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Incidence and risk factors for secondary pulmonary infections in patients hospitalized with coronavirus disease 2019 pneumonia

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ABSTRACT

Background: Secondary pulmonary infections (SPI) have not been well described in COVID-19 patients. Our study aims to examine the incidence and risk factors of SPI in hospitalized COVID-19 patients with pneumonia.

Methods: This was a retrospective, single-center study of adult COVID-19 patients with radiographic evidence of pneumonia admitted to a regional tertiary care hospital. SPI was defined as microorganisms identified on the respiratory tract with or without concurrent positive blood culture results for the same microorganism obtained at least 48 h after admission.

Results: Thirteen out of 244 (5%) had developed SPI during hospitalization. The median of the nadir lymphocyte count during hospitalization was significantly lower in patients with SPI as compared to those without SPI [0.4 K/uL (IQR 0.3−0.5) versus 0.6 K/uL (IQR 0.3−0.9)]. Patients with lower nadir lymphocyte had an increased risk of developing SPI with odds ratio (OR) of 1.21 (95% CI: 1.00 to 1.47, \(p = 0.04\)) per 0.1 K/uL decrement in nadir lymphocyte. The baseline median inflammatory markers of CRP [166.4 mg/L vs. 100.0 mg/L, \(p = 0.01\)] and D-dimer (18.5 mg/L vs. 1.4 mg/L, \(p < 0.01\)), and peak procalcitonin (1.4 ng/mL vs. 0.3 ng/mL, \(p < 0.01\)) and CRP (273.5 mg/L vs. 153.7 mg/L, \(p < 0.01\)) during hospitalization were significantly higher in SPI group.

Conclusions: The incidence of SPI in hospitalized COVID-19 patients was 5%. Lower nadir median lymphocyte count during hospitalization was associated with an increased OR of developing SPI. The CRP and D-dimer levels on admission, and peak procalcitonin and CRP levels during hospitalization were higher in patients with SPI.

Keywords: Severe acute respiratory syndrome coronavirus 2; SARS-CoV-2; Coronavirus disease 2019; COVID-19; Secondary bacterial infections; Secondary pulmonary infections. [Am J Med Sci 2022;363(6):476–483.]

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Since it was first recognized in December 2019, it has resulted in the ongoing worldwide pandemic. COVID-19 primarily presents as a respiratory infection with symptoms varying from mild flu-like illness and pneumonia to acute respiratory distress syndrome (ARDS).\(^1\)\(^2\) Influenza and severe acute respiratory syndrome coronavirus (SARS-CoV) responsible for prior large outbreaks have been frequently reported to have secondary bacterial and fungal infections.\(^3\)\(^5\) While co-infection with other respiratory viral pathogens have been frequently identified in COVID-19 patients,\(^6\) secondary bacterial and fungal infections have not been well described in patients with COVID-19 pneumonia.\(^7\)\(^11\) In this study, we examined the incidence and risk factors of secondary pulmonary infections (SPI) in hospitalized COVID-19 patients with radiographically-confirmed pneumonia.

METHODS

This was a retrospective, single-center study of adult patients admitted to a regional tertiary care hospital. American College of Surgery COVID-19 Registry at Albany Medical Center was used to identify COVID-19 patients. This study was approved by the Institutional...
Review Board at Albany Medical Center. Patients with COVID-19 infection were enrolled between March 8th to June 22nd, 2020. COVID-19 infection was diagnosed via real-time reverse transcription-polymerase chain reaction (RT-PCR) from a nasopharyngeal swab in all patients. Patients with COVID-19 included in the study were aged 18-years and older and had radiographic confirmation of COVID-19 pneumonia on chest radiograph (CXR), or chest computed tomography (CT) during admission. SPI was defined as microorganisms identified on the respiratory tract with or without concurrent positive blood culture results for the same microorganism obtained at least 48 h after admission. Based on the treating clinician’s judgment, when SPI were suspected, respiratory tract cultures were obtained from either the sputum and/or endotracheal aspirate of COVID-19 patients during their duration of hospitalization irrespective of inpatient setting (ICU versus medical floor). This assessment was based on a change in clinical status involving a decline in respiratory status (increasing oxygen requirement, respiratory secretions and purulence, or respiratory distress), new-onset of unexplained fever, new-onset or worsening lung infiltrates on chest imaging that was unresponsive to diuretic, increasing vasopressor requirements, and/or worsening inflammatory markers involving erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and white cell count (WBC) that could not be contributed to underlying COVID-19 infection. Sputum samples were expectorated by non-critically ill COVID-19 patients while being isolated in a negative pressure room on the medical floor, but not induced with nebulized hypertonic saline due to the fear of aerosolization and further transmission to healthcare providers. In those who were critically ill, endotracheal aspirates were obtained by respiratory therapists by passing a new suction catheter into the endotracheal tube. If respiratory therapists were unable to initially suction adequate secretions, five ml of normal saline was injected into the endotracheal tube, and a repeat attempt was made. Respiratory specimens obtained were sent for Gram stain and culture. The choice, timing of initiation, and duration of antibiotic therapy were at the discretion of the treating clinician. We excluded COVID-19 patients as having secondary infections if 1) microorganisms identified were commonly associated with contaminants in both respiratory tract and blood cultures, 2) had an isolated positive blood culture result. Pulmonary co-infection was defined as microorganisms identified on respiratory tract culture with or without concurrent positive blood culture obtained within 48 h from admission.

The data collection was obtained by chart review of our hospital electronic medical records of COVID-19 patients. The following data elements acquired for each patient were: age; sex; ethnicity; first recorded body mass index (BMI); comorbidities such as heart disease (congestive heart failure and coronary arterial disease), lung disease (chronic obstructive pulmonary disease [COPD] and asthma), diabetes mellitus, end-stage renal disease (ESRD), smoking history, history of cancer and immunodeficiency; social origin (home or nursing home); laboratory parameters on admission involving inflammatory markers such as ferritin, CRP, d-dimer, lactate dehydrogenase (LDH), and WBC on admission.\(^{7-11}\) peak procalcitonin and CRP levels, and nadir lymphocyte count during hospitalization; highest respiratory support required such as nasal cannula, high-flow nasal cannula, and mechanical ventilation; requirement of intensive care unit (ICU); and treatment received during hospitalization involving hydroxychloroquine, antibiotics, corticosteroid, remdesivir, and convalescent plasma. The primary objective of our study was to determine the incidence and risk factors for SPI in hospitalized COVID-19 patients with pneumonia. The secondary objective was to describe the microorganisms identified in the respiratory tract culture from sputum and endotracheal aspirate. We also compared the median time to positivity of respiratory tract cultures (with or without concurrent blood cultures) after admission.

**Statistical analysis**

The continuous data were summarized by the mean and standard deviation (SD) or median and interquartile range (IQR) or range as appropriate. Statistical inference is by Student’s t-test or Mann-Whitney (MW) non-parametric test with significance accepted at \(p<0.05\). Categorical data were presented as numbers and percentages with inference by the Chi-Square test or Fisher’s exact test if the expected value in any cell is less than five. Binary logistic regression was used to estimate odds ratios with 95% confidence intervals. Minitab statistical software was used.

**RESULTS**

There were 337 COVID-19 patients admitted during the study period of March 8th to June 22nd, 2020. We excluded 93 COVID-19 patients who did not have any radiographic evidence of pneumonia (Fig. 1). Thirteen out of 244 (5%) COVID-19 patients with radiographic evidence of pneumonia had developed SPI during hospitalization. Among the 231 COVID-19 patients without SPI, eight patients had bacterial co-infections on respiratory tract culture, and two patients had rhinovirus co-infections shown in Fig. 1. Table 1 described the baseline characteristics of those with SPI compared to those without SPI in hospitalized COVID-19 patients with pneumonia. Most of the baseline characteristics were similar, except the majority of COVID-19 patients with SPI had higher baseline inflammatory markers of CRP (166.4 mg/L vs. 100.0 mg/L, \(p=0.01\)) and d-dimer (18.5 mg/L vs. 1.4 mg/L, \(p<0.01\)) when compared to those without SPI. Moreover, patients with SPI frequently required intensive care unit (ICU) level of care (92% vs. 46%, \(p<0.01\)) and mechanical ventilation (85% vs. 26%, \(p<0.01\)) compared to those without SPI.
During hospitalization, COVID-19 patients with SPI have higher peak procalcitonin (1.4 ng/mL vs. 0.3 ng/mL, \( p < 0.01 \)) and CRP (273.5 mg/L vs. 153.7 mg/L, \( p < 0.01 \)) levels than those without SPI. The median of the nadir lymphocyte count during hospitalization was significantly lower in COVID-19 patients with SPI than those without SPI at 0.4 K/uL (IQR 0.3−0.5) and 0.6 K/uL (IQR 0.3−0.9), respectively (Fig. 2). Patients with lower nadir lymphocyte had an increased risk of developing SPI with an odds ratio (OR) of 1.21 per 0.1 K/uL decrement in nadir lymphocyte (95% CI: 1.00 to 1.47, \( p = 0.04 \)). All patients with SPI had nadirs of less than or equal to 0.8 K/uL. Although all nadir lymphocyte counts greater than 0.9 K/uL were seen in patients without SPI, many patients without SPI had nadir lymphocyte counts less than 0.8 K/uL.

There were thirteen bacterial microorganisms isolated on the respiratory tract cultures after 48 h of hospitalization (Table 2). The median time to positivity of respiratory tract cultures (with or without concurrent blood cultures) in those with SPI was 9.3 days (IQR 4.6−17). All of the SPI was bacterial in origin, and none were fungal. Out of the thirteen bacterial microorganisms identified, the most common etiologies for bacterial infections were Haemophilus influenzae and Klebsiella pneumoniae in 46% of COVID-19 patients. Of those with positive respiratory tract cultures (Table 2), three out of thirteen (23%) COVID-19 patients had concurrent bacteremia involving Pseudomonas aeruginosa and Methicillin-Sensitive Staphylococcus aureus (MSSA). COVID-19 patients with SPI had significantly less 30-day hospital-free days [median 5 days (IQR 0−12)] than those without SPI [median 19 days (IQR 9–24), \( p < 0.01 \)]. However, there was no difference in all-cause hospital mortality between the two groups (\( p = 0.19 \)).

**DISCUSSION**

In our analysis of 244 COVID-19 patients with pneumonia, we found an incidence of SPI was 5% (13/244). COVID-19 patients with SPI had a significantly higher level of inflammatory markers such as CRP and D-dimer at baseline, and peak procalcitonin and CRP levels during hospitalization. Although many COVID-19 patients from both cohorts had low nadir lymphocyte count during hospitalization, those with SPI were found to have lower nadir lymphocyte count, with every 0.1 K/uL decrement increased the odds of SPI by 1.21 (95% CI: 1.00 to 1.47, \( p = 0.04 \)). Conversely, higher nadir lymphocyte counts were observed in patients without SPI. A higher proportion of COVID-19 patients with SPI required ICU admission and mechanical ventilation than those without SPI.

Many observational studies have described an incidence rate ranging from 5 to 19% for SPI in COVID-19 patients, which are often limited due to their variable criteria and sample size (Table 3).7−11 The major limitation of these studies was the lack of a clear definition of secondary infections and co-infections. There was also a lack of information on the risk factors associated with secondary infections, the specific types of microorganisms identified, how they were specifically obtained, duration of hospitalization after which they developed secondary infections, and associated outcomes. Compared to other viral-related respiratory infections responsible for prior large outbreaks, a meta-analysis of influenza patients revealed that 11–35% of critically ill patients developed secondary bacterial pulmonary infections.3,5 In severe acute respiratory syndrome coronavirus (SARS-CoV) infection, around 22% of patients developed secondary bacterial and fungal infections;

**FIGURE 1.** Flowchart for hospitalized COVID-19 patients enrolled in the study.
TABLE 1. Clinical characteristics of hospitalized COVID-19 patients.

| Variables                      | Total N = 244 | No secondary infection N = 231 | Secondary infection N = 13 | P-value |
|--------------------------------|---------------|--------------------------------|---------------------------|---------|
| Age-Years: Mean, Median (IQR)  | 62.3, 63.0 (51.0–75.0) | 62.3, 63.0 (51.0–76.0) | 62.2, 62.0 (54.5–71.5) | 0.98*** |
| Sex, N (%)                     |               |                                |                           |         |
| Male                           | 148 (61%)     | 140 (61%)                      | 8 (62%)                   | 0.95**  |
| Female                         | 96 (39%)      | 91 (39%)                       | 5 (38%)                   |         |
| Ethnicities, N (%)             |               |                                |                           |         |
| White                          | 120 (49%)     | 116 (50%)                      | 4 (31%)                   | 0.09    |
| Black                          | 63 (26%)      | 59 (25%)                       | 4 (31%)                   |         |
| Asian                          | 16 (7%)       | 13 (6%)                        | 3 (23%)                   |         |
| Other                          | 45 (18%)      | 43 (19%)                       | 2 (15%)                   |         |
| BMI- Kg/m²: Mean, Median (IQR) | 29.7, 28.5 (24.6–32.6) | 29.6, 28.3 (24.5–32.4) | 32.0, 31.0 (28.8–36.1) | 0.08*   |
| Comorbidities, N (%)           |               |                                |                           |         |
| Heart Disease                  | 47 (19%)      | 46 (20%)                       | 1 (8%)                    | 0.32    |
| Lung Disease                   | 59 (24)       | 55 (24%)                       | 4 (31%)                   | 0.74    |
| Diabetes Mellitus              | 96 (39%)      | 91 (39%)                       | 5 (38%)                   | >0.99   |
| ESRD                           | 7 (3%)        | 7 (3%)                         | 0 (0%)                    | >0.99   |
| Cancer                         | 3 (1%)        | 3 (1%)                         | 0 (0%)                    | >0.99   |
| History of Smoking             | 41 (17%)      | 39 (17%)                       | 2 (15%)                   | >0.99   |
| Immunodeficiency               | 20 (8%)       | 20 (9%)                        | 0 (0%)                    | 0.4     |
| Social Origin, N (%)           |               |                                |                           | 0.55****|
| Home                           | 95 (39%)      | 94 (41%)                       | 1 (8%)                    |         |
| Nursing Home/Chronic Care Facility | 52 (21%)  | 50 (21%)                       | 2 (15%)                   |         |
| Not Reported                   | 97 (40%)      | 87 (38%)                       | 10 (77%)                  |         |
| ICU Requirement, N (%)         |               |                                |                           | <0.01   |
| ICU                            | 118 (48%)     | 106 (46%)                      | 12 (92%)                  |         |
| Non-ICU                        | 126 (52%)     | 125 (54%)                      | 1 (8%)                    |         |
| Respiratory Support, N (%)     |               |                                |                           | <0.01   |
| Room Air                       | 28 (11%)      | 28 (12%)                       | 0 (0%)                    |         |
| Nasal Cannula                  | 127 (53%)     | 125 (54%)                      | 2 (15%)                   |         |
| High-Flow Nasal Cannula        | 18 (7%)       | 18 (8%)                        | 0 (0%)                    |         |
| Mechanical Ventilation         | 71 (29%)      | 60 (26%)                       | 11 (85%)                  |         |
| Treatment, N (%)               |               |                                |                           |         |
| Hydroxychloroquine             | 159 (65%)     | 150 (65%)                      | 9 (69%)                   | >0.99   |
| Antibiotics                    | 205 (84%)     | 193 (84%)                      | 12 (92%)                  | 0.7     |
| Remdesivir                     | 2 (1%)        | 2 (1%)                         | 0 (0%)                    | >0.99   |
| Corticosteroid                 | 216 (89%)     | 204 (88%)                      | 12 (92%)                  | >0.99   |
| Convalescent Plasma            | 74 (30%)      | 67 (29%)                       | 7 (54%)                   | 0.07    |
| Inflammatory Markers, Mean, Median (IQR) |            |                                |                           |         |
| On Admission:                  |               |                                |                           |         |
| Ferritin (ng/mL)               | 815.0, 446.0 (239.0–1049.0) | 810.6, 432.0 (221.0–1049.0) | 889.8, 754.0 (534.5–1086.0) | 0.05*  |
| CRP (mg/L)                     | 127.0, 105.4 (36.5–189.0) | 123.1, 100.0 (35.3–186.3) | 195.5, 166.4 (123.8–287.8) | 0.01*  |
| D-dimer (mg/L)                 | 11.6, 1.5 (0.8–5.6) | 10.6, 1.4 (0.8–4.8)           | 26.5, 18.5 (1.6–49.2)     | <0.01*  |
| LDH (IU/L)                     | 362.1, 312.5 (255.8–419.5) | 356.7, 310.0 (224.0–415.0) | 453.3, 340.0 (298.5–521.3) | 0.10*  |
| WBC (K/uL)                     | 11.7, 7.4 (5.2–10.7) | 11.8, 7.3 (5.2–10.3)          | 11.0, 10.7 (6.8–15.2)     | 0.03*   |
| Lymphocyte Count (K/uL)        | 1.1, 0.8 (0.6–1.3) | 1.1, 0.8 (0.6–1.3)            | 0.8, 0.9 (0.4–1.0)        | 0.35*   |
| During Hospitalization:        |               |                                |                           |         |
| Peak Procalcitonin (ng/mL)     | 3.3, 0.4 (0.1–1.4) | 3.1, 0.3 (0.1–1.4)           | 5.5, 1.4 (0.6–6.3)        | <0.01*  |
| Lowest Lymphocyte Count (K/uL) | 0.8, 0.6 (0.3–0.9) | 0.8, 0.6 (0.3–0.9)           | 0.4, 0.4 (0.3–0.5)        | 0.03*   |
| Time to Lowest Lymphocyte Count (Days) | 3.0, 1.0 (0.0–4.0) | 2.9, 1.0 (0.0–3.0)         | 5.3, 3.5 (1.3–7.3)        | 0.02*   |
| Peak CRP (mg/L)                | 171.4, 159.9 (78.9–252.8) | 166.4, 153.7 (68.5–247.4) | 260.2, 273.5 (151.6–353.6) | <0.01*  |

P values by Fisher’s Exact test unless otherwise reported.

* Mann-Whitney Test.
** Chi-Square test.
*** Student’s t-test.
**** Test compares home versus nursing home without regarding the missing.
however, this data was published in non-English literature. The lower incidence of SPI in our study could be due to the lack of routine surveillance cultures and the high threshold of obtaining cultures to minimize exposures with COVID-19 patients. There was no significant difference in demographics, comorbidities, and treatment received in COVID-19 patients with SPI and those without SPI.

The lower nadir lymphocyte count was a significant risk factor for the development of SPI. Every 0.1 K/uL decrement in nadir lymphocyte count increased the odds of SPI by 1.21. This is the first study that examined lymphocytopenia as a risk factor for SPI to the best of our knowledge. However, multiple studies have regarded lymphocytopenia as one of the hallmarks of COVID-19 regardless of underlying secondary infections. High lymphocyte counts may be protective against SPI in COVID-19 patients, as shown in Fig. 2. Lymphocytopenia commonly occurs within two weeks from COVID-19 presentation and may result in an immunodeficiency state that can promote secondary infections. We found that the median days to reach nadir lymphocyte after admission was around three to four days (Table 1). It is also possible that the widespread use of corticosteroids in our study may have contributed to the development of lymphocytopenia. With recent studies showing the effectiveness of corticosteroid therapy in hospitalized patients with COVID-19 pneumonia, there is a theoretical concern for increased risk of developing secondary infections with the use of corticosteroids. However,

![FIGURE 2.](image)

**FIGURE 2.** Lymphocyte nadir was significantly less (Mann-Whitney, *p* = 0.03) in patients with secondary pulmonary infections (SPI). Data points were plotted on the left. In the box plots, the central rectangle spans the first quartile to the third quartile (the interquartile range or IQR) with the horizontal line within the rectangle marking the median. The square symbol marks the mean. The “whiskers” above and below the box are drawn to the furthest point within 1.5 x IQR from the box (the non-outlier range) with “X” marking outliers.

### TABLE 2. Microorganisms isolated from respiratory tract and concurrent blood cultures of COVID-19 patients.

| Microorganisms identified        | Patients (N) | Sources (N) | Median Time to Positivity of Cultures After Admission (Days) |
|---------------------------------|--------------|-------------|-------------------------------------------------------------|
| Haemophilus influenzae*          | 3            | (3) Respiratory Culture | 2                                                          |
| Klebsiella pneumoniae*           | 3            | (3) Respiratory Culture | 17                                                         |
| Corynebacterium striatum*        | 2            | (2) Respiratory Culture | 6                                                          |
| Enterobacter cloacae             | 2            | (2) Respiratory Culture | 6                                                          |
| Klebsiella aerogenes             | 2            | (2) Respiratory Culture | 14                                                         |
| Methicillin-Resistant Staphylococcus aureus | 2            | (2) Respiratory Culture | 17                                                         |
| Methicillin-Sensitive Staphylococcus aureus** | 2            | (2) Respiratory Culture, (1) Blood Culture | 9                                                          |
| Pseudomonas aeruginosaa**        | 2            | (2) Respiratory Culture, (1) Blood Culture | 10                                                         |
| Citrobacter freundii*            | 1            | (1) Respiratory Culture | 25                                                         |
| Moraxella catarrhalis*           | 1            | (1) Respiratory Culture | 2                                                          |

*Two or more microorganisms identified in the same respiratory culture from more than one COVID-19 patient.

**Microorganism found in both respiratory and blood cultures.*
our study was not powered or designed to assess the association with the use of corticosteroids in the development of SPI, given that 89% of our patients received corticosteroids. We also did not observe any difference in the incidence of SPI among COVID-19 patients who had comorbidity of immunodeficiency compared to those who were not immunodeficient (Table 1).

Procalcitonin level has been used to guide the identification of secondary bacterial infection in patients with viral pneumonia. However, procalcitonin levels are frequently elevated in COVID-19 patients irrespective of secondary bacterial infections. Du et al. have suggested based on a study of 179 COVID-19 patients with pneumonia, high concentrations of CRP and procalcitonin levels may be used to diagnose secondary bacterial infections. However, there was a lack of clear information on when the CRP and procalcitonin levels were exactly obtained in this observational study. In our study, we did find a significant difference in peak procalcitonin levels in patients with SPI. Furthermore, COVID-19 patients with an elevated CRP level on admission were associated with an increased risk of developing secondary bacterial pulmonary infections. The findings of high CRP levels on admission as a predictor of secondary bacterial infections, especially pulmonary in origin, have been well-described in influenza patients, but not in COVID-19 patients.

The microorganisms identified in our study were similar to those identified in the respiratory tract and blood culture on other observational studies of COVID-19 patients (Table 1). No evidence of fungal microorganisms was identified in the respiratory tract and blood cultures in our study. Chen et al. and Yang et al. have reported fungal infections in the respiratory tract and/or blood cultures in their study. Still, it is unclear whether these microorganisms are related to central line-associated bloodstream infections or colonization of airways (tissue invasion was not assessed with Aspergillus infection). Torrego et al. reported that microorganisms identified in critically ill COVID-19 patients are no different from microorganisms isolated in critically ill non-COVID-19 patients suffering from other respiratory illnesses.

The majority of patients with COVID-19 pneumonia in our study were treated with empiric antibiotics (84%), these findings are identical to previously published data (71–100%) in Table 3. This could be due to the lack of specificity in clinical and radiographic features of COVID-19 pneumonia, which are not helpful in distinguishing between COVID-19 and secondary bacterial infection-related pneumonia. Based on the low incidence of SPI in our study, which was similar to the rate of secondary infections seen in other observational studies (Table 3), empirical antibiotic therapy may not be warranted in all hospitalized COVID-19 patients. Nevertheless, it is also possible that empirical antibiotic therapy could have caused the low incidence rate of secondary infections in various observation studies. Studies

| Study          | Total Patients (N) | Incidence Rate (%) | Region     | Specimen                          | Most Common Bacterial Microorganisms | Most Common Fungal Microorganisms |
|----------------|-------------------|--------------------|------------|-----------------------------------|--------------------------------------|----------------------------------|
| Zhou et al.    | 191               | 15                 | China      | Respiratory Tract and Blood Culture | Not Described                        | Not Described                    |
| Chen et al.    | 99                | 5                  | China      | Not Described                     | Acinetobacter baumannii, Klebsiella pneumoniae | Candida glabrata, Candida albicans, Aspergillus flavus |
| Yang et al.    | 52                | 13                 | China      | Respiratory Tract and Blood Culture | Klebsiella pneumoniae, Pseudomonas aeruginosa, Staphylococcus aureus | Aspergillus flavus, Aspergillus fumigatus |
| Huang et al.   | 41                | 10                 | China      | Respiratory Tract and Blood Culture | Not Described                        | Not Described                    |
| Du et al.      | 179               | 5                  | China      | Respiratory Tract                 | Klebsiella pneumoniae, Acinetobacter baumannii, Escherichia coli | Not Described                    |
| Torrego et al. | 93                | 19                 | Spain      | Respiratory Tract                 | Pseudomonas aeruginosa, Staphylococcus aureus, Enterobacter species | Not Described                    |
| Current Study  | 244               | 5                  | USA        | Respiratory Tract and Blood Culture | Pseudomonas aeruginosa, Methicillin-Sensitive Staphylococcus aureus | Not Detected                     |

TABLE 3. Observational studies of secondary infections in COVID-19 patients.
by Zhou et al. and Van Arkel et al. have reported that the diagnosis of secondary infections was often made between a median of 12–17 days from onset of COVID-19 presentation. This could be due to the widespread use of empirical antibiotics, analgesics, and even corticosteroids that mask the underlying clinical symptoms of untreated or partially treated infections. The findings in our study did not differ from other observational studies, where the median days for cultures to return positive after admission was 9.3 days (Table 2).

We also compared the outcome of patients who developed SPI with those who did not develop SPI. We found that, although SPI was associated with a decrease in 30-day hospital-free days, there was no difference in all-cause hospital mortality. These findings differed from large studies involving influenza pneumonia, where SPI is associated with increased morbidity and mortality. These differences could be due to the small sample size, leading to inadequate power to detect a significant mortality difference.

The limitations of our study are that it is a single-center, retrospective study with a small sample size. Being retrospective in nature, we cannot adequately differentiate between colonization, contamination, and actual infection. We may have underdiagnosed many secondary infections, as cultures were obtained when there was a sudden deterioration in the patient’s clinical status or worsening chest imaging findings that cannot be explained by the underlying illness. Surveillance cultures were not routinely performed on our patients. These limitations were also noted in other observational studies. The routine microbiological testing may be reduced due to fear of prolonged exposure to COVID-19 patients. Additionally, bronchoscopy was not performed to obtain adequate respiratory specimens. The judicious use of corticosteroids received by 89% of hospitalized COVID-19 patients in our study could be a confounding factor for inducing lymphocytopenia. Furthermore, the type, dose, and time to initiation of corticosteroid therapy were inconsistently documented among the different cohorts of COVID-19 patients assessed. However, our study is one of the few studies in hospitalized COVID-19 patients with pneumonia that focuses on the incidence and risk factors of developing SPI. Based on the data from our study, it is possible that patients with SPI were more likely critically ill than those who did not develop SPI. These findings may explain the high levels of inflammatory markers, severe degree of lymphocytopenia, and increased requirement of ICU level of care and mechanical ventilation, observed in our study.

Our study demonstrated that the incidence of SPI in hospitalized COVID-19 patients was 5%. One risk factor for developing SPI was low nadir median lymphocyte count during the hospital course, whereas high nadir lymphocyte count could be protective against developing SPI. Patients with SPI had elevated baseline CRP and d-dimer level, and peak procalcitonin and CRP levels during hospitalization. Secondary pulmonary infections were associated with increased ICU admissions, mechanical ventilation requirements, and increased hospital length of stay but not all-cause hospital mortality.

AUTHOR CONTRIBUTION
Woon H. Chong: Conceptualization, Methodology, Investigation, Data curation, Writing — original draft; Hau Chieng: Conceptualization, Methodology, Investigation, Data curation, Writing — review and editing; Anupama Tiwari: Conceptualization, Methodology, Supervision, Writing — review and editing; Scott Beegle: Conceptualization, Methodology, Supervision, Writing — review and editing; Paul J. Feustel: Data Curation, Formal analysis, Writing — review and editing; Sana Ghalib: Methodology, Investigation, Data curation; Ali Hani Al-Tarbsheh: Methodology, Investigation, Data curation; Esha Jain: Methodology, Investigation, Data curation; Jeannette Mullins: Methodology, Investigation, Data curation; Megan Keenan: Data curation, Project administration; Amit Chopra: Conceptualization, Methodology, Investigation, Data curation, Supervision, Project administration, Writing — review and editing.

CONFLICTS OF INTEREST
Dr. Feustel received funding as a statistical consultant for Transonic Systems and is a scientific advisor with shares in Penrose TherapeuTx, LLC. The remaining authors have disclosed that they do not have any potential conflicts of interest.

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