Article published online: 2024-01-16

Original Article

A Retrospective Analysis of Incidence and Risk Factors for the Development of Secondary Infections Following COVID-19

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J Health Allied Sci[NU]

Abstract

Introduction The SARS-CoV-2 virus primarily affects the lungs causing a heightened immune response due to viral and host cell interaction, which prompts the release of proinflammatory cytokines and reduces the defense mechanisms of the immune system, making the patient vulnerable to secondary infections. The study aims to identify the incidence and risk factors for secondary infections developing after COVID-19.

Methods and Materials A retrospective study was conducted on 669 patients who were readmitted after COVID-19 to a tertiary care hospital. The development of secondary infections in these populations was identified. The data were collected from the medical records department.

Statistical Analysis Incidence was calculated by the ratio of the total number of patients who developed secondary infections among readmitted patients divided by the total number of readmitted patients during the study period. Univariate analysis was performed to identify the statistically significant variables that were used in logistic regression for identifying the risk factors for secondary infection. Statistical analysis was performed in SPSS version 28.0.

Results and Discussion In this study, 85 patients were found to have developed secondary infections with an incidence of 12.7%. Among the reported six infections, mucormycosis showed the highest incidence (34.1%), followed by sepsis and urinary tract infection. Nine patients developed tuberculosis as a post-COVID-19 secondary infection. General risk factors for secondary infections include male gender, presence of comorbidities such as diabetes mellitus and chronic kidney disease (CKD), intensive care unit (ICU) admission, elevated levels of interleukin-6 (IL-6) and D-dimer, and administration of steroids particularly medium-dose steroids.

Conclusion Secondary infections can occur within 43 days of COVID-19 infection for every 12.7 per 100 patients in whom there is bacterial or fungal infections. Of these secondary infections, incidence of mucormycosis and sepsis was found to be higher in our study. COVID-19-infected patients who have either of these factors such as elevated inflammatory

Keywords
- post-COVID
- secondary infections
- mucormycosis
- sepsis
- urinary tract infection
- tuberculosis
- post-COVID complications

DOI https://doi.org/10.1055/s-0043-1778667.
ISSN 2582-4287.

Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

markers (Il-6 and D-dimer), the presence of comorbidities such as diabetes mellitus and CKD, ICU admission, and the use of steroids are at risk of developing secondary infections. Through proper screening, we can prevent patients who are at risk of developing secondary infections.

Introduction

COVID-19 had a disastrous impact throughout the world. As of June 21, 2023, 768 million people have been infected and 6 million patients succumbed to COVID-19.[1] COVID-19 can cause mild to moderate respiratory distress, which can last up to a few weeks. However, in some cases, people continue to experience symptoms long after their initial recovery, which may then manifest into some serious complications including recurrence of COVID-19 or infection by other organisms due to reduced immunity of the patient. One in seven COVID-19 patients is at risk of developing secondary infections.[2] SARS-CoV-2 virus binds to angiotensin converting enzyme-2 (ACE-2) present in type 2 alveolar epithelial cells (AEC-II), which triggers the recruitment of macrophages, monocytes, and neutrophils, along with the innate response by T-helper cells.[3] When the virus and host cells react, a heightened immune response is produced, which results in the release of proinflammatory cytokines (such as interleukin-6 [IL-6], interleukin-2, and tumor necrosis factor-α), and anti-inflammatory cytokines (such as interleukin-4 and interleukin-10). This reduces the defense mechanisms of the immune system, making the patient vulnerable to developing secondary infections.[4] Consequently, post-COVID-19 patients are prone to latent bacterial, fungal, or viral reactivation. There have been reports of reactivation of SARS-CoV-2 infection,[5] as well as the development of secondary bacterial and fungal infections,[6] highlighting the prevalent immunosuppression and dysregulation mechanisms. During treatment for primary COVID-19 infection, several factors such as steroid administration, intensive care unit (ICU) admission, ventilator support, and severity of COVID-19 were found to increase the patient's risk of developing secondary infections due to bacteria or fungus.[7] The mortality of secondary infection in patients with severe or critical COVID-19 infection was much higher compared with milder infections.[8] In places with a high burden of multidrug-resistant organisms in ICU settings, such as in India, secondary infections in COVID-19 patients pose a significant challenge in treatment, which leads to increased mortality. The aim of this study is to identify the incidence and elucidate the risk factors for secondary infections after COVID-19.

Materials and Methods

Study Design and Patients

A retrospective study was conducted on 669 patients who were infected with COVID-19 and readmitted to a tertiary care hospital from October 2020 to March 2021. Waiver of consent was obtained from the ethical committee as the patient data were collected from the case files in the medical record department of the hospital.

Data Collection

The patient data were entered into data collection forms, which consist of two sections. The first section contains the patient's demographics and details about their COVID-19 infection, while the second part includes data about secondary infections that are developing. The inclusion criteria were patients readmitted after COVID-19 during the study period, age older than 18 years, measurement of inflammatory markers (IL-6, ferritin, D-dimer, and lactate dehydrogenase [LDH]) during COVID-19 infection, and a minimum hospital stay of 10 days during primary COVID-19 infection. Pregnant women, the pediatric population, and patients who succumbed to COVID-19 infection were excluded from the study.

Outcomes

Patients who have developed secondary infections after the primary COVID-19 infection.

Statistical Analysis

The statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) for Windows, version 28.0 released in 2021 (IBM Corp., Armonk, NY). Continuous variables such as age and number of days were represented as mean ± standard deviation. For elucidation of risk factors, initially univariable analysis was performed to identify statistically significant variables, which were later used in binary logistic regression analysis to identify risk factors for the development of secondary infections and multinominal logistic regression analysis to find out the risk factors for each infection. Patients who did not develop secondary infections were used as reference categories for multinominal logistic regression analysis. A *p*-value less than 0.05 was considered statistically significant. For calculating the incidence of secondary infections, the following formulas were used:

Incidence for secondary infections after COVID-19 = total number of patients who developed secondary infections among the readmitted patients/total number of readmitted patients after COVID-19 during the study period.

Incidence for individual post-COVID sequelae = no. of patients who developed specific secondary infection/total number of patients who developed secondary infections.

Results

In this study, 669 patients were readmitted during the study period, of which a total of 85 patients developed secondary infections after COVID-19. The age of the patients ranged from 24 to 90 years with an average of 56 ± 14.9 years, with male patients nearly double the number of female patients. The duration of hospitalization of patients admitted during the primary COVID-19 infection averaged 10.39 ± 14.1 days. Most patients did not require ICU admission and those who required stayed for an average of 2.68 days. A computed tomography (CT) severity score of less than 12 was seen in the majority of the study population. Lesser number of patients required oxygen supplementation of more than 8 L/min. The study population involved patients with either no comorbidities or the presence of comorbidities such as type 2 diabetes mellitus, hypertension, coronary artery disease (CAD), lung disease, chronic kidney disease (CKD), dyslipidemia, and hypothyroidism as depicted in ►**Table 1**. On checking the laboratory parameters on admission, elevated levels of D-dimer, LDH, IL-6, and ferritin were found in 37.7% ($n = 252$), 37.8% ($n = 253$), 39.3% ($n = 263$), and 56.2% ($n = 376$) patients, respectively. During COVID-19, patients were treated with anticoagulants such as enoxaparin (58.2%, $n = 390$), heparin (4.1%, $n = 28$), the antiviral drug remdesivir (56.1%, $n = 375$), and steroids such as hydrocortisone, methylprednisolone, and prednisolone. The steroids were divided into three categories: high dose (>32 mg), intermediate dose (>16 mg), and low dose (≤8 mg) steroids.

Incidence

Among the readmitted patients, 85 developed secondary infections, reporting an incidence of 12.7%. Six different secondary infections were diagnosed, of which mucormycosis showed the highest incidence followed by sepsis and urinary tract infection (UTI), whereas candidiasis, lower respiratory tract infection (LRTI), and tuberculosis were reported in lower numbers, as shown in ►**Table 2**. Of the 85 patients, 5 (5.8%) developed UTI with sepsis and 7 (8.2%) developed mucormycosis and sepsis. The average number of days for developing post-COVID infections was found to be 47.3 days with a median of 24 days. Additionally, on average, mucormycosis, sepsis, and UTI developed within 37.6, 37.4, and 48.8 days, respectively.

Risk Factors

Variables included for risk factors for the analysis include age, gender, presence of comorbidities such as diabetes mellitus, hypertension, lung disease, CAD, lung disease, CKD, dyslipidemia, hypothyroidism, ICU stay, CT severity score, oxygen supplementation, administration of anticoagulants, remdesivir and steroids, and laboratory parameters such as IL-6, D-dimer, ferritin, and LDH observed during COVID-19 infection. The univariate analyses of the variables showed statistical significance for male gender ($p = 0.01$), comorbidities of diabetes mellitus ($p < 0.001$), CKD ($p < 0.001$), higher CT severity score ($p = 0.001$), need for ICU stay ($p < 0.001$), higher oxygen supplementation ($p < 0.001$), administration of steroids ($p = 0.002$), medium-dose steroids ($p = 0.020$), low-dose steroids ($p = 0.040$), and elevated levels of IL-6 ($p < 0.001$), D-dimer ($p < 0.001$), and LDH ($p < 0.001$).

Binary logistic regression performed to identify risk factors for developing secondary infections, as represented in ►**Table 3**, showed that male gender, comorbidities such as diabetes mellitus, CKD, ICU stay, administration of medium-dose steroids, IL-6, D-dimer, and LDH increased the risk of post-COVID infections. Multinominal logistic regression was performed to identify the risk factors for different secondary infections, which are shown in ►**Table 4**. The risk factors for candidiasis, LRTI, and TB could not be analyzed as they were relatively less.

Mucormycosis

Patients with comorbidity of diabetes mellitus were at an increased risk of developing mucormycosis by 2.14 times ($p = 0.048$). Also, laboratory investigations such as IL-6 and D-dimer increased the risk of developing mucormycosis by 3.63 times ($p = 0.002$) and 2.40 times ($p = 0.022$), respectively.

Sepsis

The presence of comorbid conditions of diabetes mellitus and male gender significantly increased the risk by 2.57 ($p = 0.045$) and 3.6 times ($p = 0.046$), respectively. The lower limit of the odds ratio for male gender was less than 1 and therefore it cannot be considered a risk factor. ICU admission and elevated D-dimer levels during COVID-19 increased the risk by 14.20 times ($p < 0.0001$) and 2.76 times ($p = 0.043$), respectively, for developing sepsis.

Urinary Tract Infection

The patients with comorbid conditions of CKD had an increased risk of developing UTI by 14.96 times ($p = 0.007$). Admitted to the ICU ward and administration of steroids during COVID-19 increased the risk of UTI by 5.20 times ($p = 0.040$) and 4.4 times ($p = 0.039$), respectively.

Tuberculosis

The novel finding of the study was the identification of patients developing tuberculosis, which was observed in nine patients, whose details are specified in ►**Table 5**. On average, tuberculosis developed within 101.1 ± 89 days after COVID-19 infection. The mean age of patients was 56 ± 14 days, with male patients outnumbering the female patients. Diabetes mellitus is the most common comorbid among patients who develop tuberculosis. All patients had a CT severity score of more than 18/25. Of the nine tuberculosis patients, an 82-year-old male patient who was a diabetic succumbed to tuberculosis.

Candidiasis

All the seven patients who developed candidiasis were elderly, with males ($n = 6$) outnumbering females ($n = 1$). On average, candidiasis developed within 14.9 ± 8.2 days of COVID-19 infection. Apart from one patient, all of them had a comorbidity of diabetes mellitus.

Table 1 Demographics of the study population

Characteristics	Parameters	No. of patients ($N = 669$)	Percentage
Age (y)	<60	393	58.7
	>60	276	41.3
Gender	Male	431	64.4
	Female	238	35.6
CT severity score (X/25)	<12	423	63.2
	>12	246	36.8
Oxygen supplementation	<8 L/min	528	79
	>8 L/min	141	21
Comorbidities	Type 2 diabetes mellitus	272	40.7
	Hypertension	210	31.4
	Coronary artery disease	49	7.3
	Lung disease	61	9.2
	Chronic kidney disease	19	2.8
	Dyslipidemia	18	2.7
	Hypothyroidism	41	6.1
	None	258	38.6
Intensive care unit (ICU) stay	Yes	152	22.7
	No	517	77.3
Steroids	High dose	322	48.1
	Medium dose	189	28.3
	Low dose	46	6.9
	None	112	16.7
Serum ferritin	<300 ng/mL	293	43.8
	>300 ng/mL	376	56.2
Interleukin-6	<50 pg/mL	406	60.7
	>50 pg/mL	263	39.3
D-dimer	<1 mg/L	417	62.3
	>1 mg/L	252	37.7
Serum lactate dehydrogenase	<333 U/L	416	62.2
	>333 U/L	253	37.8

Table 2 Incidence of secondary infections after COVID-19

Post-COVID infectious complications	No. of patients ($n = 85$)	Percentage
Mucormycosis	29	34.1
Sepsis	27	31.8
Urinary tract infections	18	21.2
Tuberculosis	9	10.6
Candidiasis	7	8.2
Lower respiratory tract infections	7	8.2

*Among the 85 patients, 5 patients had developed both urinary tract infection and sepsis and 7 patients had developed mucormycosis and sepsis.

Table 3 Risk factors for secondary infections calculated using binary logistic regression

Variables	Odds ratio (lower limit–upper limit)	*p*-value
Diabetes mellitus	1.98 (1.22–3.20)	0.005
Chronic kidney disease	3.1 (1.10–8.73)	0.032
Intensive care unit (ICU) stay	2.37 (1.42–3.94)	0.001
Interleukin-6	2.34 (1.43–3.83)	0.001
D-dimer	2.3 (1.42–3.71)	0.001
Administration of steroids	2.13 (1.35–4.31)	0.035
Gender	2.01 (1.16–3.48)	0.013
Medium-dose steroids	2.41 (1.14–5.08)	0.02
Low-dose steroids	0.23 (0.03–1.82)	0.16

Table 4 Risk factors for individual secondary infections calculated using multinominal logistic regression

Complications	Risk factors	Odds ratio	*p*-value
Mucormycosis	Diabetes mellitus	2.14 (1.17–4.56)	0.048
	D-dimer	2.40 (1.14–5.08)	0.022
	Interleukin-6	3.63 (1.58–8.34)	0.002
Sepsis	Diabetes mellitus	2.57 (1.24–6.99)	0.045
	Intensive care unit (ICU) stay	14.20 (3.73–54)	$<$0.0001
	D-dimer	2.76 (1.3–7.37)	0.043
	Female sex	3.6 (0.98–6.61)	0.046
Urinary tract infection	Chronic kidney disease	14.96 (2.10–106.36)	0.007
	ICU stay	5.20 (1.25–34.48)	0.04
	Administration of steroids	4.4 (1.19–23.8)	0.039

Table 5 Characteristics of post-COVID tuberculosis patients

Age (y)	Gender	Incidence of tuberculosis after COVID-19 infection (d)	Comorbid conditions	CT severity score (X/25)
38	Female	24	Diabetes mellitus, asthma	Moderate (8–18/25)
63	Male	57	Diabetes mellitus	Severe (19–25/25)
58	Female	155	Diabetes mellitus, chronic kidney disease	Moderate (8–18/25)
61	Male	166	Diabetes mellitus	Moderate (8–18/25)
82	Male	10	Diabetes mellitus	Severe (19–25/25)
59	Male	11	Ischemic heart disease	Severe (19–25/25)
36	Male	64	None	Moderate (8–18/25)
45	Male	264	None	Severe (19–25/25)
47	Male	46	Diabetes mellitus	Moderate (8–18/25)

Lower Respiratory Tract Infection

The mean age of the seven patients who developed LRTI was 58 ± 18 years, where the number of males (4) were greater than females (3). On average, LRTI developed within 73.1 ± 49.5 days of COVID-19 infection. Comorbidities such as diabetes mellitus, asthma, and hypertension were seen in the patients who developed LRTI.

Discussion

In this study, the incidence of secondary infections was found to be 12.7 per 100 patients who were infected with COVID-19. Among the secondary infections, the incidence of mucormycosis and sepsis was the highest in fungal and bacterial infections, respectively. Nine patients developed tuberculosis. Predisposing factors to the development of secondary infections include male gender, comorbidities such as CKD, diabetes mellitus, ICU stay, elevated laboratory values such as D-dimer and IL-6, and administration of steroids.

Incidence

The incidence of secondary infections found in the study was 12.7%, which is comparatively higher than the findings in Ceccarelli et al where the incidence of secondary infections among post-COVID patients was 1.86%.[9] Other studies have estimated the incidence of the development of bacterial and fungal infections after COVID-19 infection at 2.23 and 8%, respectively.[10,11] The mean time span for the incidence of post-COVID infections is 47.3 days, which is greater than the 10.6 days reported in a retrospective cohort study.[12]

The incidence of sepsis was found to be 31.8%, which is higher compared with another study conducted by Yoon et al, which reported an incidence of 6.6%.[13] The incidence of LRTI in our study was 8.2%, which is lower than the 21.6% reported in other studies. This could be due to the similarity of clinical manifestations in COVID-19 and LRTI.[13] The incidence of UTI estimated in this study was 21.2%, which is comparatively higher than the 1.52% reported in another study.[9] Candidiasis was observed in 8.2% of the subjects in this study, which is higher compared with the observational study conducted by Tiseo et al who estimated the incidence of post-COVID candidiasis to be 2.7% among 983 subjects.[14] The incidence of mucormycosis was 34.1% in this study, while Selarka et al reported an incidence of 1.8% in a population of 2,567 subjects.[15] A novel finding of this study was the incidence of tuberculosis in nine patients, giving an incidence of 10.6%. A systemic review by Alemu et al reported this incidence to be 33%, among subjects from 13 countries from where data were collected.[16]

Risk Factors

The overall risk factors observed for secondary infections include male gender, comorbidities such as diabetes mellitus and CKD, elevated laboratory values (such as IL-6, D-dimer), ICU admission, and administration of steroids particularly at medium dose. Risk factors for the development of post-COVID infections were found to be D-dimer levels greater than 1 µg/mL,[4] comorbidities of diabetes mellitus, use of corticosteroids, and ICU admission.[17]

Mucormycosis

In our study, the presence of diabetes mellitus and higher levels of IL-6 and D-dimer were found to increase the risk of developing mucormycosis. According to the Directorate General of Health Services (DGHS) guidelines, risk factors include comorbid conditions of diabetes mellitus and irrational use of steroids in managing primary COVID-19 infection.[18] Nayak et al showed elevated levels of D-dimer to be risk factors in precipitating infection.[19] Another study revealed that high IL-6 levels were associated with COVID-associated mucormycosis.[20] Therefore, the presence of comorbidity of diabetes mellitus, and laboratory investigations such as IL-6 and D-dimer could be the potential risk factors for the development of post-COVID Mucormycosis.

Sepsis

Our study shows that the patients who needed ICU admission, had comorbidity of diabetes mellitus, and elevated D-dimer levels had increased risk of sepsis. Studies have shown the need for ICU stay,[9] comorbidities of diabetes mellitus,[21] and elevated levels of D-dimer[22] are risk factors for developing sepsis. Therefore, we can elucidate that patients who are diabetic, require ICU admission, and have elevated D-Dimer levels can develop sepsis.

Urinary Tract Infections

The presence of comorbid conditions of CKD, the need for ICU admission, and the use of steroids were identified as risk factors for UTI. The presence of risk factors such as CKD,[23] administration of steroids such as methylprednisolone,[24] and ICU stay[25] were more prone to develop UTIs. Hence, it is evident that the risk factors for the development of UTI are comorbidity of CKD, steroid administration, and ICU stay.

Tuberculosis

Nine patients in this study were diagnosed with tuberculosis, of which all the patients except two had underlying comorbid conditions such as diabetes mellitus, and had a moderate to severe CT severity score. Similar to these findings, according to a study by Motta et al, older patients with multiple comorbidities, particularly diabetes mellitus, are at risk of developing post-COVID tuberculosis and subsequent mortality.[26]

Candidiasis

Although we were not able to isolate risk factors for candidiasis, it was seen that diabetes mellitus was present in most of the patients. Risk factors for oral candidiasis after COVID-19 include comorbid conditions such as diabetes mellitus.[27] The duration between COVID-19 infection and incidence of oral candidiasis was found to be 15 days in this study, which was higher compared with another study where the duration was found to be 10 days.[27]

Lower Respiratory Tract Infection

For LRTIs, we found a higher number of patients had comorbidities of hypertension, asthma, and diabetes mellitus occurring after 73 days of COVID-19 infection. Bhaskaran et al reported that LRTI usually precipitates about a week after being discharged for COVID-19 infection, with most patients having at least one preexisting comorbid condition.[28]

This study does, however, have certain limitations. It was conducted after the first wave of COVID-19 and does not account for the complications that developed after the second wave as a higher number of complications were reported. Also, this being

a retrospective study, some of the files did not contain complete data of the patients.

Conclusion

Secondary infections can occur within 43 days of COVID-19 infection in 12.7 of 100 patients. Both bacterial and fungal infections can occur after COVID-19 in which the incidence of mucormycosis and sepsis are predominant. The presence of comorbidities of diabetes mellitus and CKD makes the patient susceptible to developing secondary infections. Also, a higher CT severity score, higher levels of inflammatory markers such as IL-6 and D-dimer, and administration of steroids can adversely weaken the immune system further, increasing patient vulnerability to infections. Through proper screening of patients, we can identify the patients at risk of developing secondary infections after COVID-19 and prevent the development of post-COVID infections through routine follow-up visits.

Ethical Approval

The study was approved by the Institutional Human Ethics Committee on April 28, 2022 (Reference number: 22/101). The study was conducted in accordance with the Declaration of Helsinki.

Author Contributions

All the authors were involved in the conception and design of the study, data collection, and manuscript preparation. R.P., S.K.G., T.S., and R.G. were involved in the literature review and data analysis/statistical analysis of the study. All the authors have reviewed and approved the final version of the manuscript.

Funding

None.

Conflict of Interest

None declared.

Acknowledgments

We wish to express our gratitude to the HOD of the Department of Pharmacy Practice, and the Principal of PSG College of Pharmacy, Coimbatore, for their encouragement and support. This project could not have been completed without the resources provided by the Medical Records Department of PSG Hospitals, Coimbatore.

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