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Original Research Article

Increased surge of secondary bacterial infections leading to sepsis among COVID 19 patients in a tertiary care centre in South India

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ABSTRACT

Background: Secondary bloodstream infections (BSIs) remain one of the frequent and life-threatening complications among COVID 19 infected patients. The present study has been undertaken to determine the prevalence of secondary BSIs in patients with COVID-19

Materials and Methods: This is an observational case control study, conducted between May2020 and April 2021 in a tertiary care centre in South India. The study population were further divided into three groups—one case group (COVID group), and two control (non-COVID group 2020-21 and 2019-20). Blood cultures sent from a suspected care of secondary blood stream infection were processed and outcomes like blood culture positivity rate, clinically relevant growth, contaminant rate and multidrug resistant organism rate were compared between the COVID group and non-COVID control groups.

Result: Among the COVID group 307 (17%) of the episodes were found to show clinically relevant growth compared with 3570 (15.4%) in control group 2020-21 ($p<0.05$) and 3974(12%) in control group 2019-20 ($p<0.001$). In all the 3 groups, gram negative bacterial infections were found to be the majority with 50% (COVID group), 57% and 58% (non-COVID groups). Among all the MDR organisms isolated from the COVID group of patients, carbapenem resistant *Acinetobacter baumannii* contributes about 88%.

Conclusion: In COVID-19 patients, the prevalence of secondary bacterial sepsis due to multidrug resistant organisms are higher when compared to non-COVID patients. Non-adherence to strict infection control practices are the possible causes for the higher infection rate among the COVID group of patients.

1. Introduction

Secondary bloodstream infections (BSIs) remain one of the frequent and life-threatening complications that occur in patients with severe viral infections of the respiratory tract and have formerly been reported to be associated with increased mortality and morbidity.[1] Most of these secondary BSIs are reported to be caused by multidrug-resistant bacterial pathogens prevalent in the hospital environment. The most likely underlying reason for increased secondary BSIs in COVID-19 patients could be because of the practice of continuous use of gloves by the healthcare professionals (HCPs) in COVID care locations without changing it in between the patient; extremely poor hand hygiene compliance due to false belief of being protected by donning the gloves, prolonged hospital stay of the patients with COVID-19.[2,3] Therefore, epidemiological data of secondary BSIs might play a noteworthy role in preventing poor disease outcomes in patients with COVID-19.

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The studies in the literature reported varied associations of secondary BSI in COVID-19 patients. While some authors reported lower bacteraemia rates in COVID-19 patients than in control arms, there are reports of increased rates of secondary BSI in COVID-19 patients as well.[2,4,5] More so, the practice of routinely sending blood cultures and the characteristics of COVID-19 patients differ considerably between healthcare facilities (HCFs) and geographical settings, which further contributes to the diverse prevalence of bacteremia in COVID-19 patients. To the best of our knowledge, there are no studies on the secondary BSIs in COVID-19 patients available in the literature from Indian settings. Understanding the pressing need, the present study has been undertaken to determine the prevalence of secondary BSIs in patients with COVID-19, and to find out the diversity of microorganisms in blood cultures, which will help the clinical team for better implementation of appropriate treatment and infection control practices.

2. Materials and Methods

2.1. Study design

This is an observational case-control study, conducted between May 2020 and April 2021, at the Department of Microbiology at a large-scale tertiary care teaching centre, located in Southern India. The patients with clinically suspected bloodstream infections, for which the blood cultures were collected, were enrolled in the study. The study population was further divided into three groups—one case group (COVID group), and two control (non-COVID) groups.

COVID group: Patients with COVID-19 admitted to our hospital between May 2020 to April 2021, from whom a blood culture investigation was sent were enrolled in this group. The diagnosis of COVID-19 was made by reverse transcriptase real-time PCR detecting SARS-CoV-2 RNA in the respiratory secretions.

Non-COVID group 2020-21: It was a contemporary control group, that enrolled the patients admitted during the same period (as for the COVID group), but tested negative for COVID-19 by RT-PCR test, and blood culture investigations were sent. During the first quarter of the study period, COVID-19 testing was only performed for the symptomatic patients; but subsequently, as the pandemic continued to grow, all admitted patients were subjected to testing. Therefore, the non-COVID group 2020-21 comprised a small proportion of patients not tested for COVID-19. However, as the COVID-19 test was performed for all symptomatic patients, it is reasonable to assume that the 'not tested patients' would be negative for COVID-19.

Non-COVID group 2019-20: This was a historical control group, comprised of the patients admitted between May 2019 to April 2020, from whom the blood culture investigations were sent.

2.2. Study Methodology

Blood cultures from the patients with suspected BSI were collected in BacT/ALERT FA Plus aerobic bottles and were sent to the microbiology laboratory where they were incubated in BacT/ALERT VIRTUO (bioMerieux) automated blood culture system for five days. Bottles flagged positive were subjected to Gram staining, and plating on suitable culture media. The colonies grown on the agar plates were identified by MALDI-TOF MS (VITEK MS, bioMerieux). Antimicrobial susceptibility testing was performed by the VITEK® 2 automated AST system and the results were interpreted following Clinical Laboratory Standard Institute (CLSI) guidelines interpretation criteria.

Testing for SARS-CoV-2 was performed using two different RT-PCR assays: cobas SARS-CoV-2 (Roche Molecular Systems), Truenat SARS-CoV-2 (Molbio, India); targeting the E- and RdRP-genes.

The final report of blood cultures was recorded as 'sterile' (bottles not flagged positive); 'pathogen' (organism seen in direct gram stain and isolated from a pair of blood culture bottles) or 'contaminant' (growth of skin commensals). The pathogens isolated from the blood cultures of the same patient collected within 72 hours were collectively considered as a 'single episode'.

2.3. Data collection and statistical analysis

The data were collected in Microsoft Excel and statistical analyses were performed with IBM SPSS Statistics V21.0 software. The blood culture results in patients with COVID, non-COVID 2020/21, and non-COVID 2019/20 were compared using Pearson's chi-square test. Values of $P < 0.05$ were considered as statistically significant.

3. Results

A total of 7851 blood culture episodes were included from 57695 patients during the study period. Out of which 307 episodes were from the COVID group and 3974 and 3570 episodes were from the non-COVID 2019-20 and 2020-21 control groups respectively. (Figure 1)

The data of bloodstream infection episodes in COVID and non-COVID control groups are shown in Table 1. Among the COVID group, 307 (17%) of the episodes were found to show clinically relevant growth compared with 3570 (15.4%) in the control group 2020-21 ($p<0.05$) and 3974(12%) in the control group 2019-20 ($p<0.001$). The contaminants rate was found to be 265(15%) among the COVID group when compared with 3057 (13.2%) episodes in the control group-2019-20 ($p<0.05$) and 3724 (11%) in the non-COVID 2020-21 ($p<0.001$) respectively (Table 1 and Figure 2).

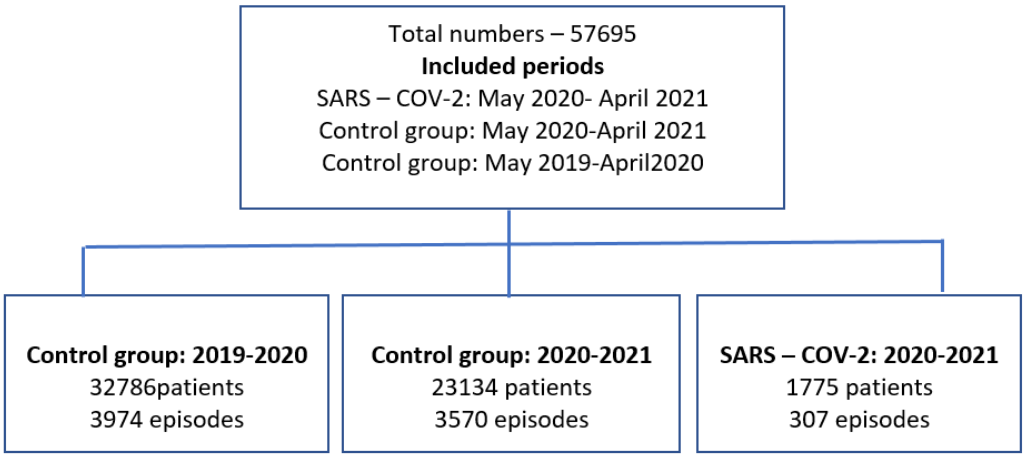

Figure 1: Flow chart of the study population

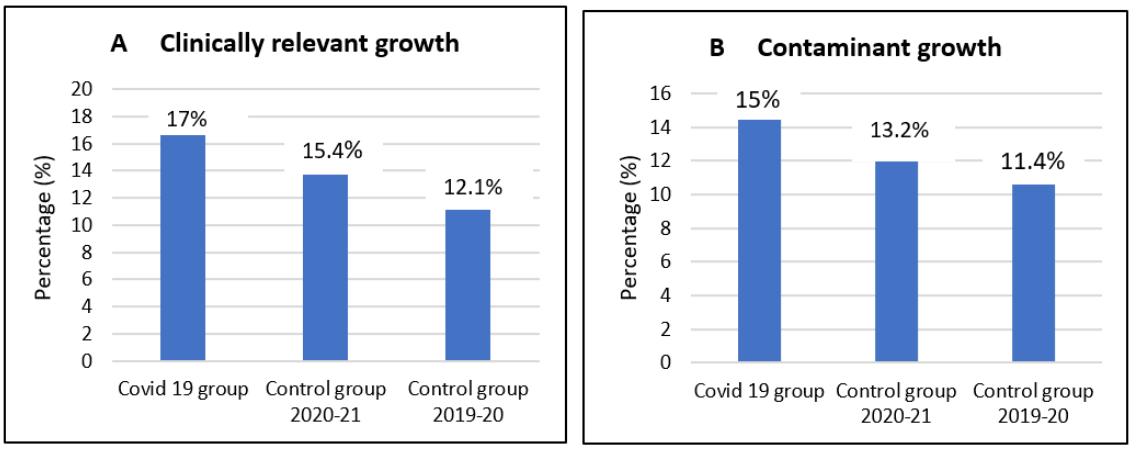

Figure 2: Blood culture episodes with clinically relevant growth (**A**) and with contaminant growth (**B**) Total number of episodes includedfor analysis were COVID-19 group: 307
Control group-2020: 3570
Control group-2019: 3974

The distribution of episodes with pathogens growth in COVID-19 and both the non-COVID control groups are given in (Table 2). In all the 3 groups, gram-negative episodes were found to be in the majority (Table 2).

The distribution of various pathogens isolated in both COVID-19 and the non-COVID groups in detail is shown in (Table 3). Among the non-COVID control groups, *E. coli* was found to be the commonly isolated gram-negative pathogen (23.6% and 25.8%) whereas *A. baumannii is* the common organism isolated gram-negative pathogen among the COVID group (36.1%). *Staphylococcus aureus* is the common pathogen isolated gram-positive pathogen in both the non-COVID groups (36% and 46%) whereas *Enterococcus* species is the commonly isolated gram-positive organism among the COVID group (58%). Distribution of yeast episodes shows that *Candida tropicalis* is the most common yeast isolated among all three groups with the highest (53%) among the COVID group.

When the relationship between the organisms isolated and the hospital location was analysed, we found that among the COVID group, the pathogen rate was higher in ICU (22%) than in emergency medical service (EMS) (18%) whereas the contamination rate was almost same in ICU (15%), ward (15%) and EMS (14%). The distribution of pathogen and contamination isolation rates among the non-COVID groups 2019-20 and 2020-21 are shown in (Table 4).

The comparison of the isolation of drug-resistant organisms in the COVID group and both the non-COVID groups is shown in (Table 5). Among all the MDR organisms isolated from the COVID group of patients, carbapenem-resistant *Acinetobacter baumannii*

contributes about 88% followed by carbapenem-resistant Enterobacteriaceae 59% and MRSA 42%. Carbapenem-resistant *Pseudomonas aeruginosa* were commonly isolated among the non-COVID control groups (39% and 33%) whereas it is only 14% among the COVID group. Vancomycin-resistant *Enterococcus* isolation rates were almost the same among the COVID group (17%) and among the non-COVID groups (16% and 18%). Carbapenem-resistant *Acinetobacter baumannii* is the most common MDR organism isolated among all three groups, the COVID group (88%) and non-COVID control groups (78% and 69%).

4. Discussion

There are only very few studies that analysed secondary bloodstream infections in COVID-19 patients. But there is no doubt that secondary bloodstream infections are one of the main reasons for the mortality and morbidity among COVID-19 patients. In our study, the overall blood culture positivity rate is higher among the COVID patients (32%) when compared to both the non-COVID control groups (29% and 23%). Also, the clinically relevant growth was 17% in the COVID group when compared to 15.4% (p-value <0.05) and 12% (p-value < 0.05) among the 2020-21 and 2019-20 non-COVID control groups respectively, and was found to be statistically significant. This clearly shows the high prevalence of bloodstream infections among COVID-19 patients. The main reasons for the higher prevalence of BSI among COVID patients in various studies were found to be due to prolonged hospital admission, ICU admission, and cytokine storm.[6]

Few studies also show a low prevalence of BSI among the COVID patients when compared to the control groups. A study done in New York in 2020 showed only a 3.8% BSI rate among COVID patients whereas it was 8% among the non-COVID control group.[7] The incidence of bloodstream infections among COVID-19 patients was found to increase after ICU admission as it commonly occurs in patients who are severely ill or in patients with sepsis.[2] In our study also the incidence of bloodstream infections is higher among COVID patients in ICU patients (22%) followed by EMS (18%) and ward patients(11%). This may be due to the prolonged hospital admission leading to hospital-acquired infections or continuous use of the same gloves by the health care worker without changing it between the different patients or may be due to improper hand hygiene practice.

The distribution of various microorganisms that caused secondary blood infections shows that gram-negative organisms have contributed to the majority of the BSI episodes followed by gram-positive organisms in the COVID group and also in both the control groups. Similar results were obtained from a multicentric study done in India during 2021, where the gram-negative organisms were found to cause 78% of the BSI episodes.[8] Also, another Indian study done in 2021 showed similar findings with a high rate of gram-negative BSI infections among COVID-19 patients.[9] In contrast to this, an Italian study done in 2019 showed that BSI with gram-positive organisms was predominant when compared to the gram-negative organisms in an ICU setup.[10]

If we analyse the distribution of all the gram-negative organisms that caused BSI in our study, *Acinetobacter baumannii* followed by *Klebsiella pneumoniae* is the most commonly isolated organism among the COVID group, whereas, among both the non-COVID groups, it is *E. coli* followed by *Klebsiella pneumoniae*. In concordance with our observation, an Indian study done in 2021 and an Italian multicentric study also showed *A. baumannii* followed by *Klebsiella pneumoniae* to be the commonest gram-negative organisms isolated among the COVID-19 group.[6,9]

Analysis of the gram-positive pathogens showed that *Enterococcus* species (58%) are the most commonly isolated among the COVID group whereas among both the non-COVID groups, *Staphylococcus aureus* is the commonest among all the gram-positive organisms isolated. In a study done by Giacobbe et al., unexpected high incidences of BSI with *Enterococcus* species were encountered and the possible explanation thought was due to the cross-contamination between patients as a result of prolonged use of personal protective equipment and improper infection control measures.[10] Another possible reason considered was the translocation of the *Enterococcus* from the gut due to the intestinal wall inflammation that occurs in COVID-19-infected individuals.[10] BSI episodes with candida species were found to be a little higher among the COVID group (11%) when compared to the non-COVID groups (8% and 4%). *C. tropicalis* is the commonest candida species isolated among all three groups. In contrast to this observation, an Indian case-control study done by Rajni et al. showed a high incidence of *Candida auris* infection among critically COVID-19 patients followed by *Candida tropicalis*.[11]

Analysing the data on antimicrobial resistance, we found that carbapenem-resistant *Acinetobacter baumannii* is the predominant resistant isolate in all three groups with the highest isolation rate among the COVID-group (88%) followed by carbapenem-resistant Enterobacteriaceae (59%) and Methicillin-resistant *Staphylococcus aureus* (42%). Similar findings were observed by Pasquini Z et al., in 2021 which showed an increased incidence of Carbapenem-resistant *A. baumannii* and *K. pneumoniae* in COVID-19 patients. In a study done by Baiou et al., in 2021 showed that *S. Maltophilia* is the most frequently isolated MDR organism followed by Carbapenem-resistant Enterobacteriaceae.[12] The major risk factors for infection with Carbapenem-resistant *A. baumannii* are prolonged ICU stay, mechanical ventilation, and other invasive procedures. Carbapenem-resistant *pseudomonas aeruginosa* were

Table 1: Blood stream infection episodes data for patients in COVID-19 and both non-COVID control groups

	COVID group	Non-COVID group 2020-21	Non-COVID group 2019-20
Total Blood culture utilization	1775	23,134	32,784
Sterile episodes	1203 (68%)	16507(71%)	25086(77%)
Total Episodes with growth	572(32%)	6627(29%)	7698(23%)
Episodes with pathogens growth, n (%)	307 (17%)	3570 (15.4%)	3974(12%)
Episodes with contaminant growth %	265(15%)	3057 (13.2%)	3724 (11%)

Denominator = Total blood culture utilization

Table 2: Distribution of episodes with pathogens growth in COVID-19 and both non-COVID control groups

Distribution of episodes with pathogens growth		COVID group	Non-COVID group 2020-21	Non-COVID group 2019-20
Total episodes with pathogen growth		307	3570	3974
1	**Gram-negative episodes**	50% (152)	57%(2039)	58%(2302)
2	**Gram-positive episodes**	31%(96)	27%(954)	26%(1024)
3	**Yeast episodes**	11%(34)	8%(268)	4%(160)
4	**Polymicrobial episodes**	8%(25)	9%(309)	12%(488)

Denominator = Total episodes with pathogen growth

Table 3: Organism distribution in patients with bloodstream infections in COVID-19 and both non-COVID control groups

	COVID group (307)	Non-COVID group 2020-21 (3570)	Non-COVID group 2019-20 (3974)
Pure Gram-negative episodes	**152**	**2052**	**2543**
Escherichia coli	(14.4%)22	(23.6%)485	(25.8%)658
Klebsiella pneumoniae	(26.3%)40	(20%)407	(19.4%)493
Pseudomonas aeruginosa	(3.2%)5	(8.5%)175	(7.2%)184
Acinetobacter baumannii	(36.1%)55	(18.1%)374	(15.3%)388
Other gram- negative bacteria	(20%)30	(30%)611	(32.3%)820
Pure Gram-positive episodes	**96**	**924**	**1111**
Staphylococcus aureus	(19%)18	(36%)332	(46%)510
Enterococcus species	(58%)56	(31%)292	(20%)218
Beta-hemolytic streptococci	0	(16%)146	(10%)111
Other gram positive - bacteria	(23%)22	(17%)154	(24%)272
Pure Yeast episodes	**34**	**312**	**202**
Candida albicans	(8.8%)3	(10.5%)33	(17%)34
Candida parapsilosis	(14.7%)5	(10%)31	(13%)26
Candida tropicalis	(53%)18	(30%)93	(31%)62
Candida auris	(14.7%)5	(21%)66	(11%)23
Other Candida species	(8.8%)3	(28.5%)89	(28%)57
Polymicrobial infections (mixed)	25	282	118

Table 4: Numbers and proportions of pathogens and contaminants in blood cultures from different hospital locations

	COVID group			Non-COVID group 2020-21			Non-COVID group 2019-20		
	Total episodes (1775)	**Pathogen (307)**	**Contaminant (265)**	**Total episodes (23134)**	**Pathogen(3570)**	**Contaminant(3057)**	**Total episodes(32786)**	**Pathogen (3974)**	**Contaminant(3724)**
ICU	832	185(22%)	126(15%)	3595	730(20%)	434(12%)	1361	177(13%)	185(14%)
Ward	709	80(11%)	106(15%)	13953	2040(15%)	1811(13%)	19511	2216(11%)	2007(10%)
EMS	234	42(18%)	33(14%)	5586	800(14%)	812(15%)	11914	1581(13%)	1532(13%)

Denominators = Total episodes in ICU/WARD/EMS respectively

Table 5: Comparison of antimicrobial resistance pattern in COVID patients with sepsis and non covid control groups

	COVID group	Non-COVID group 2020-21	Non-COVID group 2019-20
Carbapenem resistant *Enterobacteriaceae*	39/66 (59%)	276/852 (32%)	277/880 (31.4%)
Carbapenem resistant *Pseudomonas aeruginosa*	1/7 (14%)	51/131 (39%)	42/127 (33%)
Carbapenem resistant *Acinetobacter baumannii*	45/51 (88%)	272/349 (78%)	196/283 (69%)
Methicillin resistant Staphylococcus aureus (MRSA)	5/12 (42%)	73/209 (35%)	55/284 (19%)
Vancomycin resistant *Enterococcus faecium* (VRE)	8/46 (17%)	43/274 (16%)	32/178 (18%)

Denominators = Total Enterobacteriaceae/*P.aeruginosa/ A.baumannii/S.aureus/ Enterococcus* sps in each group respectively

found to be isolated more from the non-COVID control groups (39% and 33%) than the COVID groups (14%). Apart from patients with COVID-19 infection, increasing incidences of carbapenem-resistant Acinetobacter species and Enterobacteriaceae are being reported in many regions of the world and cause high mortality among those patients.[13,14]

Increased AMR rates in COVID patients are mainly attributed to the practice of prescribing antibiotics considering the increased incidence of secondary bacterial infections in COVID patients that leads to increased mortality.[15] A study conducted by Chen et al., in the year 2020 revealed that, despite a verified bacterial co-infection prevalence of under 1%, 71 percent of COVID-19-positive hospitalized patients received antibiotics.[16] It also has been documented that 68.9% of COVID-19 patients had received antibiotics (mostly azithromycin and ceftriaxone) and the self-medication rate of 33.0% was documented before hospital admission.[17] There is no doubt that COVID-19 is accelerating the antimicrobial-resistant threat which is already in the increasing phase. Hence it is very essential to use antibiotics with utmost caution and to implement antimicrobial stewardship programs to protect us from the threat of antimicrobial drug resistance.

5. Conclusion

In COVID-19 patients, the prevalence of secondary bacterial sepsis due to multidrug-resistant organisms is higher when compared to non-COVID patients. Strict adherence to infection control protocols and implementation of robust antimicrobial stewardship practices are essential in reducing the incidence of sepsis among these patients.

6. Source of Funding

None.

7. Conflict of Interest

None.

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