Infection and Drug Resistance

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ORIGINAL RESEARCH

# Profile of Secondary Bacterial and Fungal Infections in Hospitalized COVID-19 Patients in a Tertiary Care Centre

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**Introduction:** SARS CoV-2, a novel corona virus, has emerged in December 2019. The COVID-19 associated mortality is documented in elderly with co morbidities. To have better insight on this issue, the secondary bacterial infections with multi-drug-resistant bacteria in COVID-19 patients need to be studied to evaluate the impact of these infections on the outcome.

**Aim and objectives:** To determine the proportion of secondary infections in COVID-19 patients. To study the spectrum of pathogens and antibiogram of the bacteria isolated from secondary infections in such patients. To evaluate the co-existing co-morbidities, treatment and outcome in these patients.

**Methodology:** The retrospective study was conducted in Departments of Medicine and Microbiology, KMC hospitals Attavara and Ambedkar circle, Mangaluru, including all the hospitalized microbiologically confirmed cases of SARS CoV-2 infection. Details pertaining to the study population were collected using a structured proforma. Descriptive data were entered in the form of mean, median and proportions. The categorical values were analyzed using Chi square test. Values of $p < 0.05$ were considered as statistically significant.

**Results:** Two hundred COVID-19 hospitalized patients were included.28 out of 200 patients (14%) studied developed secondary infections. The types of secondary infections were Respiratory infections (50%), blood stream infections (17%), UTI (14%), Rhinocerebral Zygomycosis (17%). The predominant organisms were *Klebsiella pneumoniae* (44%), Zygomycetes (17%). The rates of antibiotic resistance in Gram negative bacilli were 33% to Cefuroxime,25% to aminoglycosides and fluoroquinolones and 16% to carbapenems. The mortality of 42.8% was observed in patients with secondary infections.

**Conclusion:** Close monitoring and follow up especially in high-risk group of severe COVID 19 patients is crucial for better management and outcome.

**Keywords:** COVID-19, SARS CoV 2, secondary infections, Klebsiella pneumoniae, antibiotic resistance

## Introduction

SARS CoV-2, a novel corona virus, has emerged in December 2019. Since then, the virus has spread globally triggering the much known COVID-19 pandemic. The virus is highly infectious. The COVID-19 associated mortality is documented in elderly with co-existing co morbidities.[1]

The classic clinical manifestations include fever, cough, fatigue, anorexia, dyspnea. The diagnosis of COVID −19 relies on the direct detection of SARS-CoV-2 RNA by reverse-transcription polymerase chain reaction (RT-PCR) from the upper respiratory tract.[2]

The virus spreads from person to person via inhalation or direct contact. Following the virus entry and recognition by the alveolar epithelial cells and macrophages, there is massive release of pro-inflammatory cytokines and chemokines

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such as Interleukin-1β (IL1β), IL-2, IL-6, IL-8, IL-10, tumor necrosis factor-α (TNF-α), interferon γ (IFN-γ), D-dimer, erythrocyte sedimentation rate (ESR), and C-reactive peptide (CRP). The virus damages the lungs and the associated cytokine storm is responsible for Multiorgan failure[3].

A significant observation in hospitalized COVID-19 patients was the alteration in the fecal microbiota leading to subsequent colonization and infections with opportunistic pathogens.[4]

The immunosuppression seen in the course of this viral infection predisposes the individual to a variety of bacterial infections. Bacterial infections severely affect the outcome in these patients.[5]

The secondary infections reported in COVID-19 patients were predominantly bacterial (91.8%) followed by viral (31.5%) and fungal (23.3%) infections. A systemic review and meta-analysis by Louise Lansvury et al reiterated the fact that 7% of the hospitalized COVID 19 patients had bacterial secondary infections. Higher rates were reported in ICU settings.[6]

The spectrum of pathogens reported are *Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Haemophilus influenza, Streptococcus pneumoniae, Staphylococcus aureus, Aspergillus fumigatu*s in all the cases of COVID −19.[7]

The lessons learnt from the previous pandemics of seasonal flu suggest that bacterial coinfections worsen the prognosis in these cases.[8]

The rates of secondary bacterial infections were highest in critically ill cases (34.5%) compared to moderate and mild ones (3.9% and 8.3%, respectively).[9]

Antibiotics are being used to combat the bacterial pathogens causing secondary infections in COVID-19 patients. The effect of this usage on the global prevalence of antibiotic-resistance is to be investigated. The study published in 2021 reports that the incidence of MDR bacterial infections was higher in COVID 19 patients (29%), compared to Non COVID 19 patients (19%) with *Klebsiella pneumoniae* as the major bug. At present, there are no studies depicting the rates of secondary bacterial infections by antibiotic-resistant bacteria in this region.[10]

Virus and drug-induced immunosuppression in critically ill COVID 19 patients predisposes to the increased risk of developing secondary infections consequently leading to increased mortality.[11]

The impact of COVID-19 outbreak on the rates of antibiotic-resistant bacteria is unclear.[12]

To have better insight on this issue, the secondary bacterial infections with multi-drug-resistant bugs in COVID 19 patients need to be studied to evaluate the impact of these infections on the outcome.

## Aim

To study the spectrum of secondary infections in COVID 19 patients and its association with outcome.

## Objectives

1. To determine the proportion of secondary infections in COVID-19 patients.
2. To study the bacterial spectrum and antibiogram of the bacteria isolated from secondary infections in such patients.
3. To evaluate the co-existing co-morbidities, treatment and outcome in these patients.
4. To study the association of secondary infection with outcome in COVID 19 patients.

## Material and Methods

Study setting: Departments of Medicine and Microbiology, KMC hospitals Attavara and Ambedkar circle, Mangaluru, Karnataka.

### Study Population

Inclusion criteria: 200 hospitalized microbiologically confirmed cases of SARS COV-2 infection. For the secondary infections Secondary infections were identified by infection that developed during ICU stay but after admission of more than 48 h duration, meaning not present at the time of presentation with COVID-19.[13]

Exclusion criteria: Patients tested negative/inconclusive for SARS- COV-2 infection and those patients tested positive for SARS- COV-2, but not hospitalized.

Study design: Retrospective study

Study duration: 6 months February 2021 to June 2021

Sampling Method: Nonprobability convenient sampling method.

## Methodology

The study was conducted retrospectively on 200 hospitalized COVID −19 patients.

Data collection: Details pertaining to the study population including sociodemographic, clinical, laboratory, other comorbidities, treatment and outcome were collected using a structured proforma.

For the cases with documented bacterial infection, details on the type of infection, identity of the bacterial isolate and antibiogram of the bacterial isolates was collected from the Laboratory information system.

Clinical samples (blood, lower respiratory samples: Sputum, bronchoalveolar lavage, exudate, urine) from the suspected cases were processed for bacterial culture and sensitivity. The identification of the bacterial isolates was done by standard methods and the Automated Vitek 2 Compact system. Blood culture in suspected cases of sepsis was processed using BacT alert system. The antibiotic susceptibility testing of the bacterial isolates was performed by Modified Kirby Bauer disc diffusion method and Vitek 2 Compact system and the results were interpreted using CLSI guidelines[14].

The study has received approval from the Institutional ethics committee at KMC Mangaluru.

Data Analysis: Descriptive data were entered in the form of mean, median and proportions. The categorical values were analyzed using Chi square test. Values of $p < 0.05$ were considered as statistically significant.

## Results

A total of 200 COVID 19 infected hospitalized patients were included in the study from February to June 2021. The demographic information with the information on the age, sex and the occupation is shown in Table 1. The symptoms at presentation in COVID-19 patients were 89% of the patients presented with fever, headache and upper respiratory symptoms, 35% with musculoskeletal symptoms and 20% with Gastrointestinal symptoms.

The mean duration of hospital stay in patients with secondary infections was 15 days compared to a mean of 6.4 days in patients without secondary infections.

Twenty-eight out of 200 patients (14%) studied developed secondary infections in the course of COVID 19. The type of secondary infections and the spectrum of pathogens are depicted in Figures 1 and 2 respectively.

**Table 1** Demographic Data of the COVID−19 Patients

| Demographic Variable | | Number (%) |
|---|---|---|
| **Age** | **>60 years** | 85 (42.5%) |
| | **45–60 years** | 73 (36.5%) |
| | **19–45 years** | 39 (19.5%) |
| | **≤18 years** | 3 (1.5%) |
| **Sex** | **Male** | 138 (69%) |
| | **Female** | 62 (31%) |
| **Occupation** | **Health care worker** | 3 (1.5%) |
| | **Non-Health care worker** | 173 (98.5%) |

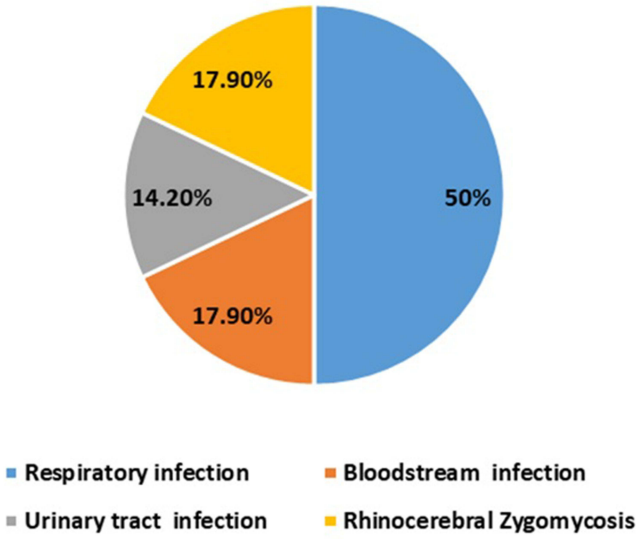


**Figure 1** Type of Secondary infections in COVID 19 patients.

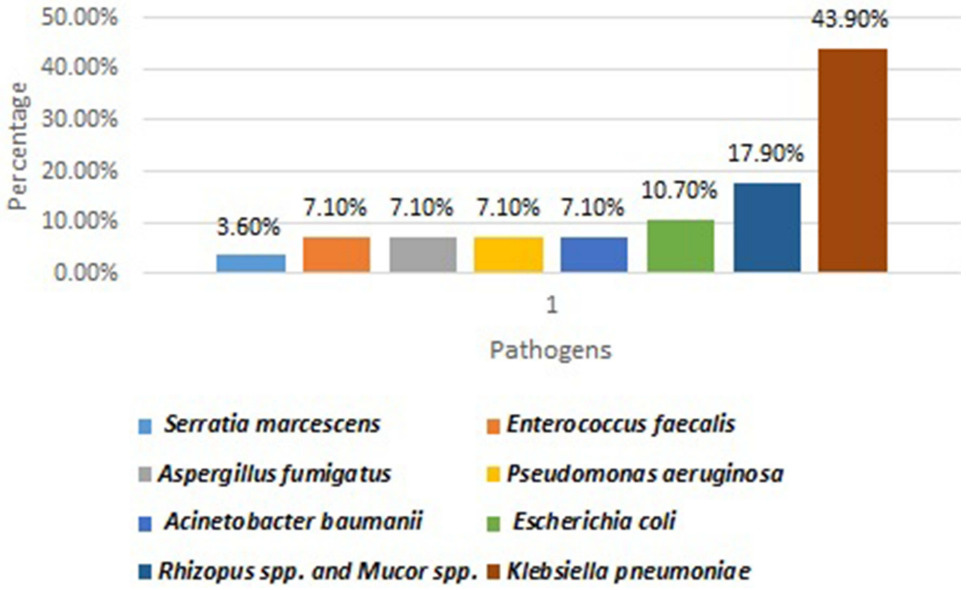


**Figure 2** Spectrum of pathogens in Secondary infections in COVID 19.

Out of the 12 *Klebsiella pneumoniae*., 10 isolates were from respiratory samples,1 from blood and 1 from urine. 33.4% of the isolates were resistant to Cefuroxime,25% to fluoroquinolones and aminoglycosides and 16.6% to carbapenems 0.2 isolates of *Acinetobacter baumannii complex*. from respiratory sample and blood were resistant to all the antibiotics.

Three (10.7%) had more than 1 documented secondary infection. Case 1 had 2 separate episodes of bloodstream infections due to *Escherichia coli* and *Acinetobacter baumannii complex* and an episode of Ventilator associated Pneumonia caused by *Pseudomonas aeruginosa*. The patient was elderly, non-diabetic with severe disease on mechanical ventilation. The patient was on steroids. The patient succumbed to the secondary infections. Case 2 a middle-aged lady, known hypertensive and diabetic, COVID 19 positive developed Rhinocerebral Zygomycosis and infection with *Aspergillus fumigatus*. The Zygomycete identified in this case was Rhizopus spp, supplemented by Histopathological observation of broad aseptate hyphae in the tissue section. She was given IV Amphotericin and Voriconazole followed by

Posconazole. She recovered. Case 3, known hypertensive and diabetic developed Rhinocerebral Zygomycosis and an episode of VAP due to *Klebsiella pneumoniae*. He recovered.

The other laboratory parameters in the 28 cases with secondary infections were significant for elevated levels of CRP, D dimer and leucocyte count in CBC.

D dimer levels were elevated in all the COVID positive patients with documented secondary infection. On the contrary, the levels were normal in patients with no secondary infection. This finding emphasizes the utility of D dimer as a biomarker in predicting the course and severity of COVID-19.

Five patients developed Rhinocerebral Zygomycosis with 3 cases isolating Mucor spp.,2 Rhizopus spp. Poorly controlled diabetes was a risk factor in this group. Nasal debridement with endoscopic sinus surgery was performed. Liposomal Amphotericin B was started in all these cases. Three cases recovered and 2 succumbed.

The comorbidities were compared among the two groups: With secondary infection and without secondary infection. The data is depicted in Table 2. Among the comorbidities, the significant ones were diabetes mellitus (64.3%) and hypertension (50%). The association of secondary infections in COVID 19 with the severity and outcome is shown in Table 3.

The antibiotics used in the management of secondary infections in COVID-19 in our setup were Cefuroxime (9 cases), BL/BLI combination (21 cases), carbapenem (10 cases), fluoroquinolones (4 cases) aminoglycoside (2 cases), antifungals (11 cases).

One case of VAP due to Carbapenem resistant *Klebsiella pneumoniae* was managed with Ceftazidime-avibactam with Aztreonam and 2 cases of Carbapenem resistant *Klebsiella pneumoniae* and *Acinetobacter baumannii* were managed with Polymyxin B.

**Table 2** Association of Comorbidities with Secondary Infections in COVID 19 Patients

| Comorbidity | | With Secondary Infection | Without Secondary Infection |
|---|---|---|---|
| **HTN** | Yes | 14 (50%) | 67 (38.9%) |
| | No | 14 (50%) | 105 (61.1%) |
| **DM** | Yes | 18 (64.3%) | 92 (53.5%) |
| | No | 10 (35.7%) | 80 (46.5%) |
| **PTB** | Yes | 0 | 1 (0.6%) |
| | No | | 171 (99.4%) |
| **Chronic Lung disease** | Yes | 2 (7.2%) | 13 (7.6%) |
| | No | 26 (92.8%) | 159 (92.4%) |
| **Heart disease** | Yes | 3 (10.7%) | 26 (15.2%) |
| | No | 25 (89.2%) | 146 (84.8%) |
| **Renal disease** | Yes | 1 (3.6%) | 15 (8.8%) |
| | No | 27 (96.4%) | 157 (91.2%) |
| **Cancer** | Yes | 3 (10.7%) | 5 (2.9%) |
| | No | 25 (89.3%) | 167 (97.1%) |
| **Steroid use** | Yes | 18 (64.3%) | 100 (58.5%) |
| | No | 10 (35.7%) | 72 (41.8%) |
| **Mechanical ventilation** | Yes | 6 (21.4%) | 0 |
| | No | 22 (78.5%) | 0 |

**Table 3** Association of Secondary Infections in COVID 19 with Comorbidity, Severity and Outcome

| | | With Secondary Infection | Without Secondary Infection | X2 value | p value |
|---|---|---|---|---|---|
| **Comorbidity** | **Present** | 25 (89.28%) | 122 (70.9%) | 4.012 | *0.045 |
| | **Absent** | 3 (10.72%) | 50 (29.1%) | | |
| **Severity** | **Asymptomatic** | 0 (0%) | 33 (100%) | 10.232 | 0.017* |
| | **Mild** | 11 (16.7%) | 56 (83.3%) | | |
| | **Moderate** | 6 (10.9%) | 49 (89.1%) | | |
| | **Severe** | 11 (24.4%) | 34 (75.6%) | | |
| **Outcome** | **Recovered without progression** | 6 (21.4%) | 25 (14.5%) | 12.25 | 0.007* |
| | **Progression and resolution** | 10 (35.7%) | 119 (69.2%) | | |
| | **Deceased** | 12 (42.8%) | 28 (16.3%) | | |

**Note**: *p value <0.05 is significant.

The overall mortality in COVID-19 patients was 20%. The mortality of 42.8% was observed in patients with secondary infections compared to rate of 16.3% in patients without secondary infections (p value 0.007). The mortality associated with COVID 19 was seen only in ICUs.

## Discussion

COVID-19 pandemic declared in 2020 by WHO continues to scare the mankind with its surge in the number of cases, rapidity of spread and emerging variants. The spectrum of clinical presentation in COVID-19 infection ranges from asymptomatic to severe cases requiring ICU admission, use of steroids and mechanical ventilation. All these factors predispose the hospitalized patients to an array of secondary infections.

The published literature on the incidence of secondary bacterial infections in SARS CoV 2 infection reports a rate of 3.6%.[15] Haocheng et al have reported a higher incidence of secondary infections (57.8%) in severe COVID-19 patients.[16] Another study has reported a rate of 12.6%.[17] Prompt diagnosis and adequate management go a long way in minimizing the mortality. Our study picked up 14% of COVID-19 patients falling prey to a battery of secondary pathogens. This high rate bells an alarm for the clinicians to be vigilant on critically ill patients.

The severity of COVID-19 infection is graded as mild, moderate and severe. Mild cases are those with mild symptoms and no abnormal radiological findings. Moderate cases are symptomatic with features of Pneumonia on CT scan of chest. Severe cases have symptoms of moderate category plus respiratory distress and low oxygen saturation <93%.[18] The distribution of COVID-19 cases in this study was mild (33.6%), moderate (28%), severe (22.6%) and asymptomatic (6.6%.) Severity of 5.3% was reported in a previous published study, implicating the higher rate of severity in the present study.[19]

The findings of this study point towards a male preponderance (69%) and majority of the patients falling in the age group (>60 years): 42.5%. The previous studies have reported a median age of 53 years in the hospitalized patients, reiterating the fact that severity and progression in COVID 19 is positively associated with advancing age.[20]

The higher rates of COVID-19 infection in males reported in this study are on par with the previous published reports. Higher levels of type 1 interferon (IFN), a potent antiviral cytokine in female compared to male explains the above fact on sex distribution of COVID 19 cases.[21]

The COVID 19 patients in our study presented with fever, headache and respiratory symptoms (89%), musculoskeletal symptoms (35%), gastrointestinal symptoms (20.5%). The findings match up the common clinical presentation in COVID-19 in previously published study.[22]

Respiratory tract (50%) was the commonest site of secondary infection in COVID-19 infection followed by blood stream infection (17.9%), Rhinocerebral Zygomycosis (17.9%) and urinary tract (14.2%). The distribution of the pathogens were *Klebsiella pneumoniae*. (43.9%), Zygomycetes (17.9%), *Escherichia coli* (10.7%), *Acinetobacter baumanii* (7.1%), *Pseudomonas aeruginosa* (7.1%) and *Enterococcus faecalis*. (7.1%). The predominant respiratory pathogens in our study were *Klebsiella pneumoniae and Acinetobacter baumanii* consistent with the findings of previous study.[23]

Fourteen cases out of the 28 cases with documented secondary infections were diagnosed with pneumonia. Six out of the 14 cases were on mechanical ventilation. Severe COVID-19 patients with falling oxygen saturation require mechanical ventilation. The dark side of this story is subsequent development of ventilator-associated pneumonia with multi-drug-resistant bugs, requiring strict vigilance on the infection control practices.

17.9% of the secondary infections were Blood stream infections (BSI) with *Escherichia coli* as the predominant pathogen. Study by Palaniswamy et al has reported 8.5% BSI with *Acinetobacter baumannii* and *Klebsiella pneumoniae (*32.8% and 21.9%).[24] The presence of comorbidities, advancing age and mechanical ventilation are associated with development of BSI.[25] This is consistent with the findings of our study.

The antibiotic resistance rates among the Gram negative pathogens were 33% to Cefuroxime,16% to carbapenems and 25% to fluoroquinolones and aminoglycosides. The rising resistance rates in this pandemic era ring an alarm to awaken and strengthen the antibiotic stewardship programme and infection control practices.[26]

Rhinocerebral Zygomycosis was diagnosed in 5 cases of our study population. Pre-existing diabetes, prolonged hospitalisation and steroid-induced immunosuppression predisposes to development of Rhinocerebral Zygomycosis.[27] In our study, all the 5 cases were diabetic and on steroids for treatment.2 cases succumbed to this deadly combination.

One of the cases of Rhinocerebral Zygomycosis had isolation of *Aspergillus fumigatus* in sputum. Previous studies have reported an incidence of 19.6–33.3% of Pulmonary Aspergillosis. The clinicians need to be aware of this infection. Prompt fungal culture and galactomannan detection could provide diagnosis. This is of importance in critically ill patients.[28]

In our study, among the 200 hospitalized COVID-19 patients, 2 confirmed cases of coinfection of Typhoid fever and Leptospirosis were noted. There are reports of coinfection with Measles, Dengue, *Pneumocystis jirovecii, Legionella spp., Chlamydia and Mycoplasma* spp in COVID 19 positive patients.[29]

D dimer levels, CRP and leucocyte count were significantly raised in all the patients with secondary infection. Thus, patients with higher levels of D dimer must be on close watch[30].

89.28% of patients with secondary infection had an underlying comorbidity (p value 0.045). The common ones associated with secondary infections were diabetes mellitus (64.3%), hypertension (50%). The incidence of comorbidities was higher in severe cases (67.1%) compared to moderate group (37.8%).[31]

Diabetes mellitus is linked to impaired phagocytic cell capabilities. An elevated level of ACE-2 increase the risk of COVID-19 in diabetic patients. ACE-2 inhibitors used in the management of hypertension upregulate expression of the ACE-2 receptor, thereby increasing the susceptibility to SARS CoV 2 infection. Thus, co-existence of diabetes and Hypertension in secondarily infected COVID 19 patients contributes to increased morbidity.[31,32] The associated risk factors in our study were steroid use (64.3%) and mechanical ventilation (46.4%). The fact emphasizes that prolonged mechanical ventilation and ICU stay are associated with secondary infections.

Association of secondary infection with severity: 24.4%,10.9% and 16.7% of the severe, moderate and mild COVID 19 infection developed secondary infections, respectively. Secondary infections were positively associated with severe infection (p value0.017). The finding is similar to a study by Vaillancourt et al, in which the higher rates of secondary bacterial infections were significantly associated with outcome severity.[33]

Association of secondary infection with outcome: a positive association was observed between secondary infections and mortality as discussed below. The overall mortality reported in COVID 19 infected was 10.6% and the mortality among patients with secondary infection was 56.7% in a study previously published. The overall mortality in this study is 20% and among those who develop secondary infections in the course of COVID 19 the rate soared up to 42.8% (p value0.007). This is on par with the findings by Nag V et al which reported a greater incidence of severe infection and mortality in COVID-19 patients attributed to secondary infections.[34]

Thus, COVID −19 represents a danger especially in terms of hospitalization of complications that it brings. No longer as a disease in its own right.

## Conclusion

The findings of the current undertaken study on COVID-19 patients has strongly established the association of presence of comorbidities like diabetes mellitus and hypertension with poor prognosis. Secondary infections were predominantly seen in severe COVID 19 patients. This risk group with comorbidities are vulnerable to respiratory tract infections, blood stream infections and rarely urinary tract infections. As expected, the common bugs were *Klebsiella spp*. followed by *Escherichia coli, Acinetobacter spp*. and *Pseudomonas* spp. Fortunately, there was no significant change in the rates of antibiotic resistance compared to pre COVID era. This second COVID 19 peak was also associated with a cluster of secondary fungal infections: Rhinocerebral Zygomycosis, Aspergilllosis. The overall mortality was 42.8% in patients with secondary infection compared to the rate of 16.3% in patients without secondary infections.

The limitations of this study were that we had chosen 200 inpatients for the study. The study did not include outpatients. Better inferences could have been drawn, if the sample size was more and had included outpatients.

To conclude, close monitoring and follow up especially in high-risk group of severe COVID 19 patients is crucial for better management and outcome.

## Data Sharing Statement

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

## Ethics Statement

The study is approved by the Institutional Ethics committee, Kasturba Medical College, Mangalore (IEC KMC MLR 01-2021/32). The Institutional Ethics committee has waivered the patient consent as the research is a retrospective study based on only the records and laboratory data. There is no risk to the patient and no direct contact between the researcher and the patient. The identity of the patients and no images related to the patients are displayed in the manuscript. The study is in compliance with the Declaration of Helsinki.

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## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

## Disclosure

The authors declare no conflicts of interest in relation to this work.

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