda G, *et al.* Bloodstream infections in critically ill patients with COVID-19. Eur J Clin Invest 2020;50:e13319.
7. Fu Y, Yang Q, Xu M, Kong H, Chen H, Fu Y, *et al*. Secondary bacterial infections in critical ill patients with coronavirus disease 2019. Open Forum Infect Dis 2020;7:ofaa220.
8. Schouten J, De Waele J, Lanckohr C, Koulenti D, Haddad N, Rizk N, *et al*. Antimicrobial stewardship in the ICU in COVID-19 times: The known unknowns. Int J Antimicrob Agents 2021;58:106409.
9. Kermali M, Khalsa RK, Pillai K, Ismail Z, Harky A. The role of biomarkers in diagnosis of COVID-19 – A systematic review. Life Sci 2020;254:117788.
10. Sadeghi Haddad Zavareh M, Bayani M, Shokri M, Ebrahimpour S, Babazadeh A, Mehraeen R, *et al.* C-reactive protein as a prognostic indicator in COVID-19 patients. Interdiscip Perspect Infect Dis 2021;2021:1-5.
11. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, *et al*. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: A descriptive study. Lancet 2020;395:507-13.
12. Coomes EA, Haghbayan H. Interleukin-6 in COVID-19: A systematic review and meta-analysis. Rev Med Virol 2020;30:1-9.
13. Bonazzetti C, Morena V, Giacomelli A, Oreni L, Casalini G, Galimberti LR, *et al*. Unexpectedly high frequency of enterococcal bloodstream infections in coronavirus disease 2019 patients admitted to an Italian ICU: An observational study. Crit Care Med 2021;49:e31-40.
14. Vijay S, Bansal N, Rao BK, Veeraraghavan B, Rodrigues C, Wattal C, *et al*. Secondary infections in hospitalized COVID-19 patients: Indian experience. Infect Drug Resist 2021;14:1893-903.
15. Elabbadi A, Turpin M, Gerotziafas GT, Teulier M, Voiriot G, Fartoukh M. Bacterial coinfection in critically ill COVID-19 patients with severe pneumonia. Infection 2021;49:559-62.
16. Montrucchio G, Corcione S, Sales G, Curtoni A, De Rosa FG, Brazzi L. Carbapenem-resistant *Klebsiella pneumoniae* in ICU-admitted COVID-19 patients: Keep an eye on the ball. J Glob Antimicrob Resist 2020;23:398-400.
17. Pascale R, Bussini L, Gaibani P, Bovo F, Fornaro G, Lombardo D, *et al*. Carbapenem-resistant bacteria in an intensive care unit during the coronavirus disease 2019 (COVID-19) pandemic: A multicenter before-and-after cross-sectional study. Infect Control Hosp Epidemiol 2022;43:461-6.
18. Jain R, Danziger LH. Multidrug-resistant *Acinetobacter* infections: An emerging challenge to clinicians. Ann Pharmacother 2004;38:1449-59.
19. Wu YL, Hu XQ, Wu DQ, Li RJ, Wang XP, Zhang J, *et al.* Prevalence and risk factors for colonisation and infection with carbapenem-resistant enterobacterales in intensive care units: A prospective multicentre study. Intensive Crit Care Nurs 2023;79:103491.
20. Vogelaers D, De Bels D, Forêt F, Cran S, Gilbert E, Schoonheydt K, *et al*. Patterns of antimicrobial therapy in severe nosocomial infections: Empiric choices, proportion of appropriate therapy, and adaptation rates – A multicentre, observational survey in critically ill patients. Int J Antimicrob Agents 2010;35:375-81.