ISSN:0975 -3583,0976-2833 VOL14, ISSUE 06, 2023

IMPACT OF SECONDARY INFECTIONS ON THE OUTCOME OF PATIENTS OF SARS-COV-2 ADMITTED IN ICU OF A TERTIARY CARE HOSPITAL OF CENTRAL INDIA

Dr Nitin Nahar[1], Dr Anurag Tiwari[2], Dr Rajbali Adivasi[3], Dr Arvind kumar mittal[4] , Dr Simmi Dube[5]

[1] Associate Professor, Department of Medicine, Gandhi Medical College Bhopal, Madhya Pradesh

Email id- drnitinnahar@gmail.com

Mob –9424481895

[2] Post Graduate Resident, Department of Medicine, Gandhi Medical College Bhopal, Madhya Pradesh

Email id-dr.anurag1627@gmail.com

Mob-9424707092

[3] Post Graduate Resident, Department of Medicine, Gandhi Medical College Bhopal, Madhya Pradesh

Email id-raj4aug1995@gmail.com

Mob-8965902827

[4] Assistant Professor, Department of Medicine, Gandhi Medical College Bhopal, Madhya Pradesh

Email id-dravimit@gmail.com

[5] Professor & head of department, Department of Medicine, Gandhi Medical College Bhopal, Madhya Pradesh

Email id-simmi33@gmail.com

Corresponding Author-

Dr Anurag Tiwari

Post Graduate Resident, Department of Medicine, Gandhi Medical College Bhopal, Madhya Pradesh

Email id-dr.anurag1627@gmail.com

Mob-9424707092

ABSTRACT

Background -. The prevalence incidence and characteristics of secondary infection in patients infected with Covid-19 is not well understood and has been raised as an important knowledge gap. Critically ill patients are susceptible for the development of secondary bacterial infections. Due to a combination of virus- and drug-induced immunosuppression, these patients may even have a higher risk of developing a secondary infection. These secondary infections can increase the severity of illness and raise the risk of death. Further research on secondary infections in COVID-19 patients is essential. Therefore, the objective of this study objective of this study was to investigate the incidence of secondary bacterial infections and to assess the impact of secondary infections on the outcome of critically ill patients infected with SARS-CoV-2.

ISSN:0975 -3583,0976-2833 VOL14, ISSUE 06, 2023

Material & Methods – The present study was undertaken among Covid-19 patients admitted in ICU of Gandhi Medical College and Hamidia Hospital, Bhopal. Blood and urine samples of patients was taken on the day of admission in ICU and repeated on 3rd day if feasible and was sent for bacterial and fungal culture to determine the presence of secondary infection, causative organism and all patients were followed till discharge/death to determine the effect of secondary infection on outcome. All the data analysis was performed using appropriate statistical software (Epi Info Version-6).

Results

Positive growth in blood was seen in 18 (54.5%) of the patients with secondary infection, while urine culture was positive in 11 (32.3%) patients. Both blood and urine culture were positive in 12.1% of the patients. Among the 40 isolates obtained from 33 patients with secondary infection, 8 (20.0%) patients had gram positive infections. Among 33 patients with secondary infection, 5 (15.2%) succumbed while in patients without secondary infection, 9 (13.4%) deaths were observed. Among the 5 deaths happened in 33 patients with secondary infection. All 5 (100.0%) were due to gram negative organisms. **Conclusion -.** Gram negative infections were common among the patients admitted in ICU. These data were captured when the COVID-19 cases were on the rise. Those with secondary infections had a longer stay in ICUs and the most common organisms leading to mortality in such patients were gram negative in nature.

Keywords – COVID-19, Secondary Infections. Outcome, Gram Negative

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the aetiology behind the ongoing pandemic of coronavirus disease (COVID-19). The spectrum of disease severity is very wide: from an asymptomatic carrier state to severe LRTI and critical illness with intensive care unit (ICU) requirement[1]

Critically ill patients, in general are susceptible for development of secondary bacterial infections such as, bloodstream infection of unknown origin, secondary pneumonia and-catheter related sepsis. It is noted that critically ill patients infected with SARS-CoV-2 are at a higher risk of developing secondary infections due to a combination of virus- and drug-induced immunosuppression[2]. Secondary infections often lead to a lower discharge rate and higher death rate[3]. Hence further research on secondary infections in COVID-19 patients is essential.

There is a wide variation in reported incidences and outcomes of secondary bacterial infections in critical ill COVID-19 patients in the available literature. A recent systematic review reported an incidence of secondary infections ranging from 7% up to 51% in critically ill patients infected with SARS-CoV-2[4]. The most common complication of COVID-19 was secondary pneumonia including ventilator-assisted pneumonia (VAP). A recent multicentre study described a cumulative incidence of VAP of 50% in patients with COVID-19 admitted to the Intensive Care Units[5]. Data on bloodstream infections in critically ill COVID-19

ISSN:0975 -3583,0976-2833 VOL14, ISSUE 06, 2023

patients are rather scarce. It has been postulated that bloodstream infections are the second most common secondary infection in critically ill COVID-19 patients with incidences ranging from 3.4 to 50%[6-7].

Identification of the pathogens responsible for the development of secondary infections in creates new possibilities such as individually tailored empiric antibiotic therapy in those patients with early signs of a secondary infection. And also, identification of possible risk factors associated with secondary bacterial infections may lead to development of new prevention strategies for secondary infections.

Therefore, the objective of this study was to investigate the incidence of secondary bacterial infections and to assess the impact of secondary infections on the outcome of critically ill patients infected with SARS-CoV-2.

Aims and Objectives

To study the impact of secondary infections on the outcome of critically ill COVID-19 patients admitted in Intensive Care Unit

Material and Methods

Study Type: Prospective (Hospital based) Observational Study

Study Centre: Department of Medicine Gandhi Medical College, & associated Hospitals (Hamidia Hospital) Bhopal.

Study Duration: January 2021 to May 2022

Study Subjects: Covid-19 patients admitted in ICU of Gandhi Medical College and Hamidia Hospital, Bhopal.

Methodology

After approval of the study protocol by the Institutional Ethics Committee, written consent taken. The study was done in Department of Medicine, Gandhi medical collage & Hamidia hospital Bhopal to investigate secondary infection in patients admitted in Covid ICU. 100 patients aged 18 years and above giving consent were enrolled for the study. Blood sample and urine sample of patients was taken on the day of admission in ICU and repeated on 3rd day if feasible.

These blood and urine sample was sent for bacterial and fungal culture to determine the presence of secondary infection, causative organism and all patients were followed till discharge/death to determine the effect of secondary infection on outcome. Other relevant investigations were also sent during the due course. The findings of blood culture and urine culture at D1/2/3 was useful in pointing out the presence of secondary infection. Predilection

ISSN:0975 -3583,0976-2833 VOL14, ISSUE 06, 2023

on the basis of selected important demographic variables like age/sex in the development of secondary infections was also studied. Inflammatory markers like CRP, Procalcitonin and TLC was done to assess the severity of infection. Whether presence of comorbidities as well culture positivity has any role in outcome of patient admitted in Intensive Care Unit was studied. Role of elevated LFT and RFT values on the outcome of COVID-19 patients admitted in Intensive care Unit was also examined. All the relevant data was then entered in MS Excel

- **Inclusion criteria: -** Covid Positive patient with consent aged 18 years or more admitted in ICU.
- **Exclusion criteria:** -
    - Patient or attender not willing for consent
    - Communication impairment
- **Sample size:** 100 Patients

Investigation

- Blood Culture/Sensitivity for bacteria and fungi
- Urine Culture/sensitivity for bacteria and fungi
- CBC
- RFT
- LFT
- HbA1c
- Procalcitonin level

Statistical analysis:

All the data analysis was performed using appropriate statistical software (Epi Info Version-6). Frequency distribution and cross tabulation was used to prepare the tables. Quantitative variables were expressed as the mean and standard deviation. Categorical data was expressed as percentage. Microsoft office was used to prepare the graphs. Student t- test was used to compare the means. Chi Square test was used to compare the categorical data. P value of < 0.05 is considered as significant.

RESULTS

Half of the patients included in the study was males, while the other 50.0% were females. 34.0% of the patients belonged to the age group of 56-70 years followed by 31.0% from the age group of 26-40 years. Mean age of patients was found to be 48.11 years with a SD of 15.36. 66.0% had no comorbidities, while 15.0% had HTN, and 6.0% had DM. Both HTN and DM was observed in 13.0% of the participants.

ISSN:0975 -3583,0976-2833 VOL14, ISSUE 06, 2023

Figure 1 – Distribution of patients according to presence of secondary infection/Growth on culture during stay in hospital

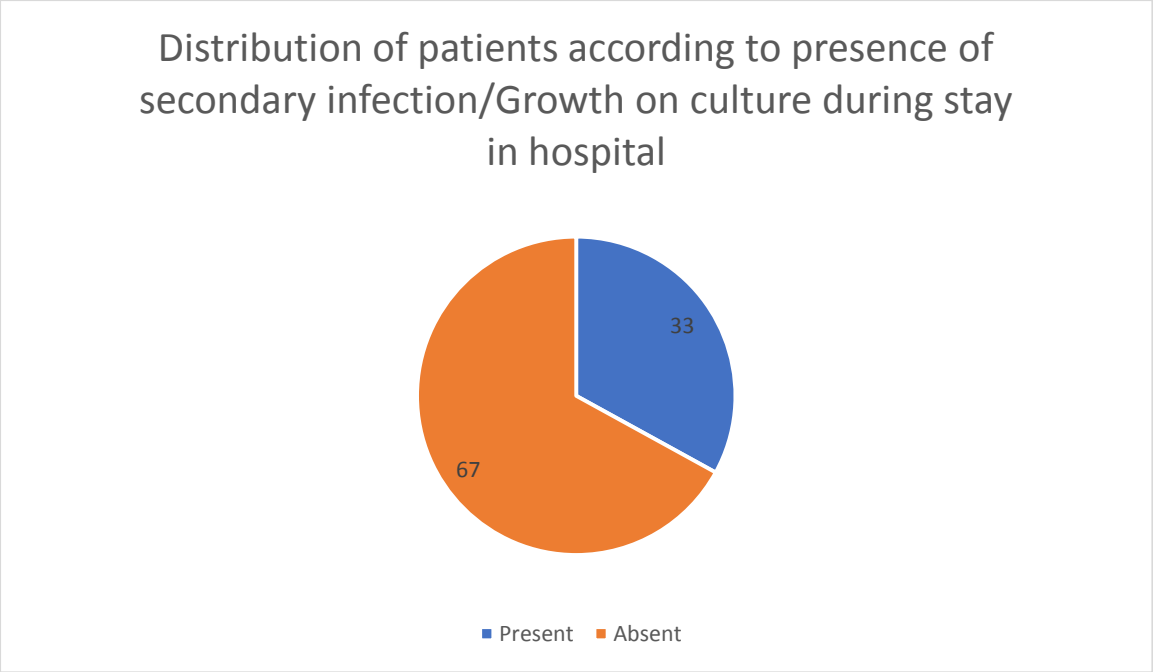


Table 1 - Distribution of patients with presence of secondary infection/Growth according to the gram staining properties (Multiple responses)

S No	Gram stain	Frequency	Percentage
1	Positive	8	24.2
2	Negative	32	96.9

Among the 40 isolates obtained from 33 patients with secondary infection, 8 (20.0%) patients had gram positive infections, while the rest had gram negative infection. Among 33 patients, 26 (78.8%) were having infection with single organism, while 7 (21.2%) had infection with more than one organism

Among 33 patients with secondary infection, majority belonged to the age group of 56-70 years. 12 (36.4%) were from the age group of 26-40 years. Only 2 (6.1%) were above 70 years old, while among 33 patients with secondary infection, majority had no co morbidities. 5 (15.2%) were having HTN, while 4 (12.1%) had both HTN and DM. Only 2 (6.1%) patients had diabetes alone as the co morbidity.

Distribution of patients with secondary infection according to the etiology shows that Citrobacter was the most common etiology in 9 (27.3%) patients, while staphylococcus aureus was responsible for infections in 8 (24.2%) patients. E coli was responsible for infections in another 18.2% patients followed by Enterococci in 12.1% patients

ISSN:0975 -3583,0976-2833 VOL14, ISSUE 06, 2023

Table 2 – Distribution of patients according to total duration of stay in hospital in days and presence of secondary infection

No of days	Secondary Infection		Total	Chi Square value P value
	Absent	Present		
	N (%)	N (%)	N (%)	2.444
≤7	28 (42.4)	18 (54.5)	46 (46.0)	
8-15	29 (43.3)	13 (39.4)	42 (42.0)	0.326
≥16	10 (15.2)	2 (6.1)	12 (12.0)	
Total	67 (100.0)	33 (100.0)	100 (100.0)	

Distribution of patients according to duration of stay at facility and presence of secondary infection shows that among the 33 patients with secondary infection, majority had a stay of less than or equal to 7 days. 13 (39.4%) had stay of 8-15 days, while 2 (6.1%) had stay of more than 16 days in the hospital.

Table 3– Distribution of patients according to outcome

Outcome	Secondary Infection		Total	Chi Square value P value
	Absent	Present		
	N (%)	N (%)	N (%)	0.054
Discharge	58 (86.6)	28 (84.8)	86 (86.0)	
Death	9 (13.4)	5 (15.2)	14 (14.0)	0.519
Total	67 (100.0)	33 (100.0)	100 (100.0)	

Among 33 patients with secondary infection, 5 (15.2%) succumbed while in patients without secondary infection, 9 (13.4%) deaths were observed.

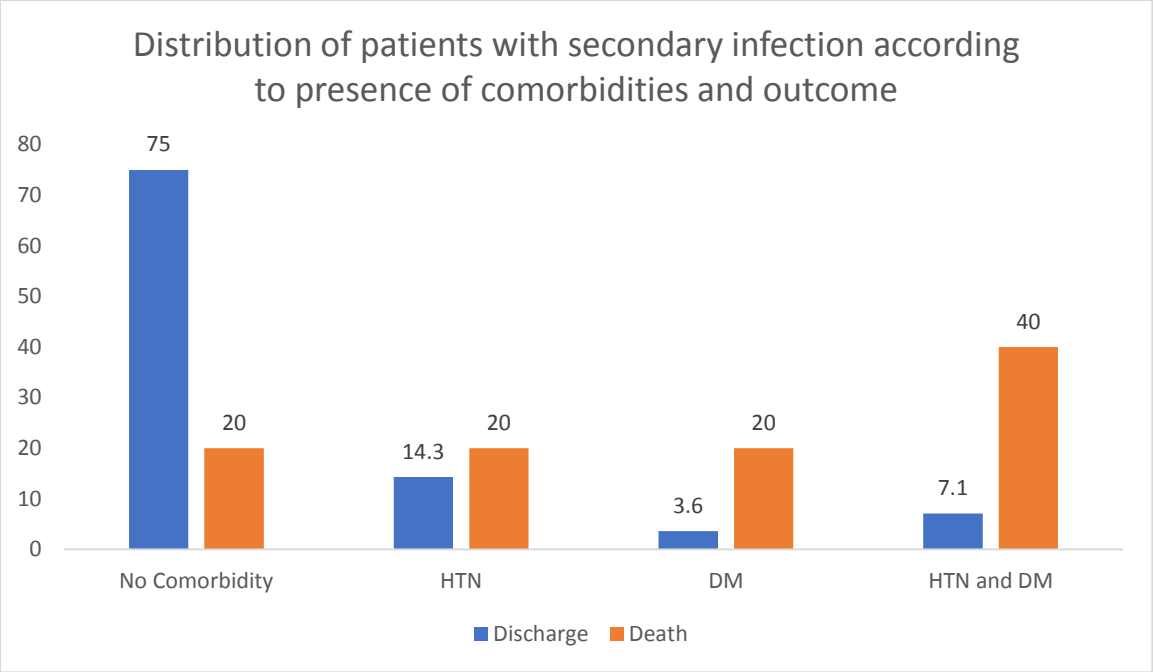
Table 4– Distribution of patients with secondary infection according to gram staining nature of etiological agent and outcome

Gram staining	Outcome		Total	Chi Square value P value
	Discharge	Death		
	N (%)	N (%)	N (%)	
Positive	8 (28.6)	0 (0.0)	8 (24.2)	
Negative	20 (71.4)	5 (100.0)	25 (75.8)	
Total	28 (100.0)	5 (100.0)	33 (100.0)	

Among the 5 deaths happened in 33 patients with secondary infection. All 5 (100.0%) were due to gram negative organisms.

ISSN:0975 -3583,0976-2833 VOL14, ISSUE 06, 2023

Figure 2– Distribution of patients with secondary infection according to presence of comorbidities and outcome



Among the total 33 patients who developed secondary infection, 28 were discharged. Among both groups of discharged and death patients, 75.0% in discharge group had no comorbidities. HTN and DM in combination was observed in 40.0% of the patients with secondary infection who succumbed to death, while HTN alone was the major factor common in individuals with secondary infection who got discharged.

Discussion

In the present study, half of the patients included in the study was males, while the other 50.0% were females. 32 (84.21%) patients were male in the study undertaken by **Haocheng Zhang et.al[8] (2020)**

Secondary infection in the form of growth in either urine or blood culture was witnessed in 33.0% of the patients. Positive growth in blood was seen in 18 (54.5%) of the patients with secondary infection, while urine culture was positive in 11 (32.3%) patients. Both blood and urine culture were positive in 12.1% of the patients with secondary infections. 22 (57.89%) patients developed secondary infections in the study by **Haocheng Zhang et.al[8] (2020)** and a microbiologically documented infection was diagnosed in 68/731 patients (9.3%) in the study undertaken by **Marco Ripa et.al[9] (2021).**

In the present study, Among the 40 isolates obtained from 33 patients with secondary infection, 8 (20.0%) patients had gram positive infections, while the rest had gram negative infection.

Distribution of patients with secondary infection according to the etiology shows that Citrobacter was the most common etiology in 9 (27.3%) patients, while staphylococcus

ISSN:0975 -3583,0976-2833 VOL14, ISSUE 06, 2023

aureus was responsible for infections in 8 (24.2%) patients. E coli was responsible for infections in another 18.2% patients followed by Enterococci in 12.1% patients. A total of 52 pathogens were confirmed in respiratory infection patients, most of which were gram-negative bacteria (26, 50.00%), following by gram-positive bacteria (14, 26.92%), virus (6, 11.54%), fungi (4, 7.69%) and others (2, 3.85%). Most common pathogens encompassed Klebsiella pneumoniae (11), Enterococcus faecium (9), Acinetobacter baumannii (8), HSV1(5) as reported by **Haocheng Zhang et.al[8] (2020).** The majority of BSIs were due to Gram-positive pathogens (76/106 isolates, 71.7%), specifically coagulase-negative staphylococci (53/76, 69.7%), while among Gram-negatives (23/ 106, 21.7%) Acinetobacter baumanii (7/23, 30.4%) and Escherichia coli (5/23, 21.7%) predominated in the study of **Marco Ripa et.al[9] (2021).** He also described that pLRTIs were caused mainly by Gram-negative pathogens (14/26, 53.8%), principally Pseudomonas aeruginosa (6/14, 42.9%)

Among the 33 patients with secondary infection, majority belonged to the age group of 56-70 years. 12 (36.4%) were from the age group of 26-40 years. Only 2 (6.1%) were above 70 years old and majority had no co morbidities. 5 (15.2%) were having HTN, while 4 (12.1%) had both HTN and DM. Only 2 (6.1%) patients had diabetes alone as the co morbidity.
Among 33 patients with secondary infection, 5 (15.2%) succumbed while in patients without secondary infection, 9 (13.4%) deaths were observed.
In the study by **Haocheng Zhang et.al[8] (2020),** Patients without secondary infection had a significantly higher 60-day discharge rate improvement different from patients with secondary infection (P<0.001) Among 16 non-infection patients with severe and critical SARS-CoV-2 infection, 15 (93.75%) patients had discharged from the hospital within 60 days, and the median duration from ICU admission to discharge was 31 (IQR 27–39) days. 8 (36.36%) of 22 secondary infection patients had died by 60 days. Compared with non-infection patients, patients with secondary infection were more likely to receive invasive mechanical ventilation (86.36% (19/22) vs 25.00% (4/16), P < 0.0001). **Marco Ripa et.al[9] (2021)** described that among overall, 194/731 patients (26.5%) died: 30/68 (44.1%) with secondary infections and 164/663 (24.7%) without further infectious events (p 0.001). Median time to death after the first secondary infection was 9 days. Overall mortality among admitted COVID-19 patients, in these ten hospitals, was 11.6% (range 2.5%–45%), and mortality among COVID-19 patients with SIs was 56.7% (27%–78.9%). Mortality was higher in critically ill patients (in ICUs), i.e. 68% (313/459) as compared to patients in wards 27.6% (50/181) (p=0.0016). Mortality following incidence of SIs was 55% (248/451) in male patients and 56% (107/189) in female patients. Out of the patients who died with SIs, 72% had Gram-negative infections, 10.8% had Gram-positive infections, 8% had mixed infections with Gram-positive and Gram-negative pathogens, 4% had fungal pathogens with Gram-negative pathogens and 6% of patients had fungal infections as described by **Sonam Vijay et.al[10] (2021).**

There is a significant longer ICU stay and need of ventilation(P<0.001) for patients with secondary infection as described by **Astrid De Bruyn et.al[11] (2022).** Similar findings were observed in the present study as well.

ISSN:0975 -3583,0976-2833 VOL14, ISSUE 06, 2023

Conclusion

In conclusion, prevalence of secondary infections in hospitalized Indian patients with COVID-19 is high; and whenever such infections are present, they cause severe disease with worst outcomes. Gram negative infections were common among the patients admitted in ICU. These data were captured when the COVID-19 cases were on the rise. Those with secondary infections had a longer stay in ICUs and the most common organisms leading to mortality in such patients were gram negative in nature.

References

1. Yang X, Yu Y, Xu J, Shu H, Liu H, Wu Y, Zhang L, Yu Z, Fang M, Yu T, Wang Y. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. The lancet respiratory medicine. 2020 May 1;8(5):475-81.
2. Suarez-de-la-Rica A, Serrano P, de-la-Oliva R, Sánchez-Díaz P, Molinero P, Falces-Romero I, Ferrando C, Rello J, Maseda E. Secondary infections in mechanically ventilated patients with COVID-19: An overlooked matter? Revista Española de Quimioterapia. 2021;34(4):330.
3. Zhang H, Zhang Y, Wu J, Li Y, Zhou X, Li X, Chen H, Guo M, Chen S, Sun F, Mao R. Risks and features of secondary infections in severe and critical ill COVID-19 patients. Emerging microbes & infections. 2020 Jan 1;9(1):1958-64.
4. Grasselli G, Scaravilli V, Mangioni D, Scudeller L, Alagna L, Bartoletti M, Bellani G, Biagioni E, Bonfanti P, Bottino N, Coloretti I. Hospital-acquired infections in critically ill patients with COVID-19. Chest. 2021 Aug 1;160(2):454-65.
5. Rouzé A, Martin-Loeches I, Povoa P, Makris D, Artigas A, Bouchereau M, Lambiotte F, Metzelard M, Cuchet P, Boulle Geronimi C, Labruyere M. Relationship between SARS-CoV-2 infection and the incidence of ventilator-associated lower respiratory tract infections: a European multicenter cohort study. Intensive Care Medicine. 2021 Feb; 47:188-98.
6. Giacobbe DR, Battaglini D, Ball L, Brunetti I, Bruzzone B, Codda G, Crea F, De Maria A, Dentone C, Di Biagio A, Icardi G. Bloodstream infections in critically ill patients with COVID□19. European journal of clinical investigation. 2020 Oct;50(10):e13319.
7. Buetti N, Ruckly S, de Montmollin E, Reignier J, Terzi N, Cohen Y, Siami S, Dupuis C, Timsit JF. COVID-19 increased the risk of ICU-acquired bloodstream infections: a case–cohort study from the multicentric OUTCOMEREA network. Intensive care medicine. 2021 Feb; 47:180-7.
8. Zhang H, Zhang Y, Wu J, Li Y, Zhou X, Li X, Chen H, Guo M, Chen S, Sun F, Mao R. Risks and features of secondary infections in severe and critical ill COVID-19 patients. Emerging microbes & infections. 2020 Jan 1;9(1):1958-64.
9. Ripa M, Galli L, Poli A, Oltolini C, Spagnuolo V, Mastrangelo A, Muccini C, Monti G, De Luca G, Landoni G, Dagna L. Secondary infections in patients hospitalized with COVID-19: incidence and predictive factors. Clinical Microbiology and Infection. 2021 Mar 1;27(3):451-7.

ISSN:0975 -3583,0976-2833 VOL14, ISSUE 06, 2023

10. Vijay S, Bansal N, Rao BK, Veeraraghavan B, Rodrigues C, Wattal C, Goyal JP, Tadepalli K, Mathur P, Venkateswaran R, Venkatasubramanian R. Secondary infections in hospitalized COVID-19 patients: Indian experience. Infection and drug resistance. 2021; 14:1893.
11. De Bruyn A, Verellen S, Bruckers L, Geebelen L, Callebaut I, De Pauw I, Stessel B, Dubois J. Secondary infection in COVID-19 critically ill patients: a retrospective single-center evaluation. BMC infectious diseases. 2022 Dec;22(1):1-7.