ORIGINAL ARTICLE

Predictive Factors and Impact of Secondary Pulmonary Infection on Mortality in Patients with Hypoxemic COVID-19 Pneumonia: A Retrospective Cohort Study

Sarawut Krongsut, MD[1], Wipasiri Naraphong, RN, PhD[2], Pannaporn Thongsuk, MD, MSC[3]

[1] Department of Internal Medicine, Faculty of Medicine, Saraburi Hospital, Saraburi, Thailand; [2] Boromarajonani College of Nursing, Saraburi, Faculty of Nursing, Praboromarajchanok Institute, Ministry of Public Health, Saraburi, Thailand; [3] Division of Infectious Disease, Department of Internal Medicine, Phichit Hospital, Phichit, Thailand

Background: Secondary pulmonary infection (SPI) is a severe complication in patients with COVID-19.

Objective: To investigate the risk factors, mortality rates, and complications associated with SPI in hypoxemic COVID-19 pneumonia patients.

Materials and Methods: A retrospective cohort study was conducted at Saraburi Hospital, analyzing medical records of 512 hospitalized COVID-19 patients. The Fine-Gray model identified risk factors for SPI.

Results: SPI was diagnosed in 25.4% of hypoxemic COVID-19 pneumonia patients. SPI patients (mean age of 65.9±15.1 years) had higher inflammation biomarkers, increased in-hospital mortality (IHM), and more complications than non-SPI patients. The primary pathogens causing IHM were gram-negative bacteria in 59.23%. Risk factors for SPI included age of 65 years or older (sHR 1.52; 95% CI 1.03 to 2.25; p=0.032), obesity (sHR 1.52; 95% CI 1.04 to 2.23; p=0.028), invasive mechanical ventilation (sHR 2.87; 95% CI 1.64 to 5.02; p<0.001), lactate dehydrogenase (LDH) level of 520 U/L or more (sHR 2.37; 95% CI 1.69 to 3.33; p=0.027), and catheter-related bloodstream infection (sHR 2.74; 95% CI 1.71 to 4.40; p<0.001). SPI patients had an IHM rate of 74.62%. Multivariable analysis showed higher IHM in SPI patients (aOR 5.29; 95% CI 2.70 to 10.36) compared to non-SPI patients.

Conclusion: SPI is a common and harmful complication in hypoxemic COVID-19 pneumonia. Older age, obesity, invasive mechanical ventilation, elevated LDH levels, and catheter-related bloodstream infection are significant risk factors for SPI. Early detection and prevention strategies are crucial to mitigate the short-term consequences of SPI in COVID-19 patients.

Keywords: COVID-19; Secondary pulmonary infection; Mortality; Risk factors

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A novel coronavirus (2019-nCoV) outbreak, officially known as coronavirus disease 2019 (COVID-19), was first detected in Wuhan, China in late 2019. It rapidly spread to almost every country around the world[1]. Obesity, diabetes, lymphopenia, and inflammatory and coagulation cascade stimulation are predictive factors for severe respiratory disease. Meanwhile, mortality from acute respiratory distress syndrome was associated with increased comorbidities, septic shock, and acute renal failure[2]. Critically ill COVID-19 patients with invasive mechanical ventilation (IMV) to correct hypoxia require invasive procedures such as tracheotomy, nasogastric tube and urinary catheter placement, central vein catheterization, continuous renal replacement therapy, and extracorporeal membrane oxygenation for treatment. These procedures can increase the risk of secondary pulmonary infection (SPI) and death[3]. Studies found secondary bacterial infections during the 1918 influenza pandemic in Spain. These infections were estimated to be the cause of 95% of deaths during the pandemic[4,5]. In the 2009 influenza pandemic in the United States, there was a significant 1.6-fold increase in bacterial coinfection among hospitalized patients[6]. According to the studies in China[7], Hong Kong[8], and Mexico[9], a secondary bacterial infection was reported in 6% to 12% of patients with COVID-19 and a meta-analysis

Correspondence to:

Krongsut S.

Department of Internal Medicine, Saraburi Hospital, 18 Tessaban Road, Pakpreaw District, Saraburi 18000, Thailand.

Phone: +66-86-1350858

Email: sarawut-kron@moph.go.th

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of the overall proportion of patients with COVID-19 with bacterial infection was 6.9% (95% CI 4.3 to 9.5). Bacterial coinfection was the most common in critically ill patients.

The present study period coincided with the pandemic of the delta and omicron variants. Currently, the omicron variant has supplanted the delta variant. Omicron is a coronavirus variant. BA.5 and BA.2.75 refer to omicron subvariants or strains. BA.5 is a strain that has properties associated with increased virus transmission, which caused it to become prevalent in the United States and globally. There was great concern with XBB and BQ.1.1, the mutations of omicron lineages. These have immune-evasion capabilities and might render monoclonal antibody therapy ineffective[10,11]. Infection surveillance is necessary for immunocompromised people and others at high risk of serious disease.

SARS-CoV-2, termed COVID-19, can directly damage the lung epithelium and cause a 'cytokine storm' leading to multiorgan failure[12]. As a result, SPI caused by pulmonary insults is a serious clinical concern. Acute or chronic sterile or infection-driven pulmonary inflammation predisposes to subsequent infections. SPI frequently causes a fatal synergy with primary lung infection or sepsis. This increased sensitivity is due to different mechanisms, including disruption of lung barrier integrity and decreased host defense[13]. Immunosuppressive drugs are widely used to treat dysregulated activation of the immune system[14,15]; therefore, combination treatment with antiviral and immunosuppressive drugs tends to increase the risk of SPI, leading to death and other complications.

There are few studies on SPI in patients with hypoxemic COVID-19 pneumonia in Thailand, thus, the goal of the present research was to highlight the factors that predict SPI in patients with hypoxemic COVID-19 pneumonia. This was crucial to recognize the significance of SPI's impact on severe clinical outcomes and identify predictive factors. The authors anticipated that this knowledge would assist healthcare professionals in early SPI detection, facilitating vigilant monitoring and tailored treatment strategies for high-risk patients. Consequently, timely and appropriate infection management can reduce complications and mortality rates in individuals with hypoxemic COVID-19 pneumonia.

Materials and Methods

Study population

Five hundred twelve patients with hypoxemic COVID-19 pneumonia admitted between June 1, 2021 and June 30, 2022, to the intensive care unit (ICU) and a medical ward at Saraburi Hospital, Thailand, a large tertiary hospital with 700 inpatient services, were included in the present retrospective observational study.

The authors recruited all consecutive adult patients aged 18 years or older admitted with SARS-CoV-2 infection. All patients had a confirmed diagnosis of COVID-19 pneumonia from a chest radiograph (CXR) that confirmed pneumonia and a nasopharyngeal swab reverse transcription-polymerase chain reaction positive for COVID-19. Hypoxemic pneumonia was defined as a case requiring oxygen supplementation to achieve an oxyhemoglobin saturation (SpO_2) of more than 94%[16].

SPI was diagnosed when patients developed clinical symptoms, new findings of pulmonary infiltrates on chest imaging [CXR or chest computed tomography (CT)], abnormal results in laboratory tests [including complete blood count, C-reactive protein (CRP), and serum galactomannan], positive culture of bacteria or fungi in respiratory specimens from the lower respiratory tract, and the onset occurred more than 48 hours after admission. The respiratory specimens were obtained by invasive bronchoscopy-guided bronchoalveolar lavage (BAL), or a bronchial aspirate (BRASP) if BAL was not feasible. An endotracheal aspirate was collected from patients with IMV (tracheal intubation or tracheotomy). Samples were excluded if sputum cultures showed *Candida* spp.[17]. Invasive pulmonary aspergillosis (both probable and possible) was classified based on diagnostic criteria established by Blot et al.[18]. These included evaluation of host's risk factors, abnormal findings on CXR and chest CT, and mycological criteria (direct tests on sputum such as cytology, direct microscopy, or culture), BAL fluid, or bronchial brush, indicating presence of fungal elements or culture recovery *Aspergillus* spp. or indirect tests (detection of antigen or cell-wall constituents) for galactomannan antigen detected in plasma, serum, or BAL fluid. The clinician would conduct respiratory cultures when SPI was suspected by clinical signs or worsening respiratory symptoms correlated with laboratory results or CXRs. In practice, BAL and BRASP were not used to screen for infection. The galactomannan assay was used when the physician suspected patients with invasive aspergillosis. Patients for whom no microbiology specimens were requested were considered not having a secondary infection.

Regarding other definitions, obesity was an abnormal or excessive fat accumulation represented a health risk with a body mass index (BMI) of 30 kg/m² or more[19]. Diabetes mellitus (DM) criteria were (i) a random plasma glucose of 200 mg/dL or more, or (ii) a fasting plasma glucose of 126 mg/dL or more, or (iii) a HbA1c of 6.5% or more (≥48 mmol/mol)[20]. Chronic kidney disease (CKD) was defined as kidney damage or a glomerular filtration rate (GFR) of less than 60 mL/minute/1.73 m² for three months or more, irrespective of cause[21]. Failure weaning from oxygen supplementation [IMV, high flow nasal cannula (HFNC), and low flow nasal cannula (LFNC)] refers to patients who were unable to sustain spontaneous breathing or maintain SpO_2 of 95% or more for 48 hours or longer after extubation, discontinuation of HFNC, or LFNC.

Respiratory specimen collection and processing

Sputum for culture and sensitivity was collected using two methods, (i) in patients who were able to cough and expel sputum, (ii) and by suction with a specimen container connected to a sputum suction device. The sputum in the container was examined immediately. Ventilator joints were cleaned with 70% alcohol before collecting aspirate specimens in patients with endotracheal intubation or tracheotomy. A specimen of 1 to 5 mL of sputum was suctioned and taken to the laboratory within two hours. If delivery was not possible, it was kept in a refrigerator at 2°C to 8°C for no more than 24 hours.

Bacteria from sputum and BAL and BRASP specimens were identified by gram stain. Polymorphonuclear leukocyte: squamous epithelium cell (SEPC) ratio of 10:1 or greater and SEPC of less than 25/low-power field were considered adequate sputum specimens. The specimens were then seeded on MacConkey agar, blood agar, and chocolate agar and incubated at 35±2°C for 24 hours to determine colony pattern and grade colony. If the colony had only one pattern, the Vitek 2 Compact platform (BioMerieux, Marcy L'Etoile, France) was used for identification and drug sensitivity. If colony growth of more than two patterns was found, a biochemical test together with incubation for another 24 hours was used. Antimicrobial susceptibility testing with the disk diffusion test was used to identify the pathogen and reported according to the Clinical and Laboratory Standards Institute Guideline 2022. The authors used MALDI-TOF mass spectrometry to identify yeasts and the lactophenol cotton blue dye to identify molds based on microconidia and macroconidia with an Olympus CX31 microscope. The E-test was used to detect drug susceptibility for fungi.

Data collection

The medical records of all enrolled patients were obtained from the digital database. Collected baseline prognostic factors included age, gender, BMI, symptoms, underlying disease, vital signs, SpO_2, disease severity [the pneumonia severity index (PSI/PORT score), quick sepsis related organ failure assessment score, and CURB-65], history of vaccination against COVID-19, the World Health Organization (WHO) ordinal scale[22] at baseline and at 28 days after admission, length of hospital stay, CXR results (categorized into five groups with category 1 for normal, no abnormality detected; category 2 for features favoring technical issues such as suboptimal inspiration or off-center exposure, but not affecting film interpretation, irrelevant abnormalities such as old tuberculosis, mild cardiomegaly, or aortic atherosclerosis; category 3 for some features such as subtle, poorly defined opacities that can be due to early, mild, or atypical COVID-19 pneumonia or other causes such as pseudo-lesions or other diseases requiring clinical correlation and follow-up or repeated CXR; category 4 for single or multifocal, unilateral poorly defined ground-glass opacities or consolidations; and category 5 for multifocal, bilateral peripheral opacities or opacities with round morphology)[23], laboratory results, treatment, complications, and outcomes. Pneumonia due to SARS-CoV-2 infection was identified based on the International Classification of Diseases, Tenth Revision, and Clinical Modification codes with diagnosis code J12.81.

Outcome

The primary outcome was risk factors of SPI in hypoxemic COVID-19 pneumonia patients and the secondary outcome was serious adverse events including mortality (14 and 28 day-mortality, and IHM), complications [acute respiratory failure, acute kidney injury (AKI), shock, disseminated intravascular coagulation (DIC), pulmonary embolism, pneumothorax, upper gastrointestinal hemorrhage (UGIH), catheter-related bloodstream infection (CRBSI), atrial fibrillation with rapid ventricular response (AF with RVR), length of stay (LOS) of more than 14 days, duration of oxygen supplementation or more than 14 days] and failure weaning oxygen supplementation (IMV, HFNC, and LFNC) to investigate the relationship between SPI

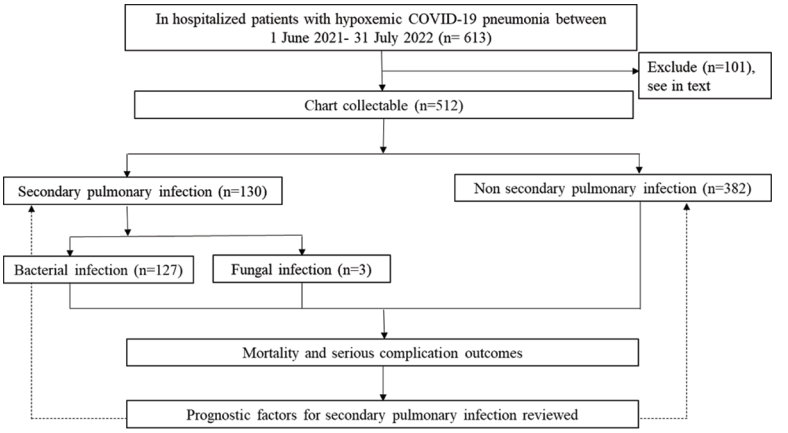

Figure 1. Study flow diagram.

and mortality, complications and failure weaning oxygen supplementation. Additional analyses included SPI incidence with frequency of pathogen isolates from patients with hypoxemic COVID-19 pneumonia.

Statistical analysis

The database was calculated, and the results displayed with the Stata Statistical Software, version 16 (StataCorp LLC, College Station, TX, USA). Baseline characteristics were analyzed using descriptive statistics and were reported as proportions, means with standard deviation, or medians with interquartile range as appropriate. The chi-square test or Fisher's test was used to analyze categorical variables. Continuous variables were compared using an unpaired t-test or the Mann-Whitney U test, as appropriate. Follow-up time zero was ICU or medical ward admission. The authors used a survival model analysis and a univariable and multivariable Cox proportional hazards model, using a competing risk analysis based on the Fine and Gray model[24]. The model was developed to follow patients' progress from ICU or the medical ward admission to hospital discharge. Factors associated with SPI were analyzed using determinants with a statistical significance of p-value less than 0.05 in univariate analyses to add them to the equation in the adjusted model, showing the results with a sub-distribution hazard ratio (sHR) and a 95% confidence interval (CI). The association between SPI on mortality outcome, complications, and failure weaning oxygen supplementation was analyzed by multivariable logistic regression (MVLR) presented with odds ratios (ORs) and 95% CI, and adjusted for potential confounding factors: age, gender, CKD, DM, cardiovascular disease, obesity, CRP, and PSI/PORT score[17,25]. Competing risk regression for the cumulative incidence of IHM was created to compare SPI and non-SPI, and to test the proportional hazard assumption model and proportion of sub-distribution from the Fine and Gray model for violations using the Schoenfeld residual. For data comparison, a p-value of less than 0.05 was considered a statistically significant difference.

Results

Clinical characteristics of patients with SPI

Patients' demographic and clinical characteristics are shown in Table 1. There were 613 patients with hypoxemic COVID-19 pneumonia at Saraburi Hospital between June 1, 2021 and June 30, 2022 (Figure 1). The authors excluded 101 patients for the following reasons, 22 had missing data on emergency treatments, five were referred to other hospitals, and 74 had missing laboratory results on initial admission. The present study included 512 patients, 130 (25.4%) were SPI and 382 (74.6%) were non-SPI. The mean age of patients was 62 years and 47.5% were male. The length of patients' stays in the hospital ranged from 1 to 69 days, with a mean of 14.7±9.2 days. The mean time of admission to onset of SPI was 12.1±7.4 days. One hundred ninety-three out of 319 patients (37.7%) of the patients with hypoxemic COVID-19 pneumonia admitted to the ICU and medical ward eventually died. All hospitalized patients with hypoxemic COVID-19 pneumonia received bacterial or fungi detection testing when SPI was suspected. The respiratory specimens were collected from sputum in 287 patients (56.1%), lung lavage in 32 patients (6.3%), and bronchial secretions from tracheal suction in 154 patients (30.1%) for microbiological tests. Patients with SPI were more

Table 1. Demographic and clinical characteristics between secondary pulmonary infection and non secondary pulmonary infection of patients with hypoxemic COVID-19 pneumonia

Variables	All patients (n=512)	Secondary pulmonary infection (n=130)	Non secondary pulmonary infection (n=382)	p-value
General characteristic				
Age (years); mean±SD	61.5±15.5	65.9±15.1	60.0±15.4	<0.001
Male; n (%)	243 (47.5)	72 (55.4)	171 (44.8)	0.036
BMI (kg/m^2); mean±SD	28.7±7.0	30.0±7.8	28.3±6.7	0.015
Coexisting conditions; n (%)				
Diabetes	240 (46.9)	59 (45.4)	181 (47.4)	0.693
Obesity	181 (35.4)	59 (45.4)	122 (31.9)	0.006
COPD	13 (2.5)	3 (2.3)	10 (2.6)	1.000
Cardiovascular disease	57 (11.1)	20 (15.4)	37 (9.7)	0.074
Cerebrovascular disease	47 (9.2)	19 (14.6)	28 (7.3)	0.013
Cirrhosis	10 (2.0)	5 (3.9)	5 (1.3)	0.133
Chronic kidney disease				
• CKD stage 3	70 (13.7)	26 (20.0)	44 (11.5)	0.007
• CKD stage 4	22 (4.3)	9 (6.9)	13 (3.4)	
• CKD stage 5	12 (2.3)	5 (3.9)	7 (1.8)	
Immunocompromise	2 (0.4)	0 (0.0)	2 (0.5)	1.000
Use steroid before	5 (1.0)	2 (1.5)	3 (0.8)	0.605
Hypertension	301 (58.8)	92 (70.8)	209 (54.7)	0.001
Dyslipedemia	177 (34.6)	46 (35.4)	131 (34.3)	0.821
Alzheimer's disease	1 (0.2)	1 (0.8)	0 (0)	0.254
History of malignancy	10 (2.0)	3 (2.3)	7 (1.8)	0.720
Thalassemia	3 (0.6)	1 (0.8)	2 (0.5)	1.000
Autoimmune disease	5 (1.0)	1 (0.8)	4 (1.1)	1.000
HIV infection	2 (0.4)	0 (0)	2 (0.5)	1.000
Gout	22 (4.3)	9 (6.9)	13 (3.4)	0.087
Psychiatric disorder	4 (0.8)	1 (0.8)	3 (0.8)	1.000
Symptoms; n (%)				
Fever	399 (77.9)	103 (79.2)	296 (77.5)	0.679
Cough	474 (92.6)	123 (94.6)	351 (91.9)	0.305
Diarrhea	82 (16.0)	24 (18.5)	58 (15.2)	0.379
Sore throat	48 (9.4)	11 (8.5)	37 (9.7)	0.679
Anosmia	61 (11.9)	15 (11.5)	46 (12.0)	0.878
Nausea	56 (10.9)	14 (10.8)	42 (11.0)	0.943
Vital sign; mean±SD				
Body temperature (℃)	37.8±2.9	37.8±1.1	37.7±3.3	0.900
SBP (mmHg)	131.0±25.5	128.3±29.0	131.9±24.2	0.174
DBP (mmHg)	76.1±15.3	75.1±17.8	76.5±14.4	0.370
RR (/minute)	30.5±6.0	33.5±5.8	29.4±5.8	<0.001
SpO_2 at room air (%)	85.7±8.4	83.7±10.0	86.4±7.6	0.001
Disease severity; mean±SD				
PSI/PORT	3.5±1.2	4.2±1.0	3.2±1.2	<0.001
CURB-65	1.9±1.4	2.7±1.3	1.6±1.3	<0.001
qSOFA	1.4±0.7	1.8±0.8	1.3±0.6	<0.001

BMI=body mass index; COPD=chronic obstructive pulmonary; CKD=chronic kidney disease; DBP=diastolic blood pressure; HFNC=high flow nasal cannula; HIV=human immunodeficiency virus; IMV=invasive mechanical ventilation; LFNC=low flow nasal cannula; PSI/PORT=pneumonia severity index; qSOFA=quick Sequential Organ Failure Assessment; RR=respiratory rate; SBP=systolic blood pressure; SpO_2=oxyhemoglobin saturation; SD=standard deviation

[a] Inactivated vaccine, CoronaVac; [b] Viral vector vaccine, the AstraZeneca ChAdOx1-S/nCoV-19 [recombinant] vaccine; [c] mRNA vaccine, Pfizer-BioNTech COVID-19 vaccine or the mRNA-1273 vaccine (the COVID-19 Vaccine Moderna)

Table 1. (continued)

Variables	All patients (n=512)	Secondary pulmonary infection (n=130)	Non secondary pulmonary infection (n=382)	p-value
Baseline WHO ordinal scale of clinical status; n (%)				
LFNC	90 (17.6)	18 (13.9)	72 (18.9)	0.196
HFNC	339 (66.2)	63 (48.5)	276 (72.3)	<0.001
IMV	85 (16.6)	50 (38.5)	35 (9.2)	<0.001
ICU admission	279 (54.5)	107 (82.3)	172 (45.0)	<0.001
General medical ward admission	233 (45.5)	23 (17.7)	210 (55.0)	<0.001
COVID-19 vaccine immunization; n (%)				
History of vaccine immunization	133 (26.0)	28 (21.5)	105 (27.5)	0.182
Type of vaccine received; n (%)				
Inactivated vaccine[a]	88 (17.19)	16 (12.3)	72 (18.9)	0.088
Viral vector vaccine[b]	63 (12.3)	16 (12.3)	47 (12.3)	0.999
mRNA vaccine[c]	8 (1.6)	2 (1.5)	6 (1.6)	0.980

BMI=body mass index; COPD=chronic obstructive pulmonary; CKD=chronic kidney disease; DBP=diastolic blood pressure; HFNC=high flow nasal cannula; HIV=human immunodeficiency virus; IMV=invasive mechanical ventilation; LFNC=low flow nasal cannula; PSI/PORT=pneumonia severity index; qSOFA=quick Sequential Organ Failure Assessment; RR=respiratory rate; SBP=systolic blood pressure; SpO_2=oxyhemoglobin saturation; SD=standard deviation

[a] Inactivated vaccine, CoronaVac; [b] Viral vector vaccine, the AstraZeneca ChAdOx1-S/nCoV-19 [recombinant] vaccine; [c] mRNA vaccine, Pfizer-BioNTech COVID-19 vaccine or the mRNA-1273 vaccine (the COVID-19 Vaccine Moderna)

likely to be old age, male, a higher BMI, obesity, cerebrovascular disease, CKD, hypertension, higher respiratory rate, lower SpO_2 at room air, higher disease severity, and history of IMV and HFNC at admission (Table 1).

Next, the authors analyzed hematological, biochemical, and inflammatory biomarkers that were immediately requested when SPI was suspected (Table 2). A t-test analysis showed significant laboratory findings. The authors compared the SPI group to patients with COVID-19 infection only when they were more likely to have a higher white blood cell count ($\times 10^3/\mu L$) [9.5 (IQR 6.5, 13.6) versus 8.4 (IQR 6.0, 11.2), p=0.013], higher absolute neutrophil count ($\times 10^3/\mu L$) [7.91 (IQR 5.3, 12.2) versus 6.8 (IQR 4.3, 9.5), p=0.008], higher blood urea nitrogen (mg/dL) [25.6 (IQR 16.2, 41.8) versus 19.5 (IQR 12.7, 29.7), p<0.001], higher creatinine (mg/dL) [1.1 (IQR 0.8, 1.6) versus 0.9 (IQR 0.7, 1.3], p<0.001), higher CRP (mg/dL) [101.3 (IQR 64.8, 142.0) versus 88.9 (IQR 48.8, 124.2), p=0.010], higher lactate dehydrogenase (LDH) (U/L) (536.1±257.4 versus 435.6±206.2, p<0.001), and lower serum albumin (g/dL) (3.3±0.5 versus 3.4±0.8, p=0.033) (Table 2).

Almost 74.6% of patients with SPI succumbed to IHM, compared to only 25.1% of patients with SARS-CoV-2 infection alone. Furthermore, a significant increase in the LOS was reported in patients with SPI compared to those infected only with SARS-CoV-2, with stays of 16 and 11 days, respectively. All the patients in the present study cohort received corticosteroid treatment. SPI patients were more likely to have more complications than patients with COVID-19 infection alone, such as increased acute respiratory failure, AKI, shock, DIC, metabolic acidosis, pulmonary embolism, pneumothorax, UGIH, CRBSI, AF with RVR, duration of oxygen supplementation, and failure weaning oxygen supplementation (Table 3).

Risk factors for SPI

The authors used the Fine-Gray sub-distribution hazard competing risk regression model to highlight probable causes of SPI. A univariable sub-distribution hazard analysis revealed that CRBSI (sHR 7.42, 95% CI 5.45 to 10.11) and IMV requirement (sHR 5.79, 95% CI 4.02 to 8.33) were the strongest predictors of SPI. Multivariable analyses showed that age of 65 years or older (sHR 1.52, 95% CI 1.03 to 2.25), obesity (sHR 1.52, 95% CI 1.04 to 2.23), IMV requirement (sHR 2.87, 95% CI 1.64 to 5.02), LDH of 250 U/L or more (sHR 1.52, 95% CI 1.04 to 2.20), and CRBSI (sHR 2.74, 95% CI 1.71 to 4.40) were independent risk factors for SPI in the present study patient cohort (Table 4). The C-statistic of independent significant risk factors in the adjusted model for SPI was 0.77.

Impact of SPI on clinical outcomes

Table 5 illustrates the odds of mortality outcome, complications, and failure weaning oxygen supplementation in patients with SPI compared to

Table 2. Laboratory parameters for the study subjects

Variables	All patients (n=512)	Secondary pulmonary infection (n=130)	Non secondary pulmonary infection (n=382)	p-value
Routine peripheral blood				
WBC ($\times 10^3/\mu L$); median (IQR)	8.6 (6.1, 11.6)	9.5 (6.5, 13.6)	8.4 (6.0, 11.2)	0.013
CBC neutrophil (%); mean±SD	80.9±11.8	81.9±11.3	80.6±12.0	0.251
CBC lymph (%); median (IQR)	12 (7, 19)	10 (6, 16)	12 (7, 19)	0.042
ANC ($\times 10^3/\mu L$); median (IQR)	7.1 (4.5, 10.2)	7.9 (5.3, 12.2)	6.8 (4.3, 9.5)	0.008
ALC ($\times 10^3/\mu L$); median (IQR)	0.9 (0.6, 1.4)	0.9 (0.6, 1.4)	1.0 (0.6, 1.4)	0.428
Hb (g/dL); mean±SD	11.8±2.2	11.7±2.4	11.8±2.09	0.649
Hct (%); mean±SD	36.6±6.7	36.3±7.4	36.6±6.5	0.654
Platelet ($\times 103/\mu L$); mean±SD	239.2±108.6	228.5±113.0	242.8±107.0	0.195
Blood chemistry				
BUN (mg/dL); median (IQR)	20.5 (13.7, 32.4)	25.6 (16.2, 41.8)	19.45 (12.7, 29.7)	<0.001
Cr (mg/dL); median (IQR)	0.9 (1.0, 1.4)	1.1 (0.8, 1.6)	0.9 (0.7, 1.3)	<0.001
Sodium (mEq/L); mean±SD	135.3±5.3	135.6±5.2	135.2±5.3	0.494
TB (mg/dL); median (IQR)	0.6 (0.5, 0.9)	0.6 (0.5, 0.9)	0.6 (0.5, 0.9)	0.431
DB (mg/dL); median (IQR)	0.2 (0.1, 0.3)	0.2 (0.1, 0.3)	0.2 (0.1, 0.3)	0.388
DB/TB ratio; median (IQR)	0.3 (0.2, 0.3)	0.2 (0.2, 0.3)	0.3 (0.2, 0.3)	0.865
AST (U/L); median (IQR)	50 (34, 75)	52 (35, 84)	49.5 (33, 70)	0.110
ALT (U/L); median (IQR)	36 (22, 59)	39 (22, 63)	35.5 (22, 59)	0.572
Albumin (g/dL); mean±SD	3.4±0.8	3.2±0.5	3.4±0.8	0.033
Blood sugar (mg/dL); median (IQR)	169 (129, 266)	186.5 (129, 268)	166.5 (128, 265)	0.471
Inflammatory markers				
CRP (mg/dL); median (IQR)	92.1 (52.1, 126.4)	101.3 (64.8, 142.0)	88.9 (48.8, 124.2)	0.010
LDH (U/L); mean±SD	461.1±224.4	536.1±257.4	435.6±206.2	<0.001
PT (seconds); mean±SD	13.6±7.6	13.9±4.3	13.6±8.5	0.654
PTT (seconds); mean±SD	25.3±5.9	25.6±7.0	25.2±5.5	0.510
CT-value (N gene); mean±SD	20.8±4.8	20.5±5.1	20.9±4.7	0.458
CXR category; n (%)				
Category 1/2/3	34 (6.6)	7 (5.4)	27 (7.1)	0.355
Category 4	76 (14.8)	24 (18.5)	52 (13.6)	
Category 5	402 (78.5)	99 (76.2)	303 (79.3)	

ANC=absolute neutrophil count; AST=aspartate aminotransferase; ALT=alanine transaminase; BUN=blood urea nitrogen; CBC=complete blood count; CRP=C-reactive protein; Cr=creatinine; CXR=chest radiograph; DB=direct bilirubin; Hct=hematocrit; IQR=interquartile range; LDH=lactate dehydrogenase; PT=prothrombin time; PTT=partial thromboplastin time; SD=standard deviation; TB=total bilirubin; WBC=white blood cell count

those with SARS-CoV-2 infection only. In the MVLR model that included age of 60 years or older, gender, obesity (BMI ≥30 kg/m²), DM, CKD, cardiovascular disease, PSI/PORT score, and CRP level. The adjusted ORs for IHM was 5.29 (95% CI 2.70 to 10.36), acute respiratory failure was 7.51 (95% CI 4.39 to 12.85), DIC was 5.81 (95% CI 1.21 to 27.89), pneumothorax was 6.78 (95% CI 1.68 to 27.33), and LOS greater than 14 days was 3.23 (95% CI 2.05 to 5.07) in patients with SPI compared to non-SPI (Table 5). Competing risk estimates for cumulative incidence showed high mortality in all patients with SPI (log-rank p<0.001) (Figure 2A). A bar graph revealed the percentage of WHO ordinary scale for clinical improvement at day 28 between patients with or without SPI (Figure 2B). Patients with SPI had a higher 28-day mortality outcome, using the WHO ordinary scale of 8, different from patients without SPI at 72.3% versus 24.1% (Figure 2B). Among 74.9% (286/382) non-SPI patients with hypoxemic COVID-19 pneumonia discharged from the hospital, the median duration from hospital admission to discharge was 11 (IQR 8, 16) days, and 63.1% (82/130) of patients with SPI died by 28 days (Table 3).

Bacteria and fungi isolation in patients with hypoxemic COVID-19 pneumonia

Overall, the authors found that 59.2% (77/130) of the coinfected patients, that eventually died were

Table 3. Comparison of treatment, complications and outcomes between secondary pulmonary infection and non secondary pulmonary infection of patients with hypoxemic COVID-19 pneumonia

Variables	All patients (n=512)	Secondary pulmonary infection (n=130)	Non secondary pulmonary infection (n=382)	p-value
Treatment; n (%)				
Antiviral drug				
• Favipiravir	181 (35.4)	43 (33.1)	138 (36.1)	0.530
• Remdesivir	330 (64.5)	86 (66.2)	244 (63.9)	0.639
Anti-inflammatory drugs				
• Dexamethasone	485 (94.7)	122 (93.9)	363 (95.0)	0.603
• IVMP	34 (6.6)	11 (8.5)	23 (6.0)	0.334
• Hydrocortisone	29 (5.7)	9 (6.9)	20 (5.2)	0.472
Use of biological immunosuppressive drugs				
• Tocilizumab	15 (2.9)	7 (5.4)	8 (2.1)	0.070
• Tofacitinib	86 (16.8)	19 (14.6)	67 (17.5)	0.441
• Baricitinib	32 (6.3)	9 (6.9)	23 (6.0)	0.714
Hemoperfusion	9 (1.8)	6 (4.6)	3 (0.8)	0.010
Hemodialysis	8 (1.6)	3 (2.3)	5 (1.3)	0.425
Complications; n (%)				
Acute respiratory failure	154 (30.1)	88 (67.7)	66 (17.3)	<0.001
Acute kidney injury	125 (24.4)	52 (40.0)	73 (19.1)	<0.001
Shock	124 (24.2)	61 (46.9)	63 (16.5)	<0.001
DIC	11 (2.2)	8 (6.2)	3 (0.8)	0.001
Metabolic acidosis	48 (9.4)	25 (19.2)	23 (6.0)	<0.001
Pulmonary embolism	4 (0.8)	4 (3.1)	0 (0)	0.004
Pneumothorax	13 (2.5)	10 (7.7)	3 (0.8)	<0.001
UGIH	25 (4.9)	16 (12.3)	9 (2.4)	<0.001
Transaminitis	78 (15.2)	22 (16.9)	56 (14.7)	0.535
DKA	14 (2.7)	6 (4.6)	8 (2.1)	0.131
CRBSI	12 (2.3)	12 (9.2)	0 (0)	<0.001
AF with RVR	21 (4.1)	12 (9.2)	9 (2.4)	0.001
Outcomes				
Duration of oxygen supplementation (days); median (IQR)	10 (7, 16.5)	16 (10, 24)	9 (6, 14)	<0.001
Hospital stays (days); median (IQR)	12.5 (9, 18)	16 (12, 25)	11 (8, 16)	<0.001
14-day mortality; n (%)	115 (22.5)	42 (32.3)	73 (19.1)	0.002
In-hospital mortality; n (%)	193 (37.7)	97 (74.6)	96 (25.1)	<0.001
28-day mortality; n (%)	173 (33.8)	82 (63.1)	91 (23.8)	<0.001
Discharged; n (%)	319 (62.3)	33 (25.4)	286 (74.9)	<0.001
Failure weaning from oxygen supplementation; n (%)				
Failure weaning from IMV	124 (81.1)	75 (86.2)	49 (74.2)	0.061
Failure weaning from HFNC	126 (32.0)	57 (67.9)	69 (22.3)	<0.001
Failure weaning from LFNC	68 (18.9)	27 (52.9)	41 (13.3)	<0.001

AF with RVR=atrial fibrillation with rapid ventricular response; CRBSI=catheter-related bloodstream infection; DIC=disseminated intravascular coagulation; DKA=diabetic ketoacidosis; HFNC=high flow nasal cannular; IMV=invasive mechanical ventilation; IQR=interquartile range; IVMP=intravenous methylprednisolone; LFNC=low flow nasal cannular; UGIH=upper gastrointestinal hemorrhage

infected with gram negative organisms (Figure 3A). Further, the authors found *Acinetobacter baumannii* was the most frequently reported organism among all other bacterial isolates, followed by *Klebsiella pneumoniae* isolates, at 62.9% and 33.6%, respectively (Figure 3B).

Discussion

The present study focused on investigating the occurrence of SPI in COVID-19 patients, as well as exploring the associated risk factors and outcomes. The respiratory system is known to be heavily impacted by SARS-CoV-2, and organ failure

Table 4. Univariable and multivariable analysis on risk of secondary pulmonary infection among patients with hypoxemic COVID-19 pneumonia

Baseline characteristics	Unadjusted analysis		Adjusted analysis	
	sHR (95% CI)	p-value	sHR (95% CI)	p-value
Age ≥65 years	2.03 (1.44 to 2.87)	<0.001	1.52 (1.03 to 2.25)	0.032
Male	1.44 (1.02 to 2.03)	0.034	1.09 (0.76 to 1.56)	0.630
Obesity	1.65 (1.17 to 2.32)	0.004	1.52 (1.04 to 2.23)	0.028
Cerebrovascular disease	2.02 (1.21 to 3.36)	0.006	1.68 (0.96 to 2.96)	0.069
Chronic kidney disease	2.05 (1.40 to 3.01)	<0.001	1.26 (0.81 to 1.96)	0.287
Hypertension	1.71 (1.18 to 2.49)	0.005	1.09 (0.72 to 1.66)	0.661
RR ≥30/minute	3.65 (2.38 to 5.62)	<0.001	1.23 (0.66 to 2.31)	0.506
SpO_2 ≤60%	0.76 (0.24 to 2.41)	0.648	#	
PSI/PORT score ≥4	4.73 (3.03 to 7.38)	<0.001	1.58 (0.91 to 2.76)	0.101
HFNC	0.43 (0.31 to 0.60)	<0.001	0.91 (0.59 to 1.40)	0.690
IMV requirement	5.79 (4.02 to 8.33)	<0.001	2.87 (1.64 to 5.02)	<0.001
ANC ≥11,000	1.74 (1.21 to 2.48)	0.002	0.97 (0.65 to 1.44)	0.891
Cr ≥0.75 mg/dL	2.26 (1.47 to 3.46)	<0.001	1.44 (0.88 to 2.35)	0.145
Albumin ≤2 mg/dL	0.45 (0.11 to 1.90)	0.281	#	
CRP ≥50 mg/dL	1.92 (1.16 to 3.19)	0.011	1.23 (0.71 to 2.12)	0.453
LDH ≥520 U/L	2.37 (1.69 to 3.33)	<0.001	1.52 (1.04 to 2.20)	0.027
Hemoperfusion	2.59 (1.34 to 5.01)	0.005	1.45 (0.57 to 3.72)	0.431
CRBSI	7.42 (5.45 to 10.11)	<0.001	2.74 (1.71 to 4.40)	<0.001

ANC=absolute neutrophil count; CI=confidence interval; Cr=creatinine; CRP=C-reactive protein; CRBSI=catheter-related bloodstream infection; HFNC=high flow nasal cannular; IMV=invasive mechanical ventilation; LFNC=low flow nasal cannular; LDH=lactate dehydrogenase; PSI/PORT=pneumonia severity index; RR=respiratory rate; sHR=subdistribution hazard ratio; SpO_2=oxyhemoglobin saturation

Not included in multivariate analysis

Table 5. Univariable and multivariable logistic regression analysis to identify effect of secondary pulmonary infection on mortality, complications, and failure weaning oxygen supplementation

Outcome	Unadjusted analysis		Adjusted analysis*	
	ORs (95% CI)	p-value	aORs (95% CI)	p-value
Mortality				
14 day-mortality	2.02 (1.29 to 3.16)	0.002	0.56 (0.31 to 1.01)	0.057
In-hospital mortality	8.75 (5.54 to 13.83)	<0.001	5.29 (2.70 to 10.36)	<0.001
28 day-mortality	5.46 (3.56 to 8.37)	<0.001	2.36 (1.33 to 4.18)	0.003
Complications				
Acute respiratory failure	10.03 (6.37 to 15.78)	<0.001	7.51 (4.39 to 12.85)	<0.001
Acute kidney injury	3.20 (2.11 to 4.85)	<0.001	1.49 (0.90 to 2.49)	0.119
Shock	4.47 (2.88 to 6.93)	<0.001	2.45 (1.46 to 4.12)	0.001
DIC	8.28 (2.16 to 31.71)	0.002	5.81 (1.21 to 27.89)	0.028
Pulmonary embolism	NA			
Pneumothorax	10.52 (2.85 to 38.87)	<0.001	6.78 (1.68 to 27.33)	0.007
UGIH	5.81 (2.50 to 13.51)	<0.001	3.41 (1.35 to 8.59)	0.009
CRBSI	NA			
AF with RVR	4.21 (1.73 to 10.25)	0.002	2.82 (1.06 to 7.47)	0.037
LOS >14 days	2.87 (1.90 to4.32)	<0.001	3.23 (2.05 to 5.07)	<0.001
Duration of oxygen supplementation >14 days	4.61 (3.02 to 7.04)	<0.001	4.43 (2.78 to 7.04)	<0.001
Failure weaning from oxygen supplementation				
Failure weaning from IMV	2.16 (0.95 to 4.93)	0.065	2.47 (0.85 to 7.18)	0.096
Failure weaning from HFNC	7.37 (4.33 to 12.53)	<0.001	5.62 (2.57 to 12.31)	<0.001
Failure weaning from LFNC	7.35 (3.87 to 13.95)	<0.001	5.03 (2.36 to 10.73)	<0.001

AF with RVR=atrial fibrillation with rapid ventricular response; CI=confidence interval; CRBSI=catheter-related bloodstream infection; DIC=disseminated intravascular coagulation; HFNC=high flow nasal cannular; IMV=invasive mechanical ventilation; LOS=length of stay; LFNC=low flow nasal cannula; ORs=odds ratios; aORs=adjusted odds ratios; UGIH=upper gastrointestinal hemorrhage

* Multivariable logistic regression model adjusted for: age ≥60 years, gender, obesity, diabetes, chronic kidney disease, cardiovascular disease PSI/PORT score, CRP level

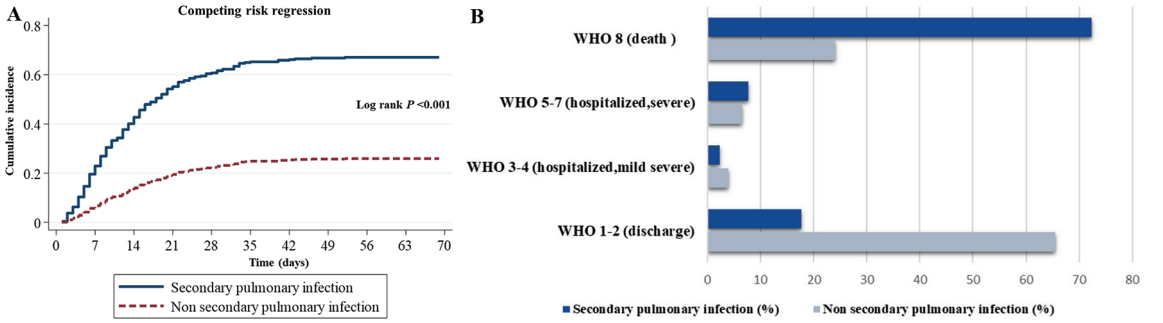

Figure 2. (A) Competing risk estimates for cumulative incidence of in-hospital mortality (B) WHO ordinary scale for clinical improvement at day 28 between patients with or without secondary pulmonary infection. The WHO Ordinal Severity Scale, which consists of 9 points of the scale are as follows: 0=no clinical or virological evidence of infection; 1=ambulatory, no activity limitation; 2=ambulatory, activity limitation; 3=hospitalized, no oxygen therapy; 4=hospitalized, oxygen mask or nasal prongs; 5=hospitalized, NIMV or HFNC; 6=hospitalized, intubation and IMV; 7: hospitalized, IMV and ECMO; 8: death

ECMO=extracardiac membranous oxygenation; HFNC=high flow nasal cannula; IMV=invasive mechanical ventilation; NIMV=noninvasive mechanical ventilation

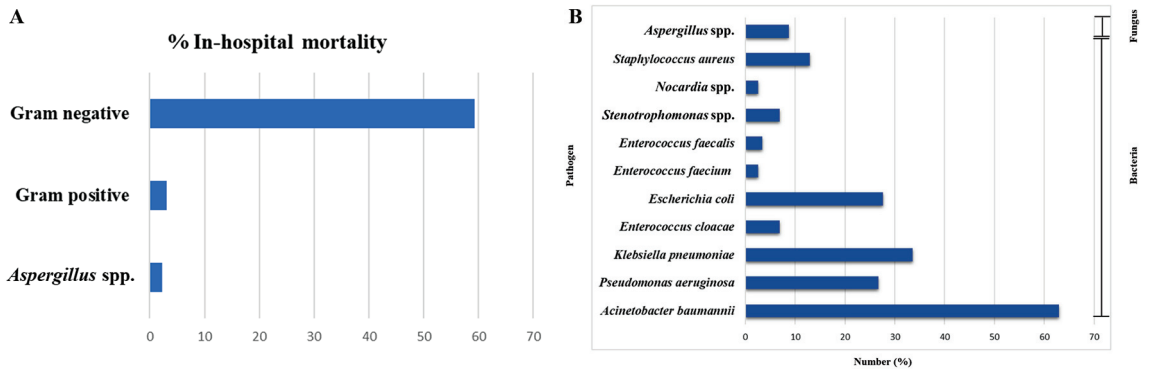

Figure 3. Isolated bacterial and fungal pathogen from secondary pulmonary infection from in hospitalized patients with COVID-19 pneumonia (A) percentage of mortality among patients with COVID-19 pneumonia infected with gram negative, gram positive bacteria or fungus; (B) frequency of type of pathogen isolates from patients with COVID-19 pneumonia.

plays a significant role in the high mortality rates observed. Critically ill patients often require invasive procedures and respiratory support, which increases their vulnerability to microbial infections, including respiratory and bloodstream infections[3]. The present study cohort comprised 512 hospitalized COVID-19 patients, and the incidence of SPI was found to be 25.4%. This percentage was higher than the previous studies in China[26], with approximately 10% incidence of secondary infections. It is worth noting that all patients in the particular cohort received corticosteroid treatment due to oxygen desaturation, which could contribute to the higher incidence of SPI. Corticosteroids have the potential to suppress the immune system and prolonged inappropriate dosing even renders patients more susceptible to infections. Risk factors associated with SPI were identified in the present study. These included age of 65 years or older, obesity, IMV, elevated LDH levels, and CRBSI. Of these, CRBSI was particularly significant, highlighting the importance of maintaining aseptic techniques in managing intravascular devices. Gram-negative bacteria were found to be the most common pathogens causing SPI, followed by gram-positive bacteria and fungi. There could be two causes. First, the authors' center accepted critically ill patients referred from nearby hospitals, which during the outbreak were a large number. This added pressure and stress on our healthcare system. Some critically ill patients with multiple devices were managed outside the ICU, leading to increased rates of CRBSI. Second, outside ICU management and the overwhelming workload due to high-volume patient care might reduce adherence to strict aseptic procedures. This problem could lead to SPI and its complications. Therefore, using the proper aseptic

techniques in managing intravascular devices could be challenging.

In the setting of SARS-CoV-2 infection, a study conducted on 731 patients in Italy provided evidence that SPI were caused by gram negative pathogens in 14 out of 26 patients (53.8%). In the multivariable analysis, the factors associated with secondary infections were a low baseline lymphocyte count, low baseline PaO_2/FiO_2, and ICU admission in the first 48 hours. These factors were also independent risk factors for secondary bloodstream infections or SPI during hospitalization[17]. Parallel to the present study findings, several studies confirmed that age of 65 years or older[26], obesity[27-29], IMV[26,30,31], LDH of 520 U/L or greater[32,33], and CRBSI[30,34,35] were independent risk factors for developing SPI in hypoxemic COVID-19 pneumonia during hospitalization. However, some findings were inconsistent with the present study. Ripa et al.[17] reported that in a multivariate analysis, age of 65 years or older was not identified as a potential risk factor for secondary infection (sHR 0.57, 95% CI 0.30 to 1.10). A low baseline lymphocyte count was a potential risk factor for secondary infection (sHR 1.93, 95% CI 1.11 to 3.35), which was inconsistent with the present findings that found no association between low baseline lymphocyte count and SPI.

Patients with SPI experienced more complications, higher mortality rates, and longer hospital stays compared to those without SPI. Bacterial superinfections have been shown to contribute to the severity of COVID-19 and increase the risk of death. Impaired immune responses and bacterial clearance mechanisms may render patients more susceptible to secondary bacterial infections during severe COVID-19[36]. In the presented study, the authors reported a high mortality among patients with COVID-19 pneumonia infected with gram negative or gram positive bacteria, or fungi. Gram negative bacterial pulmonary infection had the highest proportion of IHMs (59.2%), followed by gram positive bacteria (3.1%), and *Aspergillus* spp. (2.3%), respectively. The frequency of common pathogen isolates from patients were *Acinetobacter baumannii* (62.9%), *Klebsiella pneumoniae* (33.6%), *Escherichia coli* (27.6%), and *Pseudomonas aeruginosa* (26.7%). This pathogen distribution was similar to other COVID-19 studies in which researchers reported common pathogens including *Acinetobacter baumannii* and *Klebsiella pneumoniae* in severe COVID-19 cases[17,37,38]. The reason behind this pathogen distribution may be that most severe and critical cases were in the ICU and underwent invasive procedures, which may increase the chance of hospital-acquired infection. Furthermore, most secondary infections reported were deemed healthcare-associated infections (HAIs) rather than community-acquired diseases[39]. HAIs can arise because of ventilator-associated pneumonia, CRBSI, or catheter-associated urinary tract infections[40].

Because SPI was independently related with IHM, identifying these risk factors might reveal potential methods for prevention in patients with hypoxemic COVID-19 pneumonia. The burden of this association is estimated to confer about a 5.3-fold increased risk of IHM in patients with SPI. Detecting high-risk individuals for SPI and prevention and supportive strategies in these patients might improve their prognosis and long-term consequences. In the COVID-19 pandemic, there were patients with severe symptoms that needed immunosuppressive treatment and long hospital stays, which made them more susceptible to HAIs[41]. The findings underscore the need for prevention and management strategies targeting SPI in COVID-19 patients. Implementing measures to prevent HAIs, improving infection control practices, and promoting antimicrobial stewardship are crucial. Early identification of high-risk individuals and implementing supportive strategies have the potential to improve outcomes[42].

While the present study had strengths such as comprehensive patient information and adjustment for potential confounders, there were also limitations. The present study was conducted at a single center, limiting generalizability. The timing of SPI diagnosis was not precisely determined, and data on empirical antimicrobial use and multidrug resistance were lacking. Additionally, underdiagnosis of SPI may have occurred due to the unavailability of sputum specimens. Further research, preferably multicenter studies, is necessary to validate these findings and address the study's limitations. This would provide a more comprehensive understanding of SPI in COVID-19 patients and aid in the development of effective prevention and management strategies.

Conclusion

SPI was a frequent complication of COVID-19. In the present study cohort of hospitalized patients with hypoxemic COVID-19 pneumonia, SPI occurred in 25%. Patients aged 65 years or older, obesity, IMV, LDH of 520 U/L or more, and CRBSI were potential risk factors for SPI in the present study cohort of patients. Identification of the etiological

mechanism of SPI and the strategy aimed at prioritizing prevention and early identification of SPI are urgently required, as SPI was an independent predictor of mortality, complications, and failure weaning oxygen supplementation in patients with hypoxemic COVID-19 pneumonia.

What is already known on this topic?

From recent previous studies, it is already known that an indwelling gastric catheter, central vein catheters, IMV, hormone application, and the use of more than three antibacterial drugs, are risk factors for SPI in patients with COVID-19 infection.

What this study adds?

The incidence of SPI was 25.4%. Age of 65 years or older, obesity, IMV requirement, LDH of 520 U/L or more, and CRBSI were potential risk factors for SPI. Moreover, SPI was associated with increased odds of mortality and serious complications such as acute respiratory failure, AKI, shock, DIC, pulmonary embolism, pneumothorax, UGIH, AF with RVR, duration of oxygen supplementation of more than 14 days, and failure weaning HFNC and LFNC. The additional finding of gram negative bacterial pulmonary infection had the highest proportion of IHMs at 59.2%. The most common pathogen was *Acinetobacter baumannii* at 62.9%.

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Availability of data and materials

The datasets generated or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

All authors have made substantial contributions to this work and approved the final version of the manuscript. Concept and design: SK and WN. Acquisition of data: SK. Statistical analysis: SK. Interpretation of data: SK, WN, and PT. Writing original draft: SK and WN. Writing review and editing: all authors.

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Conflicts of interest

The authors have no conflicts of interest directly relevant to the content of this article.

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