

# Post COVID-19 Infection with *Staphylococcus Aureus* Bacteraemia: A Case Series

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## ABSTRACT

*Staphylococcus aureus* (*S.aureus*) is a leading bacterial pathogen, that causes deadly infections such as bacteraemia, Toxic Shock Syndrome (TSS) and endocarditis. It has been the main contributor to secondary bacterial infections during viral pandemics, greatly raising patient morbidity and fatality rates. It is unknown how this secondary bacteraemia would affect people who have Severe Acute Respiratory Distress Syndrome Coronavirus 2 (SARS-CoV2). Herein, the authors present a series of case studies of 8 patients, (4 males and 4 females) infected with Coronavirus Disease-2019 (COVID-19) at tertiary hospital, Hyderabad, India, who eventually developed *S.aureus* bacteraemia with widespread seeding of secondary infections including cellulitis and abscess formation. Adult patients aged 20-60 years of age who were infected with COVID-19 from June'2022-August'2022 and had positive bacterial cultures for *S.aureus* during admission were included in the study. A total of eight patients hospitalised for COVID-19 with secondary bacteraemia were identified. Of these patients admitted with severe limb infections, three patients expired after a week of ongoing treatment from their blood cultures. Multivariate analysis identified the onset of bacteraemia (>4 days from date of admission) and age as significant predictors of mortality in admitted patients. Systemic Inflammatory Response Syndrome (SIRS) scoring and blood cultures were used to identify the mortality risk with p-value=0.05 statistical significance. The patients were subsequently treated with antibiotics and given conservative management, some of the patients admitted to Intensive Care Unit (ICU) who had critical co-morbidities, expired within a week of ongoing treatment. The final outcome of the present case series was that bacteraemia caused by *S.aureus* is associated with a high mortality rate in COVID-19 patients. More research is needed to understand the relationship between COVID-19 and secondary *S.aureus* bacteraemia.

**Keywords:** Coronavirus Disease-2019, Severe Acute Respiratory Distress Syndrome Coronavirus 2, Systemic inflammatory response syndrome

## INTRODUCTION

*Staphylococcus aureus* has been previously described as the primary causative pathogen of secondary bacterial infections. Bacteria related complications, in particular, are now being documented as a result of bacterial infection [1]. According to Chertow DS et al., onset of secondary bacterial infections with influenza is typically seen within the first six days of influenza infection, when viral shedding is the highest. Bacterial pneumonia in post influenza patients have been frequently studied, and are likely facilitated by complex interactions between viruses and the host immune system and disruption of the mucosal barrier within the respiratory tract [2]. The global pandemic COVID-19 has been brought on by the rapid spread of the coronavirus 2 associated with SARS-CoV-2 [3]. Infection with COVID-19 can cause serious sequelae like Acute Respiratory Distress Syndrome (ARDS), thromboembolic events, septic shock, and multiorgan failure in addition to rapid spread through high transmission rates [4,5]. According to one study, the prevalence of bacteraemia ranged from 1.6% to 3.8%, with *S.aureus* being responsible for 13.3% of cases [6]. In COVID-19 patients, bacterial co-infection may worsen the immunocompromised state brought on by the virus, further deteriorating the clinical prognosis [7]. It is uncertain how secondary *S.aureus* bacteraemia affects SARS-CoV-2 infection-related mortality in patients. As will be covered in the present case series, the broad seeding of secondary bacterial infections in a post COVID-19 patient is potentially impacted by the multiorgan spread of COVID-19. [Table/Fig-1] demonstrates the baseline laboratory values.

## CASE SERIES

The present case series includes eight patients, who were infected with COVID-19, and presented with various skin infections. The

Investigations	Result values (reference range)
WBC (/uL) (count) x (10 <sup>3</sup> /L)	10.3 (7.48-13.2)
Platelets X 10 <sup>3</sup> /L	228 (160-306)
Serum creatinine (mg/dL)	0.98 (0.75-2.36)
Bilirubin (mg/dL)	0.66 (0.45-0.94)
Procalcitonin (ng/dL)	0.42 (0.19-1.36)
C-reactive protein (mg/dL)	155.1 (88.2-244.2)
D-dimer (ug/dL)	1.65 (1.21-3.83)
PITT bacteraemia score (IQR)	3.0 (2.0-7.0)
qSOFA scoring	1.0 (1.0-3.0)

[Table/Fig-1]: Baseline laboratory values.

WBC: White blood cells; qSOFA: quick sequential organ failure assessment; PITT: Platelet-induced thrombin generation time

cases were diagnosed based on the blood cultures obtained during admission; it was found that, most of the skin infections were caused due to *Staphylococcus* species of bacteraemia and showed very high mortality rates in persons affected with COVID-19. Blood cultures were obtained from the susceptible patients and were tested for presence of specific organisms. Phenotypic tests were the mainstay in the diagnosis of staphylococcal infections, in which coagulase tests are usually confirmatory for *S.aureus*. Coagulase testing is performed using Slide Coagulase Test (SCT) or Tube Coagulase Test (TCT). Screening for *S.aureus* was based on growth on Mannitol Salt Agar (MSA)/DNase test and confirmation was done with TCT. The inoculum from a pure culture is transferred to a sterile tube of phenol red mannitol broth and is incubated at 35-37°C for 24 hours, the results were determined with the positive test change of colour from red to yellow, indicating a pH change

and confirming the presence of *Staphylococcus* bacteria. One of the most common factors found in each patient admitted was the history of SARS-CoV2 infection.

A total of eight patients were hospitalised with COVID-19 from June'2022-August'2022, were identified to have *S.aureus* bacteraemia. These patients were found to be having a past history of severe COVID-19 pneumonia and were kept on mechanical ventilators until they recovered completely. Overall baseline characteristics with laboratory values and clinical manifestations along with intervened therapies were displayed in the [Table/Fig-2]. The mean age was 51±3 years, and 4 (50%) were males. The Body Mass Index (BMI) was 27.9 (23.8-33.0) median inflammatory baseline markers, including C-reactive protein, D-dimer; procalcitonin levels were elevated at baseline. quick Systemic Organ Failure Assessment (qSOFA) score was calculated in order to diagnose sepsis in patients and to assess them according to the level of infection. Out of eight patients admitted, 5 (62.5%) had *S.aureus* bacteraemia susceptible to Methicillin Sensitive *Staphylococcus aureus* (MSSA) and the rest 3 (37.5%) had *S.aureus* bacteraemia susceptible to Methicillin Resistant *Staphylococcus aureus* (MRSA). There were no significant differences in outcomes and characteristics between bacteraemia caused by MSSA and MRSA. Of all the eight patients with known source of bacteraemia, the most common source of entry was skin and vascular structures. The sources of entry of bacteria were confirmed based on the symptoms and physical exam findings of the patients. 2 (25%) patients with portal of entry as skin had no (+) blood cultures at admission and none of the two survived, whereas, patients with hospital onset bacteraemia had been discharged after prompt treatment and had no risk of mortality. Hence, the risk of mortality was assessed based on the time of admission to number of hospital day and the age of the patients. The median time from admission to bacteraemia onset was 8 days. The most common antimicrobial regimen used was vancomycin and cefazolin. Definitive antibiotic regimen given for patients with MRSA bacteraemia was vancomycin and linezolid, whereas, patients with MSSA bacteraemia were given antibiotic coverage of beta lactams such as cefazolin or ceftriaxone for 10-14 days.

Median WBC counts and procalcitonin at the time of blood cultures were elevated from admission, with a mean temperature of 38.0°C±0.98°C. The median PITT bacteraemia score (IQR) was elevated at 5.0 (2.0-7.0) which were found to be higher in 7 out of 8 (87.5%) patients who had 7 day mortality compared to 3 out of 8 (37.5%) patients, who survived the risk as discussed in [Table/Fig-3].

## DISCUSSION

There were 14 different cases of bacteraemia in patients admitted with COVID-19, out of which 8 cases were identified as infections caused by *S.aureus* type of bacteria. Of all the cases of bacteraemia reported, those with *S.aureus* had high mortality rates. Ever since the COVID-19 has evolved, a lot of related co-morbidities have been identified in infected persons. The presence of bacterial and/or fungal secondary infection or co-infection is likely another important factor affecting mortality and it has received inadequate attention. *S.aureus* infections are a known complication of other viral pandemics, such as the Spanish flu in 1918-1919 and the H1N1 influenza pandemic in 2009-2010 [8]. In all influenza seasons, *S.aureus* is known to function synergistically, causing an increase in illness severity and mortality [9]. The most common cause of mortality seen with *S.aureus* bacteraemia are those of hospital acquired or nosocomial infections [10]. Cusumano JA et al., reported that only 1.6% (42/2679) of patients who were admitted to a COVID-19 facility had *S.aureus* bacteraemia, although, these patients had a significant death rate [11]. From the initial positive blood culture, the hospital death rate was 54.8% after 14 days and 66.7% after 30 days. These figures are significantly higher than the published fatality rates for COVID-19 hospitalised patients [12]. Bacterial co-infection affects less than 0.5% of young, healthy people and atleast 2.5% of people over the age of 65 who are infected with flu [2]. In a recent study by Lansbury L et al., it was discovered that patients with COVID-19 have been reported to develop bacterial infections. A systematic review and meta-analysis of 30 studies, of patients infected with SARS-CoV-2 identified that out of 3834 patients, 7% had bacterial co-infections [13].

According to Sepulveda J et al., as of March 31, 1.6% of COVID-19 patients developed bacteraemia, with *S.aureus* accounting for 13%, among these cases as the second most frequent pathogen [6]. Similar data were reported by Nori P et al., who found that, *S.aureus* was the most common cause of bacteraemia in 1.9% of COVID-19 patients, accounting for 44% of bacteraemia [14]. The timing of bacteraemia in COVID-19 infection or its relationship to death was not evaluated in any of these trials. SARS-CoV-2 has primarily been demonstrated to replicate in the respiratory system, autopsy samples have also revealed the presence of SARS-CoV-2 Ribonucleic Acid (RNA) in the kidneys, liver, heart, brain, and blood, revealing multiorgan involvement [15]. The present study series of cases where, patients had multiorgan system involvement and associated co-morbidities. Additionally, COVID-19 has frequently been linked to endothelial cell dysfunction, which is a

Age/sex	Presentation/chief complaint	Co-morbidities	Diagnosis	Type	Treatment and intervention	ICU	Outcome
62/F	Fever, chills, erythema and swelling of knee joint	Hypertension	Septic arthritis	MSSA	Antibiotics (cefazolin, ceftriaxone) and vasopressors	No	Discharged
48/M	Fever, dyspnoea, severe back pain, episodes of watery diarrhoea, swelling of right wrist joint	Diabetes, hypertension	Necrotising fasciitis	MSSA	Antibiotics (cefazolin, ceftriaxone) and IV fluids	Yes	Death
61/M	Fever, erythema, tenderness of the left lower limb, 1.5 cm ulceration with draining pus	None	Bacterial cellulitis	MRSA	Antibiotics (vancomycin, linezolid) and vasopressors	Yes	Discharged
39/F	Fever, chills, diarrhoea, nausea/vomiting, macular rash on left upper arm	Diabetes, hypothyroidism	Toxic Shock Syndrome (TSS)	MSSA	Antibiotics (cefazolin, ceftriaxone) and IV fluids	Yes	Discharged
43/M	Fever, sore throat, blisters on left lower limb	None	Bacterial cellulitis	MSSA	Antibiotics (cefazolin, ceftriaxone), intubation, wound debridement	Yes	Death
59/F	Fever, chills, numbness and erythema of right foot, 1.5 cm draining foot ulcer	Diabetes, chronic kidney disease	Diabetic foot ulcer	MRSA	Antibiotics (vancomycin, linezolid), wound debridement	Yes	Discharged
46/F	Fever, pain and numbness of right lower limb with ischaemia and necrotic spread to knee joint	Diabetes, hypertension, dyslipidaemia	Necrotising fasciitis	MRSA	Broad spectrum antibiotics (meropenem/clarithromycin), wound drainage, fasciotomy	Yes	Death
51/M	Fever, neck pain, low back pain, painful right wrist with surrounding erythema and oedema	None	Epidural abscess	MSSA	Antibiotics (cefazolin, ceftriaxone), vasopressors, and surgical drainage of abscess	Yes	Discharged

[Table/Fig-2]: Clinical characteristics of patient admitted.

Bacteraemia related characteristics	Total cases n (%)	Survival n (%)	Mortality n (%)	p-value
MSSA	5 (62.5)	3 (0.6)	2 (0.6)	0.46
MRSA	3 (37.5)	2 (0.4)	1 (0.4)	0.42
<b>Bacteraemia source</b>				
Skin	3 (37.5)	2 (0.4)	1 (0.4)	0.42
Vascular	4 (0.5)	3 (0.6)	1 (0.4)	0.35
Pneumonia	1 (12.5)	0	1 (0.4)	0.19
<b>Bacteraemia onset</b>				
Hospital acquired	3 (37.5)	3 (0.6)	0	0.07
No (+) blood culture at admission	2 (0.25)	0	1 (0.4)	0.21
Time from admission to bacteraemia onset (median) (d)	8 (2-14)	12 (3-14)	4 (2-6)	0.24
<b>Laboratory values at the time of blood culture</b>				
WBC counts X 103/L	14.7 (9.2-20.3)	12.3 (8.2-20.5)	15.8 (12.6-20.0)	0.27
Procalcitonin (ng/dL)	1.02 (0.28-3.47)	1.16 (0.34-5.09)	1.02 (0.28-2.04)	0.65
Temperature (°C)	38.0±0.98	38.1±0.84	38.0±1.10	0.64
PITT bacteraemia score	5.0 (2.0-7.0)	3.0 (0.50-5.0)	7.0 (4.5-7.0)	0.004
qSOFA score	1.0 (1.0-3.0)	2.0 (0.5-3.0)	3.0 (1.5-3.0)	0.052

**[Table/Fig-3]:** Baseline laboratory values of the survived and expired individuals. Chi-square test was used for categorical variables (source and onset of bacteraemia), t-test was used for parametric variables (laboratory values) N=8.

significant factor in restricting bacterial spread during the systemic inflammatory response brought on by bacteraemia [16]. Studies involving only Intensive Care Unit (ICU) patients indicate a 14% risk of bacteraemia in COVID-19 patients [17]. This low risk of hospital-acquired super infections in comparison to other viral infections could be attributed to empiric antibiotic use, isolation measures, or host macrophage activation. As mentioned in the above case series of the present article, patients who were admitted in ICU with associated co-morbidities and didn't receive empiric treatment had high risk of bacteraemia. Patients readmitted in the hospital due to bacterial infections had severe COVID-19 infection in the past and were kept on mechanical ventilators. This was once proved by Mormeneo Bayo S et al., that super infections can be associated with ICU admissions, especially with the use of mechanical ventilation and catheters [18]. The aetiology of bacteraemia differs between COVID-19 positive and non COVID-19 patients, with COVID-19 patients typically presenting with pathogens associated with healthcare settings, such as coagulase negative *Staphylococcus species* and *Candida*. Non COVID-19 patients, on the other hand, are primarily affected by community-acquired pathogens as specified by Bhargava A et al., the majority of the bacteraemia cases associated with COVID-19 patients was discovered to be multidrug resistant [19]. As seen in the case series, there were cases of MRSA associated infections as well, which signifies that patients can be infected even with multidrug resistant bacteraemia. This can be explained by the fact that the majority of cases were presented through nursing facilities, as indwelling catheters are commonly used in nursing homes. Residents of nursing facilities who did not use indwelling catheters had a lower prevalence than those who did [20]. It has previously been noted that, bacteraemia that develops in the hospital is linked to higher mortality. Age was another factor, the authors found to be a predictor of 14 day hospital mortality [21]. This was linked to associated co-morbidities in elderly patients who were admitted in ICU in the hospital who had risk of mortality than elderly who presented without co-morbidities like diabetes and hypertension. A score of less than two has been associated with a high risk of mortality for *S.aureus*, despite the PITT bacteraemia score's original development as a method to

predict gram-negative bacteraemia mortality as depicted by Chang FY et al., [22]. In comparison to earlier *S.aureus bacteraemia* investigations, the median PITT bacteraemia score (IQR) of 5.0 (2.0-7.0) is higher. In contrast to one study, which found the mean PITT bacteraemia score to be 4, another study done by Hagg S et al., found that, the median PITT bacteraemia score (IQR) ranged from 0 to 2 [23]. As shown in [Table/Fig-3], patients with highest PITT bacteraemia score (7.0) had increased risk of 14 day mortality as, this was previously described by Ioannidis JPA et al., in his study that patients with hospital-onset bacteraemia had greater median PITT bacteraemia scores, which most likely played a role in the link between hospital-onset bacteraemia and 14 day mortality [24]. The mortality rate for patients co-infected with COVID-19 and *S.aureus* in the present series research was 61.7%, which shows a significantly higher mortality rate when compared to patients infected with COVID-19 alone [25].

Cusumano JA et al., depicted that, 76.5% of the patients in research had co-infections with COVID-19 and *S.aureus* after being admitted to the hospital, preventative actions in the community or treatment in an outpatient setting may be crucial factors in lowering mortality from healthcare associated *S.aureus* infection [11]. A post COVID-19 follow-up protocol has to be implemented in every healthcare setting, instructing patients every possible way of acquiring infections even after treatment of COVID-19, it is a deadly virus and can stay in the body for latent period. There has to be a routine health check up for patients infected with COVID-19 to get a quarterly check up, in the same way, that is followed in case of diabetic patients with their HbA1c levels. As shown in this case series, patients with co-morbidities had a longer hospital stay and recovered slowly. The mortality risk was even higher in patients with associated co-morbidities. Future high quality clinical studies examining patient outcomes are warranted and of critical importance to further expand on the findings of the systematic reviews.

## CONCLUSION(S)

The importance of the present case series was to signify the risk of bacteraemia is higher in patients with history of SARS-COV-2 infection than the patients without, and that *S.aureus* is the most common infected organism causing wide variety of infection in immunosuppressed patients. Bacteraemia caused by *S.aureus* is associated with a high mortality rate in COVID-19 patients. More research is needed to comprehend the correlation between COVID-19 and secondary *S.aureus* bacteraemia.

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