ORIGINAL ARTICLE

Understanding secondary bloodstream infections in COVID patients: Insights from Karachi, Pakistan

Fareeha Adnan, Nazia Khursheed, Adeel Zafar Nagra, Nida Ghori, Qurat ul Ain Zahid, Moiz Ahmed Khan

Indus Hospital and Health Network, Karachi Pakistan

ABSTRACT

Background: Nosocomial Bloodstream infection (BSI) in COVID patients is an emerging clinical concern for physicians. It can lead to sepsis resulting in rise in morbidity and mortality. In this study, we aimed to assess the prevalence of BSI in COVID patients admitted to Indus Hospital and Health Network in Karachi, Pakistan.

Material and Methods: This retrospective study included the Reverse-transcriptase polymerase chain reaction (RT-PCR) confirmed COVID patients from March 2020 to December 2021. Data of all the patients (n=961) was obtained from electronic medical record of the hospital which included information regarding demographics, BSI, Central line-associated blood stream infections (CLABSI), frequency of pathogens, antimicrobial resistance pattern and clinical outcome.

Results: Our data showed that 217 (22.6%) patients developed BSI from which 44.2% had CLABSI. BSI was higher in males than females (61.8% vs 38.2%) and most patients were 51-64 years of age (n=66, 30.41%). Infections with Gram-negative bacteria were predominant (46.7%), followed by Gram-positive bacteria (17.9%) and yeasts (7.2%). Among the isolates, *Acinetobacter spp.* were the most commonly identified pathogen (17%). Regarding multi drug-resistant organisms, Carbapenem-resistant *Acinetobacter baumanii (CRAB)* was the most frequently isolated (n=37), followed by Methicillin-resistant *S. aureus (MRSA) (*n=16), Carbapenem-resistant *E. coli (CRE) (*n=10), Carbapenem-resistant *Klebsiella spp. (CRE) (*n=8), Vancomycin-resistant *Enterococcus (VRE) (*n=8) and multi drug-resistant *Pseudomonas spp. (*n=3). The mortality among CLABSI in different age groups ranged from 80% to 100% while in BSI ranged from 52.38% to 92.3%.

Conclusion: In order to prevent nosocomial infections from spreading and enhance the prognosis of hospitalized COVID patients, early detection of secondary infections and adherence to appropriate infection control measures are essential.

Keywords: Bloodstream infections, BSI, COVID-19, CLABSI, Multidrug resistance

BACKGROUND

The inception of COVID-19 pandemic posed an intimidating challenge to healthcare systems around the globe.[1-4] COVID patients often need hospitalization and some patients may need intensive care management depending upon the disease severity. ICUs have often been overburdened by COVID patients increasing their susceptibility to developing secondary bacterial and fungal infections especially in patients requiring mechanical ventilation.[5-7]

Bacteria can complicate viral respiratory infections by co-infecting and colonizing respiratory epithelium leading to high morbidity and mortality.[8,9] Sepsis can occur in patients with superimposed bacterial infections which can be prevented by adopting specific measures. Sepsis and COVID-19 share clinical presentations of the disease that include tachycardia, thrombocytopenia, hemolytic anemia, vascular microthrombosis,[10] multiorgan dysfunction syndrome,[11] coagulopathy,[12] septic shock, respiratory failure, fever, leukopenia, hypotension,[13] leukocytosis, high predisposition to opportunistic infections and cytokine storm leading to Systemic inflammatory response syndrome (SIRS). [14,15] Even though several studies have reported secondary bacterial and nosocomial infections in COVID patients, the results are contradictory. However, to date, only a few studies have focused on Bloodstream infections

Correspondence: Dr. Fareeha Adnan, Consultant Microbiology, Microbiology Section, Department of Pathology, Indus Hospital & Health Network, Karachi, Pakistan

Email: fareeha.adnan@tih.org.pk

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(BSI) in COVID patients admitted in ICU.[7,16] Approximately 5.2% of ICU-admitted patients are known to develop BSI.[17]

In order to curtail the spread of multi drug-resistant organisms (MDRO) and BSI in the hospital setting, it is essential to have knowledge regarding the burden and outcome of such infections. Hence, the rationale of this study is to assess the prevalence, frequency, and distribution of microorganisms, antimicrobial susceptibility, and clinical outcomes in COVID patients with BSI.

MATERIAL AND METHODS

This retrospective study was carried out at the Indus Hospital and Health Network, Karachi, Pakistan and include COVID patients admitted from March 2020 to December 2021. All patients with confirmed COVID-19 (RT-PCR positive in nasopharyngeal swab samples) were included. A total of 971 blood cultures were enrolled from patients who were admitted for at least 48 hours in the hospital. BSI was defined by the presence of bacterial or fungal organisms in blood demonstrated by the positivity of one or more blood cultures. Moreover, Nosocomial BSI was defined as BSI acquired 48 hours after admission to the hospital. Information regarding patient demographics, antibiotic-sensitivity patterns and outcome measures were collected from electronic media record of the hospital. Contaminated blood samples were excluded from the study. Ethical approval was obtained from the 'Institutional Review Board of the Indus Hospital & Health Network' for the purpose of this study (Ref # IHHN_IRB_2021_12_010).

Blood culture samples were processed according to the standard operating procedures. Isolates were identified on the basis of biochemical reactions and API or Vitek. Central line-associated bloodstream infection (CLABSI) was defined as laboratory confirmed BSI not related to infection at any other site and which developed within 48 hours of central line placement. Carbapenem-resistant Enterobacterale (CRE) was defined with the resistance to any one of the drugs in carbapenem class of antibiotics. Multi drug-resistant organism (MDRO) was defined as an organism with acquired resistance to at least one agent in three or more classes of antimicrobial drugs.

Statistical analysis was carried out using IBM Statistical Package for Social Sciences (SPSS) software version 26. The distribution of data was analyzed by Shapiro Wilk test. Percentages and frequencies were calculated for categorical variables which included age, gender, mortality, BSI, CLABSI and frequency of pathogens. Chi-square test was applied to see any association between BSI, CLABSI and mortality among different age groups and gender. A p value of <0.05 was considered as significant.

RESULTS

During the study period (March 2020 to December 2021), 971 RT-PCR-confirmed COVID patients were admitted to our hospital. Overall, 22.6% (n=217) of hospitalized COVID patients developed BSI while the remaining 77.4 % (n=744) of patients did not develop any BSI, as shown in figure 1. Ten patients were excluded from the study population as their clinical samples were characterized as contaminated hence, the total study population comprised of 961 patients. Among BSI patients, 44.2% (n=96) developed CLABSI.

Patient demographics are summarized in Table-I. Percentage of male patients was greater (61.8%; n=134) than female patients (38.2%; n=83) in BSI group. However, there was no significant difference in mortality with regards to patient's gender in both groups (p=0.6). Patient age groups of 51-64 years and ≥65 years showed the highest frequency of BSI (30.4% and 29%). No statistical significance was observed with regards to difference in mortality among age groups in the BSI and CLABSI groups.

Out of 217 BSI patients, more than one pathogen was found in 41 patients. Most commonly identified pathogens among BSI patients were Gram-negative bacteria (46.7%), followed by Gram-positive bacteria (17.9%) and yeast (7.2%). Coagulase-negative *Staphylococcus spp.* (28%; 72/256) were the most commonly isolated, followed by *Acinetobacter spp.* (17%; 43/ 256), *Staphylococcus aureus* (10%; 26/256), *E. coli* (8%; 20/256), *Pseudomonas spp.* (8%; 20/256), *Klebsiella spp.* (7%; 19/256), *Enterococcus spp.* (7%; 18/256), *Candida spp.* (6%; 16/256) and others (9%; 22/256).

Among the isolated MDROs, Carbapenem-resistant *Acinetobacter baumanii (CRAB)* (37/43) was the most

frequently isolated, followed by Methicillin-resistant *S. aureus (MRSA)* (16/26), Carbapenem-resistant *E. coli (CRE)* (10/20), Carbapenem-resistant *Klebsiella spp. (CRE)* (8/19), Vancomycin-resistant *Enterococcus (VRE)* (8/18) and multi drug-resistant *Pseudomonas spp.* (3/20).

Table-I: Demographics of COVID patients with BSI admitted in the Indus Hospital (Mar 2020 – Dec 2021).

Gender	Total BSI (n=217)	CLABSI (n=96)	BSI (n=121)	p-value	Mortality among BSI		Median (IQR)	Mortality among CLABSI		p-value
					Alive	Expired		Alive	Expired	
Male	134 (61.8%)	58 (60.4%)	76 (62.8%)	0.70	20 (16.52%)	56 (46.28%)		9 (9.37%)	49 (51.04%)	0.13
Female	83 (38.2%)	38 (38.6%)	45 (37.2%)		15 (12.39%)	30 (24.79%)		8 (8.33%)	30 (31.25%)	0.21
Age Group 1-18 years	26 (11.98%)	5 (5.20%)	21 (17.35%)	0.02	10 (47.61%)	11 (52.38%)	8 (3-11.25)	0	5 (100%)	0.12
Age Group 19-40 years	28 (12.90%)	15 (15.62%)	13 (10.74%)		1 (7.69%)	12 (92.30%)	35 (24.25-38)	3 (20%)	12 (80%)	0.35
Age Group 41-50 years	34 (15.66%)	20 (20.83%)	14 (11.57%)		6 (42.85%)	8 (57.14%)	47 (44.75-49)	4 (20%)	16 (80%)	0.15
Age Group 51-64 years	66 (30.41%)	31 (32.29%)	35 (28.92%)		8 (22.85%)	27 (77.14%)	57.50 (54.75-60)	5 (16.12%)	26 (83.87%)	0.49
Age Group ≥65 years	63 (29.03%)	25 (26.04%)	38 (31.40%)		10 (26.31%)	28 (73.64%)	70 (65-73)	5 (20%)	20 (80%)	0.56

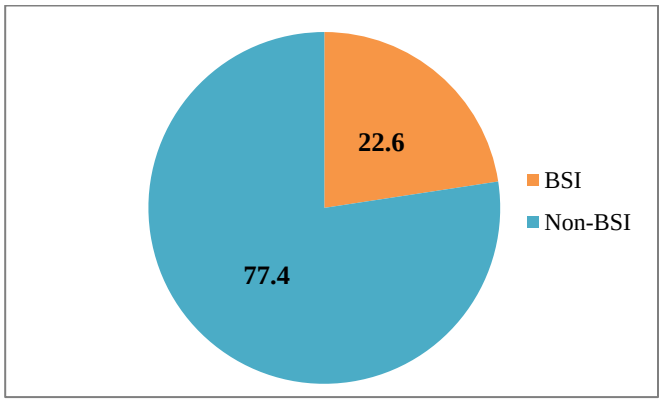

Figure-I: Percentage of COVID patients (n=971) diagnosed with BSI.

DISCUSSION

BSIs are among the significant complications of COVID that worsen the clinical course of disease and increase associated mortality. In our study, it was found that 22.6% of COVID patients developed BSI. However, a major proportion (26.9%) of the identified organisms comprised of coagulase-negative *Staphylococcus spp. (*CoNS), which are skin commensals. Identification of a high percentage of CoNS from blood of hospitalized COVID patients might indicate negligence of adequate skin disinfection before collection of blood cultures. Additionally, the high influx of patients and shortage of critical care resources and relevant healthcare staff might compromise the standards of infection control. A high percentage (15.2%) of CoNS among COVID patients was also reported in a study by Zeno P. *et al*.[18] In our study, 44.2% patients had CLABSI while Kang *et al*. reported 38% of COVID patients with CLABSI.[19] We found a relatively higher prevalence of Gram-negative bacterial infections. Similar observations were reported by Naveenraj P. *et al*. (82.8%)[20] and Vijay S. *et al*. (78%).[21] In contrast, other studies have reported a higher prevalence of Gram-positive pathogens among COVID patients admitted to ICU, varying in prevalence from 44% to 77.6%.[22] This diversity in predominance and frequency of microorganisms may be due to difference in patient set-ups, length of hospital stays, number of patients on mechanical ventilation, and identification of pathogens from different samples such as pus, urine, and respiratory samples.

Studies focusing on secondary infections and BSI in COVID patients have reported a high frequency of *Acinetobacter spp.* We have also observed a relatively higher percentage of *Acinetobacter spp.* (16%) among all the isolated pathogens. Likewise, Montrucchio G *et al*., also reported a higher percentage of *Acinetobacter spp.* among all other isolates in COVID patients admitted in ICU (32.8%).[23] *Acinetobacter spp.* were followed by *Klebsiella spp., E. coli, Pseudomonas spp.*, and *Enterococcus spp.* These pathogens have

increasingly been identified in cases of bacteremia by other studies as well.[24]

We also observed increased mortality ranging from 52% to 100% in COVID patients with BSI and CLABSI admitted in ICU. One of the reasons for increase in mortality rate among these patients may be due to the synergetic effect of the virus and bacteria. Although it is not clear to what extent the burden of mortality could be attributable to infection in our scenario, certain other factors like patient's clinical status, co-morbidities, length of ICU stay should not be undermined. Our findings were consistent with studies conducted in Turkey.[24]

Previously, other studies have reported infections with MDROs among hospitalized COVID patients. Our results also show a high percentage of MDROs in COVID patients. MDRO infections in COVID patients could be attributed to prolonged hospital stay, mechanical ventilation, empirical use of antibiotics, and poor compliance with infection control practices. Moreover, unintended use of carbapenems due to antimicrobial selection pressure, may contribute to these infections. The use of antibiotic combinations in COVID patients also increases the risk of antibiotic resistance.[25] The following factors may attribute to the development of BSI in hospitalized COVID patients:

1) COVID patients are immunocompromised and prone to secondary infections. There are two reasons for the dysregulated immune system. Increased production of cytokines due to viral attacks and a significant decrease in the production of IFN-Ɣ leads to reduction in CD4+ T-cells polarization and cytotoxic activity.
2) Prolonged hospital and ICU stay increases the likelihood of acquiring nosocomial infections among COVID patients.
3) Increased use of immunosuppressive agents such as anti-IL-6 drugs and corticosteroids.

LIMITATIONS

Our study has a few limitations. Firstly, it is a single-center study and hence, data regarding frequency of BSI and prevalence of particular pathogens may represent prevalence in our setting only and may not be generalizable to other healthcare setups in our country. Further multi-center studies are required to accurately assess the scale of BSI and predominant pathogens in the Pakistani population. Secondly, we did not ascertain whether the burden of morbidity and moratlity discussed in our study was associated with any of the factors other than infections such as patient's clinical status, co-morbidities and length of ICU stay. Nonetheless, our data regarding the organisms isolated and the percentage of nosocomial BSI is robust and provide valuable insights from our part of the world.

CONCLUSION

In order to prevent nosocomial infections from spreading and enhance the prognosis of hospitalized COVID patients, early detection of secondary infections using suitable biomarkers and adherence to appropriate infection control measures are essential. Moreover, in order to curtail the ongoing emergence of multi-drug resistant pathogens, it is critical to reinforce proper antimicrobial stewardship practices on a national level.

CONFLICT OF INTEREST

None

GRANT SUPPORT & FINANCIAL DISCLOSURE

Declared none

AUTHOR CONTRIBUTION

Fareeha Adnan, Nazia Khursheed: Conceptualization, Writing, Methodology and Overall supervision

Adeel Zafar Nagra, Nida Ghori, Qurat Ul Ain Zahid: Writing and Data analysis

Moiz Ahmed Khan: Writing and Revisions

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