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Microbiological Profile and Susceptibility Pattern of Bacterial Blood Culture Isolates in COVID-19 Patients with Septicemia from a Designated COVID Hospital in Pune

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Abstract

In severe Coronavirus disease 2019 (COVID-19), bloodstream infections (BSIs) are an increasing cause of morbidity and mortality. In critically ill patients with COVID-19, we aimed to evaluate the prevalence, clinical profiles, and outcomes of BSIs. This single-center prospective investigation was conducted at a tertiary care hospital in Western India. All patients (>18 years of age) hospitalized in the intensive care unit (ICU) or ward with RT-PCR-confirmed COVID-19 were included. Demographic information, clinical proficiency, and antibiotic resistance patterns were assessed. Of the 550 patients admitted to the COVID ICU, subsequent BSIs occurred in 7.45% of patients. Gram-negative pathogens comprised a significant proportion of BSIs (53/73, 72.6%). The most frequent isolates were *Klebsiella pneumoniae* (22/73, 30.1%), *Acinetobacter baumannii* (11/73,15.06%), and *Escherichia coli* (7/23, 9.58%). In 57.8% of the cases, multidrug-resistant organisms (MDRO) were discovered. The *Enterococcus* and *K. pneumoniae* families comprise the majority of MDRO. Gram-negative bacteria (30.18% [16/53]) were resistant to carbapenems. Increased total leukocyte count, mechanical ventilation, and the presence of comorbidities were significantly associated with the incidence of BSIs. In COVID-19-linked BSIs, we discovered a high frequency of *A. baumannii*. Clinicians should be aware of potential BSIs in the presence of comorbidities, elevated leukocyte count, and mechanical ventilation. To improve the results, empirical antibiotics must be started promptly, and the situation must be de-escalated quickly. The most frequent isolates were *A. baumannii* and *K. pneumoniae* ([11/73, 15.06%] and [22/73, 30.1%], respectively). To reduce the incidence of MDRO, infection control procedures should be strictly followed in patients with multidrug resistance.

Keywords: COVID-19, Septicemia, Blood Stream Infections, Time to Positivity, Multidrug Resistant Organisms

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 and declared as a pandemic has recently caused societal, economic, and medical desolation. Bacterial co-infections have been observed in COVID-19 positive cases and hence, it is pertinent to understand the proportion of bacteremia in COVID-19 cases in our clinical setting. Therefore, this study aimed to measure the positivity rate, time to positivity, pattern of isolates, and antimicrobial susceptibility of blood cultures sent from COVID-19 positive cases. This study aims to make an appropriate choice for the empirical treatment of bacteremia in COVID-19 cases to reduce mortality related to septicemia.

Since December 2019 there have been a large number of deaths due to COVID-19.[1] COVID-19 infections, which are said to have originated in one corner of the world, have rapidly spread globally.[2] The initial published reports of COVID-19 described the most common presenting symptoms as fever, cough, and dyspnea.[3]

Bacterial co-infections are observed in COVID-19 positive cases and blood culture samples are sent from serious patients for testing, especially in intensive care unit (ICU) settings. Understanding the proportion of bacteremia in COVID-19 cases and the types of isolates in the clinical setting is crucial.

The prevalence of viral co-infections in patients with COVID-19 appears to be low in most, but not all, studies.[4-7] Many patients with COVID-19 are seen progressing to bacteremia and septicemia; blood culture is a crucial tool for the diagnosis and management of such bloodstream infections. Limited data is available on the utilization of blood cultures in patients with COVID-19 and the proportion of these patients progressing to bacteremia and/or septicemia. Patients with severe COVID-19 are treated with empiric antibiotics for potential bacterial co-infections; however, the rate of bacteremia among these patients is unknown, and the benefit of empiric antibiotic therapy is unproven.[8]

Aims and objectives

1. To measure the proportion of blood culture positivity amongst patients with COVID-19.
2. To calculate mean time to positivity of blood cultures.
3. To identify bacterial isolates from positive blood cultures.
4. To study the antimicrobial susceptibility pattern of an isolates.
5. To study the association of demographic factors, comorbidities, and blood count with the pattern of isolates and susceptibility.

Research question

Understanding the common micro-organisms causing septicemia among patients with COVID-19 and further studying the pattern of their susceptibility to the available antimicrobial drugs. In addition, we studied the association of demographic factors, comorbidities, and blood count with patterns of isolation and susceptibility.

MATERIALS AND METHODS

Study design

An observational study was conducted on blood culture samples from patients with COVID-19 who were clinically diagnosed with septicemia which were routinely administered for aerobic bacterial culture and sensitivity.[9] The study was based on retrospective secondary data collected as part of the standard of care.

Data collection

Data was collected from April 2021 to September 2021 in a pre-devised format that included demographic profile, presence of comorbidities, blood parameters, details of blood culture samples, isolates identified, and antimicrobial susceptibility patterns.

Sample size

All blood culture samples obtained from patients with septicemia during the study period were included.

Inclusion criteria

1. All blood culture samples which were obtained from a patients diagnosed with COVID-19 and septicemia in a microbiological laboratory.
2. All isolates from positive blood culture samples from patients diagnosed with

COVID-19 and septicemia and were identified in the microbiological laboratory.

Exclusion criteria

1. Repeat blood culture isolate from patients showing an antibiotic susceptibility pattern similar to that of an earlier isolate.

Isolation of microorganisms

Aerobic adult blood culture bottles (BD BACTEC Plus) received in the microbiology laboratory were incubated in a BACTEC FX 40 blood culture instrument (Beckton-Dickenson, Franklin Lakes, NJ, USA) at 35.5 ± 1.5°C for 5 days. Blood culture samples that flashed positive for aerobic bacterial growth were studied further to identify the isolate by sub-culturing on 5% blood agar and MacConkey agar plates. The plates were then incubated aerobically at 37°C for 18–24 h for bacterial isolation. Identification of the isolate was performed using routine microbiological and biochemical methods used in the microbiology laboratory and/or using the BD Phoenix M50 semi-automated system (Beckton-Dickenson). Antimicrobial susceptibility of these isolates was determined according to CLSI guidelines, using NMIC ID/AST and PMIC AST panels per isolate in the BD Phoenix M50 semi-automated system. The antibiogram patterns of Gram-positive and Gram-negative bacterial (GPB and GNB, respectively) isolates were studied separately to draw conclusions regarding the empirical choices of antimicrobials for these microorganisms.

Statistical analysis

Data were entered and analyzed using SPSS software (ver. 20) and MS Excel. The pattern was studied with demographic details; presence of comorbidities and blood count and statistical test between dependent and independent variables was performed using the Chi square test (X^2).

Consent and confidentiality

Separate patient consent was not essential, as this study involved blood culture samples collected as a standard of care, and is based on retrospective secondary data. Blanket consent was obtained as part of the institutional policy. This study was approved by the Institutional Ethics Committee (approval no SIU/IEC/178).

Confidentiality was maintained with no linkage of the data to the identity of an individual.

RESULTS

A total of 550 patients with RT-PCR-confirmed COVID-19 were admitted to the ICU and ward over the course of the six-month study (April 2021 to September 2021). Of all the patients, 53/550 (9.6%) experienced BSIs. Table 1 summarizes the demographic and clinical features of all the patients (BSIs and non-BSIs). Patients with and without BSIs did not differ significantly in terms of age or sex (Table 1). Patients with BSIs had a significantly higher prevalence of comorbidities compared to patients without BSIs (66% vs. 34.80%). Patients with BSIs frequently had concomitant conditions, such as diabetes, hypertension, steroid intake, as well as IHD, CKD, and CLD (37.7%, 22.64%, 37.7%, and 9.43%, respectively). In the BSI group, 41.50% of the patients had central venous access. When compared to patients without BSIs, there was no significant difference (p=0.32). Patients with BSIs (43.39%) and those without (10.86%) utilized mechanical ventilation (p=0.00), which was significant. 61 (83.56%) patients with COVID-19 were having blood stream infections in ICU and 12 (16.43%) patients with COVID-19 were positive for blood culture in ward (Table 2). The most frequently used empirical antibiotic was piperacillin-tazobactam (n=46) followed by ceftriaxone (n=7) (Table 3). The antibiotics were modified in accordance with the blood culture. When patients with BSI were admitted, biochemical measurements revealed significantly elevated CRP levels. CRP levels, leukocytosis, the existence of comorbidities, and a history of steroid intake were significantly correlated with BSIs. Comorbidities, mechanical ventilation, and elevated leukocyte count were identified as independent predictors of BSIs. In this study, the BSIs were all monomicrobial (Table 1). GNB made up most of the isolates (53/73, 72.6%). All isolates

Table 1. Association of demographic factors, comorbidities, and blood count with pattern of isolate and susceptibility of patients with COVID-19

Parameters	All patients with COVID-19 n=550	Patients with positive blood culture n=53	Patients with negative blood culture n=497	P-value
Age (median IQR)	58 yrs (43–73)	63 yrs (48–78)	56 yrs (41–71)	<0.00001-S
Gender-male %	385 (70%)	32 (60%)	353 (71.02%)	0.56
Comorbidities	220 (40%)	35 (66%)	185 (37.22%)	0.017-S
Diabetes mellitus	121 (22%)	20 (37.7%)	101 (20.32%)	0.0353-S
HTN	137 (24.90%)	12 (22.64%)	125 (25.15%)	0.87
Asthma	12 (2.18%)	3 (5.6%)	9 (1.81%)	0.1079
CVA	16 (2.9%)	4 (7.54%)	12 (2.41%)	0.067
Steroid intake	25 (4.54%)	20 (37.7%)	5 (1%)	0.00001-S
Any other				
(IHD, CKD, CLD)	52 (9.45%)	5 (9.43%)	47 (9.45%)	1.0
Ventilator	83(15.09 %)	23 (43.39%)	60 (12.07%)	0.0-S
Arterial line	42 (7.63%)	9 (16.98 %)	33 (6.63%)	0.03-S
Central venous line	172 (31.27%)	22 (41.50%)	150 (30.18%)	0.32
Laboratory findings				
Hb (median-IQR)	11.5 (8.5–14.5)	10.5 (7.5–13.5)	11 (9–14)	0.00-S
CRP	98 (73–123)	130 (105–155)	96 (71–121)	0.00001-S
Organism isolated in blood culture				
E. coli		7 (9.58%)		
Klebsiella spp.		22 (30.13%)		
Acinetobacter spp.		11 (15.06%)		
Pseudomonas spp.		2 (2.73%)		
Enterobacter spp.		6 (8.21%)		
Citrobacter spp.		5 (6.84%)		
S. aureus		14 (19.17%)		
Enterococcus spp.		6 (8.21%)		

Some of the patients had more than one comorbidity, and 73 blood culture bottles from 53 patients were positive.

Table 2. Proportion of positive blood cultures among patients with COVID-19 in ward and ICU

	ICU	WARD
GPC N=20 (27.39%)	15 (20.54%)	5 (25%)
GNB N=53 (72.60%)	46 (63.01%)	7 (13.20%)
Total (N=73)	61 (83.56%)	12 (16.43%)

Note: N=73 as for 20 patients we had received paired blood culture bottles

of GPC belonged to the *Enterococcus* (11.32%) and (26.41%) *Staphylococcus* genera (Table 4). The two most prevalent GNB were *K. pneumoniae* (22/73, 30.1%), *A. baumannii* (11/73, 15.06%), and *E. coli* (7/23, 9.58%). *Pseudomonas, Enterobacter*, and *Citrobacter* contributed to a lesser extent. 57.8% of the patients had an MDRO infection. The majority of MDRO were *K. pneumonia, Acinetobacter* spp*., S. aureus,* and *Enterococcus* spp. GNB that were resistant to carbapenems (CR-GNB) were present in 30.18% (16/53) of cases. *Klebsiella* and *E. coli* showed the highest levels of resistance to ceftriaxone and piperacillin-tazobactam (Table 3). Most isolates of *K. pneumoniae* were resistant to aztreonam (77.27%) (Tabel 3). For erythromycin and ampicillin, *Enterococcus* species displayed the

Table 3. Antibiotic resistance pattern of predominant GNB isolated from blood culture of patients with COVID-19

Antibiotics	*E. coli* n=7	*K. pneumoniae* n=22	*Acineto*bacter n=11	*Pseudom*onas n=2	*Enterobacter* n=6	*Citrobacter* n=5
Amikacin	0 (0%)	6 (27.27%)	7 (63.63%)	2 (100%)	0 (0%)	0 (0%)
Tobramycin	7 (100%)	16 (72.72%)	7 (63.63%)	2 (100%)	0 (0%)	0 (0%)
Gentamicin	7 (100%)	16(72.72%)	2 (18.18%)	2 (100%)	0 (0%)	0 (0%)
Ceftriaxone	7 (100%)	22 (100%)	2 (18.18%)	-	2 (33.33%)	5 (100%)
Ceftazidime	7 (100%)	22 (100%)	2 (18.18%)	2 (100%)	2 (33.33%)	5 (100%)
Cefpime	7 (100%)	22 (100%)	2 (18.18%)	2 (100%)	2 (33.33%)	5 (100%)
Piptaz	6 (85.71%)	19 (86.36%)	7(63.63%)	0 (0%)	-	-
Ampicillin	7 (100%)	16 (72.72%)	-	-	6 (100%)	5 (100%)
Amoxiclav	3 (42.85%)	10 (45.45%)	-	-	4 (66.66%)	3 (60%)
Aztreonam	4 (57.14%)	17 (77.27%)	-	-	3 (50%)	2 (40%)
Ciprofloxacin	2 (28.57%)	8 (36.36%)	2 (18.18%)	0 (0%)	3 (50%)	2 (40%)
Levofloxacin	1 (14.28%)	5 (22.72%)	2 (18.18%)	0 (0%)	3 (50%)	2 (40%)
Ertapenem	5 (71.42%)	6 (27.27%)	-	-	2 (33.33%)	0 (0%)
Imepenem	5 (71.42%)	6 (27.27%)	3 (27.27%)	0 (0%)	2 (33.33%)	0 (0%)
Meropenem	5 (71.42%)	6 (27.27%)	3 (27.27%)	0 (0%)	2 (33.33%)	0 (0%)
Colistin	5 (71.42%)	16 (72.72%)	2 (18.18%)	0 (0%)	6 (100%)	5 (100 %)
Cotrimoxazole	6 (85.71%)	19 (86.36%)	11 (100%)	-	3 (50%)	0 (0%)
Minocycline	0 (0%)	0 (0%)	0 (0%)	-	0 (0%)	0 (0%)

Table 4. Antibiotic resistance pattern of predominant GPC isolated from blood culture of patients with COVID-19

Antibiotic	MSSA[1] n=3	MRSA[2] n=11	*Enterococcus* spp. n=6
Ampicillin	1 (33.33 %)	11 (100%)	6 (100%)
Penicillin	1 (33.33 %)	11(100%)	6 (100%)
Cipro	1 (33.33 %)	9 (81.81%)	3 (50%)
Levo	1 (33.33 %)	5 (45.45%)	3 (50%)
Erythromycin	1 (33.33 %)	9 (81.81%)	5 (83.33%)
Tetracycline	0 (0%)	4 (36.36%)	6 (100%)
Vancomycin	0 (0%)	0 (0%)	0 (0%)
Teicoplanin	0 (0%)	0 (0%)	0 (0%)
Linezolid	0 (0%)	0 (0%)	0 (0%)
Tigecycline	0 (0%)	3 (27.27%)	

[1]MSSA, methicillin-susceptible *S. aureus*
[2]MRSA, methicillin-resistant *S. aureus*

highest levels of resistance (83.33% and 100%, respectively) (Table 4). Meantime of positivity was found to be highest on 2nd and 3rd day of blood culture as per shown in Table 5.

DISCUSSION

Little data exists on secondary infections of COVID-19 and those that do are conflicting. The general prevalence of BSIs in patients in the ICU was found to be (53/550, 9.63%). A recent study from India shows the prevalence of infection to be 3.6%. Hospital and community-acquired cases were included in this study. Respiratory specimens were analyzed in addition to BSIs, which could have been contaminants or colonizers. There was 13% prevalence of secondary infections as documented by Lai *et al.*[10] There is a prevalence

Table 5. Mean time to positivity of blood culture

	Day 1	Day 2	Day 3	Day 4	Day 5
ICU (53)	2 (3.77%)	17 (32%)	25 (47.16%)	6 (11.32%)	3 (5.66%)
WARD (20)	0 (0%)	6 (30%)	11 (55%)	3 (15%)	0 (0%)
TOTAL (n=73)	2 (2.73%)	33(42.2%)	26 (35.62%)	10 (13.69%)	2 (2.73%)

of BSIs up to 50% among non-survivors of severe COVID-19 pneumonia. Further large prospective studies are needed to determine the prevalence of BSIs in severe COVID-19 and its implications on outcome.[11] Other sources of superinfection have been analyzed in previous studies. Respiratory, urinary tract, and local tissue samples have high likelihoods of contamination. The follow-up periods were either brief or incomplete. Many patients in this study had diabetes and hypertension, which play important roles in acquiring bloodstream infections. In this study, we observed elevated CRP levels in patients who developed a BSI. The usefulness of inflammatory markers in predicting antibiotic initiation in these patients is questionable. In immunosuppressive therapy, the correlation between CRP levels and bacterial co-infections has not been reported in many studies. Kreit *et al*. reported that the median CRP and procalcitonin levels did not disproportionately affect patients with or without bacterial co-infections (median procalcitonin, 0.4 vs. 0.72 ng/mL; CRP, 182 vs. 159 mg/L).[12] Therefore, inflammatory markers should be interpreted with caution. This report included many GNB. Similar observations were described in an Indian study by Elabaddi *et al*. with a predominance of GNB.[13] According to a few studies, the prevalence of GPC, particularly *S. aureus*, has increased in the ICU for COVID-19. In different patient environments, the number of patients receiving mechanical ventilation, length of hospital stay, follow-up, and isolation of the pathogen from other specimens (such as respiratory, urine, and pus samples), in addition to BSIs, may contribute to heterogeneity in the prevalence and distribution of microorganisms. We found a very high percentage of BSI with *Klebsiella* spp., *Acinetobacter*, *Enterococcus*, and methicillin-resistant *S. aureus* isolates, most of which were multidrug-resistant. According to a hypothesis proposed by Bonazetti *et al*.,[14] increased BSIs, particularly those caused by *Enterococci* spp., may be caused by SARS-CoV-2-mediated breakdown of the gut barrier and bacterial translocation. We did not offer a genotypic analysis, which would have shed some light on this incidence. Conflicting evidence has emerged regarding the incidence of MDRO during the COVID-19 pandemic. In contrast to research that demonstrated significant transmission of MDRO due to lengthy ICU stays and the use of various antibiotics in COVID-19, few studies have revealed a decreased prevalence of MDRO due to the application of infection control techniques.[15-18] We also noted a significant incidence of *A. baumannii* (15.06%) in this study. *A. baumannii* was mentioned in 90% of prior reports; however, the pool of patients in that review also included patients with mild to significant COVID-19.[19] Despite the increasing popularity of empirical antibiotics, there is insufficient evidence supporting their use. Chedid *et al*. found no significant difference in antibiotic use between patients with COVID-19 who survived and those who did not.[20] In addition, antimicrobial exposure raises the risk of drug resistance. According to a recent study, the use of combination antimicrobials has been linked to secondary infections.[21] Before reaching a consensus on the empirical use of antibiotics for COVID-19, more prospective studies are required to validate these findings. This study has several limitations, such as the use of data from a single center, which may eliminate generalizability. Many patients use corticosteroids and additional immunosuppressive medications, leading to a high rate of bacterial infections.[22-23]

CONCLUSION

When COVID-19 is severe, BSIs are associated with poor outcomes. In the ICU, we documented a significant frequency of *Klebsiella* spp. and *A. baumannii* BSIs. Practitioners should be aware of the potential for BSIs due to the presence of comorbidities and leukocytosis. CRP results should be interpreted carefully by clinicians simultaneously. Other inflammatory markers, such as procalcitonin, should be advised to patients. We recommend implementing infection control and antimicrobial stewardship strategies, because they may help prevent COVID-19 illness-related secondary bacterial infections. The precise incidence of secondary bacterial infections and their effects on mortality and morbidity in COVID-19 need more prospective research. This study will assist in making early empirical choices of appropriate antimicrobials to start in patients with COVID-19 and bacterial septicemia based

on local antimicrobial susceptibility patterns, thereby improving the prognosis of septicemia and reducing mortality in these patients.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHORS' CONTRIBUTION

Both authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

FUNDING

None.

DATA AVAILABILITY

All datasets generated or analyzed during this study are included in the manuscript.

ETHICS STATEMENT

This study was approved by the Institutional Ethics Committee, Symbiosis International (Deemed University) with approval number SIU/IEC/178.

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