Prevalence of early bacterial co-infection in hospitalized patients with COVID-19 pneumonia: a retrospective study

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Background: Identification of bacterial co-infection is crucial in determining outcomes of patients with coronavirus disease 2019 (COVID-19) pneumonia. The present study aims to evaluate the prevalence and associated factors of early bacterial co-infection in patients with COVID-19 pneumonia.

Methods: The present study is a retrospective study. Patients with COVID-19 pneumonia, who were admitted to Siriraj Hospital between April 1 and August 31, 2021, were randomly enrolled and classified as the "Early bacterial co-infection" group, defined by an infection occurring within the first 48 hours after admission, and the "Unlikely early bacterial co-infection" group.

Results: A total of 245 patients were enrolled. The prevalence of early bacterial co-infection was 15.5%. Chest X-rays showed characteristic findings for COVID-19 pneumonia in 37.6%. The median Brixia chest X-ray scores and C-reactive protein levels were significantly higher in the Early bacterial co-infection group. The most common causative pathogens included *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Stenotrophomonas maltophilia*. Patients with early bacterial co-infection had a significantly higher all-cause mortality compared to the Unlikely early bacterial co-infection group (P=0.012). The Charlson Comorbidity Index ≥4, high level of respiratory support, and mass-liked or diffuse opacities on chest X-rays were independent factors associated with the early bacterial co-infection.

Conclusions: The prevalence of early bacterial co-infection in patients with COVID-19 pneumonia was low but it was associated with mortality. There is insufficient evidence to support the empirical use of antibiotics in these patients. A further prospective study is required to confirm the results of the present study.

Keywords: Coronavirus disease 2019 pneumonia (COVID-19 pneumonia); severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); co-infection; pneumonia

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Introduction

The coronavirus disease 2019 (COVID-19) pandemic has been a global healthcare emergency, causing millions of deaths worldwide. The COVID-19 mortality rate in Thailand was 1.03%. About 64% of these deaths are patients with comorbidities. There are limited reports on well-established risk factors for disease progression and mortality in Thai patients. One of the most anticipated risk factors is a bacterial infection, including early bacterial co-infection and nosocomial bacterial infection, which the latter appears to be more frequent with a prevalence of 45–71% (1-3). The definition of early bacterial co-infection may vary among studies, but it generally refers to bacterial infection occurring within the first 48 hours of hospitalization. Diagnosing early bacterial co-infection in COVID-19 pneumonia patients is challenging because the clinical and radiological features can overlap and cannot be distinguished from viral pneumonia. The appropriate tests might be necessary, including respiratory specimen culture, other laboratory tests, and serum biomarkers. In previous reports on the influenza pandemic, the prevalence of bacterial co-infection was high, ranging from 30–50% in severe influenza which was associated with increased mortality (4-7). Several observational studies have reported the prevalence of early bacterial co-infection in patients with COVID-19 pneumonia ranging from 1.2% to 5.5% which was lower than that in influenza (8-10).

Bacterial co-infection in hospitalized patients with COVID-19 pneumonia may worsen clinical outcomes and increase mortality. However, early studies have demonstrated that early bacterial co-infection is uncommon. The most commonly reported causative pathogens included methicillin-susceptible *Staphylococcus aureus* (MSSA), *Hemophilus influenzae*, and *Streptococcus pneumoniae*, respectively (10-14). The patients with bacterial co-infection also had a 3-time higher risk of mortality and had 13 days longer hospital stay (15).

Identification of bacterial co-infection is crucial in determining patient outcomes and deciding whether to start or discontinue broad-spectrum antibiotics in order to avoid antibiotic overuse. In Thailand, the data on the prevalence of early bacterial co-infection in patients with COVID-19 pneumonia is limited. The present study aimed to evaluate the prevalence of early bacterial co-infection and its associated factors. We present this article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-1681/rc).

Methods

The present study is a single-center, retrospective study conducted at the Division of Respiratory Disease and Tuberculosis, Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Thailand. The primary outcome was to evaluate the prevalence of early bacterial co-infection in hospitalized patients with COVID-19 pneumonia at Siriraj hospital. The secondary outcomes included the predictors of early bacterial co-infection, characteristics of the patients and chest X-ray, causative pathogens, and clinical outcomes. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and approved by the Institutional Review Board of the Faculty of Medicine Siriraj Hospital (COA No. SI901/2564). Informed consent was waived due to the retrospective nature of the study.

All patients with COVID-19 pneumonia who were admitted to either intensive care units or in-patient wards between April 1 and August 31, 2021 were reviewed for eligibility. The inclusion criteria included patients at least 18 years of age, who had confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection from the nasopharyngeal swab, expectorated sputum, or tracheal aspirate using the reverse transcriptase-polymerase chain reaction (RT-PCR) technique within 7 days and were hospitalized within 48 hours at the time of SARS-CoV-2 infection diagnosis. Pneumonia is defined by having compatible signs and symptoms (fever >38 ℃ plus at least 1 symptom of cough, purulent sputum, dyspnea,

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Highlight box

Key findings
- The prevalence of early bacterial co-infection in patients with COVID-19 pneumonia was low but it was associated with mortality.

What is known and what is new?
- Early bacterial co-infection in patients with COVID-19 pneumonia is rare with variable reported prevalence across the world.
- The present study demonstrated several factors associated with an early bacterial co-infection in patients with COVID-19 pneumonia.

What is the implication, and what should change now?
- COVID-19 pneumonia patients with these associated factors, an early bacterial co-infection should be considered in order to expedite antibiotic prescription.

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pleuritic chest pain, respiratory rate >20 times per minute, crackles, rhonchi, or signs of consolidation from physical examination) and having abnormal chest X-ray, including alveolar opacities, consolidation, interstitial opacities, or ground-glass opacities. The exclusion criteria included patients who were admitted for more than 48 hours before the diagnosis of SARS-CoV-2 infection, were admitted to another hospital for more than 48 hours, had a history of hospital admission within 14 days, or had no respiratory symptoms.

Data of eligible patients were obtained from electronic medical records using specific ICD-10 codes (U07.1 COVID-19, virus identified, and J128, Other viral pneumonia). Patients were randomly enrolled using computer-based randomization. The patients were classified as the "Early bacterial co-infection" group if they had microbiological evidence of bacterial co-infection (including positive hemoculture, sputum culture, nasopharyngeal swab PCR, and sputum PCR for respiratory pathogens) obtained within 48 hours after hospitalization or met the criteria for probable bacterial co-infection, defined by having at least 2 systemic inflammatory response syndrome (SIRS) criteria and was treated with antibiotics for at least 5 days (16,17). The diagnosis of probable bacterial co-infection was confirmed by 2 pulmonologists. The remaining patients were classified as the "Unlikely early bacterial co-infection" group. Clinical characteristics, chest X-ray findings, laboratory and microbiological results, hospital course, complications, and patient outcomes were assessed. Chest X-rays were obtained within 48 hours after admission and were assessed by one pulmonologist and one chest radiologist. Radiographic findings were classified as characteristic (bilateral patchy and/or confluent, bandlike ground-glass opacity or consolidation, peripheral and mid to lower lung zone distribution), non-specific (focal, unilateral opacity, ill-defined bibasilar opacity, diffuse opacity, upper lobe predominance, mass-liked opacity, effusion), and negative (normal) according to the previously proposed radiographic classification (18). A subsequent consensus read was performed to address discrepancies between the two readers. The Brixia chest X-ray score was used to grade lung abnormalities and was interpreted by one pulmonologist and one chest radiologist who were blinded to clinical data (19,20). The overall Brixia chest X-ray score ranged from 0 to 18 which higher scores indicating more severe disease. The Brixia chest X-ray score was used to further assess the correlation between the severity of chest X-rays and outcomes (20).

Statistical analyses

Sample size estimation was performed based on the previously reported prevalence of early bacterial co-infection and the sample size equation for the descriptive study (10,21). Type 1 error, confidence interval width and expected prevalence were set at 5%, 3%, and 5.5%, respectively. The percentage of missing data was set at 10%, thus at least 245 subjects were needed for analysis.

Categorical data were presented as frequencies and percentages. Continuous data were presented as mean, range, and standard deviation (SD) if they were normally distributed, or median and interquartile range (IQR) if they were not normally distributed. Categorical data were compared using the Chi-square test or Fisher's exact test. Continuous data were compared using an independent t-test or Mann-Whitney U test. Interobserver agreement analyses were performed using Cohen's weighted kappa if the data were categorical data, and intraclass correlation coefficient if the data were continuous data. Multivariate logistic regression analysis was used to assess the factors associated with early bacterial co-infection. A P value of less than 0.05 was considered statistically significant. All statistical analyses were performed using statistical software (SPSS for Windows, version 18.0; SPSS; Chicago, USA).

Results

A total of 1,429 hospitalized COVID-19 pneumonia patients were available for selection, and 245 patients who met the inclusion criteria were randomly selected for the analysis, with the sample size determined based on a calculation to ensure adequate statistical power and generalizability of the results (*Figure 1*). The prevalence of early bacterial co-infection was 15.5% (38 patients). 48.2% of patients were men with a mean age of 60 years as shown in *Table 1*. There were more men in the Early bacterial co-infection group compared to the Unlikely early bacterial co-infection group (65.8% and 44.9%, respectively; P=0.018). The mean body mass index (BMI) was 26.6 kg/m^2. Patients in the Early bacterial co-infection group had a higher Charlson Comorbidity Index (CCI) compared to the Unlikely early bacterial co-infection group (3.5 and 2, respectively; P=0.012). Patients with early bacterial co-infection had a significantly higher proportion of the comorbidities of chronic heart failure, coronary artery disease, and chronic kidney disease without renal replacement therapy.

The median days from symptom onset (DOS) to admission was 5 days which was no difference between
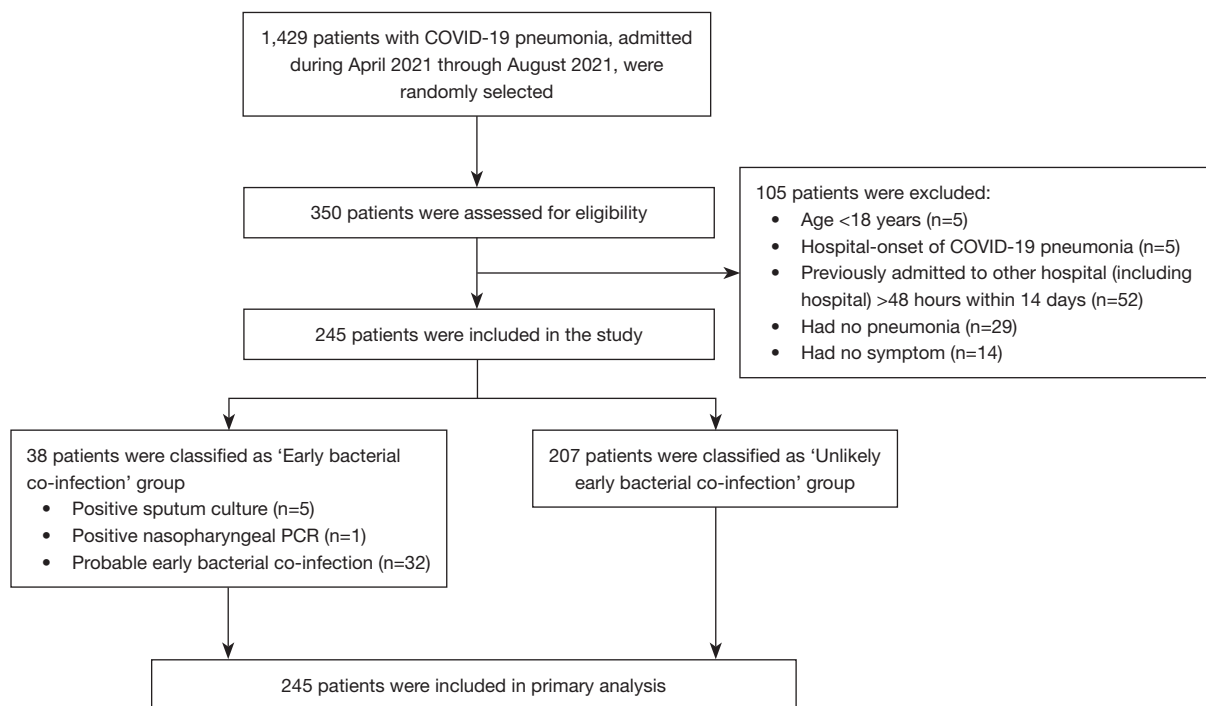
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┌─────────────────────────────────────────┐
│ 1,429 patients with COVID-19 pneumonia,  │
│ admitted during April 2021 through       │
│ August 2021, were randomly selected      │
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┌─────────────────────────────────────────┐        ┌───────────────────────────────────────────┐
│ 350 patients were assessed for           │───────▶│ 105 patients were excluded:                 │
│ eligibility                              │        │  • Age <18 years (n=5)                      │
└─────────────────────────────────────────┘        │  • Hospital-onset of COVID-19 pneumonia     │
                   │                                │    (n=5)                                    │
                   ▼                                │  • Previously admitted to other hospital    │
┌─────────────────────────────────────────┐        │    (including hospital) >48 hours within    │
│ 245 patients were included in the study  │        │    14 days (n=52)                           │
└─────────────────────────────────────────┘        │  • Had no pneumonia (n=29)                  │
                   │                                │  • Had no symptom (n=14)                     │
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38 patients were classified as 'Early bacterial co-infection' group
- Positive sputum culture (n=5)
- Positive nasopharyngeal PCR (n=1)
- Probable early bacterial co-infection (n=32)

207 patients were classified as 'Unlikely early bacterial co-infection' group

245 patients were included in primary analysis

Figure 1 Study flow chart. A total of 1,429 hospitalized COVID-19 pneumonia patients were available for selection, and 245 patients who met the inclusion criteria were randomly selected for the analysis, with the sample size determined based on a calculation. COVID-19, coronavirus disease 2019; PCR, polymerase chain reaction.

groups. Fever, shortness of breath, and cough were the most presenting symptoms (70.6%, 55.1%, and 45.7%, respectively). In the Early bacterial co-infection group, shortness of breath (78.9%), initial intensive care unit (ICU) admission (28.9%), vasopressor use (10.5%), and a presence of at least 2 SIRS criteria (97.4%) were significantly higher than those in the Unlikely early bacterial co-infection group as shown in *Table 2*. There were more patients who needed high-flow nasal cannula (HFNC) or invasive mechanical ventilation (IMV) as the initial respiratory support in the Early bacterial co-infection group compared to the Unlikely early bacterial co-infection group (50% and 23.7%, and 16.4% and 2.4%, respectively; P<0.001).

All patients performed chest X-rays within 48 hours of admission. 92 of 245 patients (37.6%) had characteristic radiographic findings for COVID-19 pneumonia which included bilateral patchy, bandlike ground-glass opacities or consolidation in peripheral and mid to lower lung zone (23.7% in the Early bacterial co-infection group and 40.1% in the Unlikely early bacterial co-infection group, P=0.055) as shown in *Table 2*. Interobserver agreement for radiographic interpretation was moderate (Kappa coefficient

0.603, P<0.001). Diffuse opacities and mass-liked opacities were found more in the Early bacterial co-infection group compared to the Unlikely early bacterial co-infection group (44.7% and 16.5%, and 10.5% and 1.9%, respectively; P<0.001). The median Brixia chest X-ray scores were 11 and 7 in the Early bacterial co-infection group and the Unlikely early bacterial co-infection group, respectively (P<0.001), with an intraclass correlation coefficient between two readers of 0.77 (95% CI: 0.71–0.82).

Compared to the Unlikely early bacterial co-infection group, patients in the Early bacterial co-infection group had a significantly higher white blood cell count, absolute neutrophil count, D-dimer levels, and C-reactive protein (CRP) levels, whereas the procalcitonin (PCT) level was no difference between groups as shown in *Table 2*.

There was no difference in the number of patients with worsening respiratory failure, length of hospital stays, length of ICU stays, and days of mechanical ventilation between groups. Higher all-cause mortality was observed in the Early bacterial co-infection group compared to the Unlikely early bacterial co-infection group (31.6% and 12.6%, respectively; P=0.012). Complications including

Table 1 Patient characteristics

Characteristics	Total (N=245)	Early bacterial co-infection (N=38)	Unlikely early bacterial co-infection (N=207)	P value	Odd ratio (95% CI)
Demographic data					
Age (years), mean ± SD (range)	60±17 (18 to 95)	64±17 (32 to 95)	60±17 (18 to 93)	0.136	1.02 (0.995–1.04)
Male, n (%)	118 (48.2)	25 (65.8)	93 (44.9)	0.018	0.42 (0.21–0.88)
Body mass index, mean ± SD	26.6±6.6	27.4±7.4	26.5±6.5	0.403	1.02 (0.97–1.07)
Charlson Comorbidity Index, median (IQR)	2 (1 to 4)	3.5 (1.8 to 5.3)	2 (1 to 4)	0.012	1.2 (1.05–1.36)
Smoking, n (%)					
Non-smoker	147 (87.0)	20 (74.1)	127 (89.4)	–	1
Current smoker	7 (4.1)	2 (7.4)	5 (3.5)	0.284	2.54 (0.46–13.99)
Ex-smoker	15 (8.9)	5 (18.5)	10 (7)	0.053	3.18 (0.98–10.26)
Comorbidities, n (%)					
Diabetes	81 (33.1)	14 (36.8)	67 (32.4)	0.59	1.22 (0.59–2.51)
Hypertension	125 (51.0)	23 (60.5)	102 (49.3)	0.202	1.58 (0.78–3.20)
Chronic heart failure	5 (2.0)	3 (7.9)	2 (1.0)	0.028	8.79 (1.42–54.48)
Coronary artery disease	22 (9.0)	9 (23.7)	13 (6.3)	0.002	4.63 (1.82–11.80)
Cerebrovascular accident	12 (4.9)	3 (7.9)	9 (4.3)	0.405	1.89 (0.49–7.31)
Peripheral arterial disease	2 (0.8)	1 (2.6)	1 (0.5)	0.287	5.57 (0.34–90.99)
Asthma	5 (2.0)	0 (0.0)	5 (2.4)	1	–
COPD	7 (2.9)	2 (5.3)	5 (2.4)	0.297	2.24 (0.42–12.02)
Chronic kidney disease					
Without RRT	15 (6.1)	6 (15.8)	9 (4.3)	0.013	4.07 (1.25–12.22)
With RRT	10 (4.1)	1 (2.6)	9 (4.3)	0.716	0.68 (0.08–5.54)
Cancer	14 (5.7)	1 (2.6)	13 (6.3)	0.702	0.40 (0.05–3.18)
Hematologic malignancy	3 (1.2)	2 (5.3)	1 (0.5)	0.064	11.44 (1.01–129.53)
Immunocompromised	8 (3.3)	2 (5.3)	6 (2.9)		1.86 (0.36–9.59)
HIV infection	3 (1.2)	1 (2.6)	2 (1.0)	0.398	2.77 (0.25–31.34)
Biologic therapy	1 (0.4)	1 (2.6)	0 (0.0)	0.155	–
Chemotherapy within 6 months	3 (1.2)	0 (0.0)	3 (1.4)	1	–
SOT/HSCT	1 (0.4)	0 (0.0)	1 (0.4)	1	–

CI, confidence interval; COPD; chronic obstructive pulmonary disease; HIV, human immunodeficiency virus; HSCT, hematopoietic stem cell transplantation; IQR, interquartile range; RRT, renal replacement therapy; SD, standard deviation; SOT, solid organ transplantation.

pneumothorax, pneumomediastinum, ventilator-associated pneumonia, hospital-acquired pneumonia, and other nosocomial infection were no significant differences between groups as shown in *Table 3*.

The microbiological data were available in 62 of 245 patients (25.3%) including 62 hemocultures (25.3%), 27 sputum or tracheal aspirate cultures (11%), 5 nasopharyngeal PCR (2%), and 4 sputum PCR (1.6%). In the Early bacterial co-infection group, 6 patients (15.8%) had microbiological confirmation, and 32 patients (84.2%)

Table 2 Clinical features of patients in the early bacterial co-infection and unlikely early bacterial co-infection groups

Variables	Total (N=245)	Early bacterial co-infection (N=38)	Unlikely early bacterial co-infection (N=207)	P value	Odd ratio (95% CI)
Days from symptoms onset to admission	5 (3 to 7)	5 (3 to 7.25)	5 (3 to 7)	0.716	1.04 (0.92–1.17)
Symptoms at admission					
Fever	173 (70.6)	28 (73.7)	145 (70.0)	0.651	1.20 (0.55–2.61)
Shortness of breath	135 (55.1)	30 (78.9)	105 (50.7)	0.001	3.64 (1.60–8.32)
Cough	112 (45.7)	18 (47.4)	94 (45.4)	0.824	1.08 (0.54–2.16)
Diarrhea	31 (12.7)	6 (15.8)	25 (12.1)	0.594	1.37 (0.52–3.59)
Mode of respiratory support in the first 48 hours					
No supplement oxygen	94 (38.4)	3 (7.9)	91 (44.0)	–	1
Low-flow oxygen	83 (33.9)	7 (18.4)	76 (36.7)	0.146	2.79 (0.70–11.18)
HFNC	54 (21.6)	19 (50.0)	35 (16.4)	<0.001	16.47 (4.59–59.14)
IMV	14 (5.7)	9 (23.7)	5 (2.4)	<0.001	54.60 (11.17–266.88)
Initial ICU admission within 48 hours after admission	20 (8.2)	11 (28.9)	9 (4.3)	<0.001	8.96 (3.40–23.61)
Vasopressor use	6 (2.4)	4 (10.5)	2 (1.0)	0.006	12.06 (2.13–68.41)
≥2 SIRS criteria	91 (37.1)	37 (97.4)	54 (26.1)	<0.001	104.83 (14.04–782.68)
Fever >38 ℃ or <36 ℃	45 (18.4)	14 (36.8)	31 (12.7)	0.001	3.31 (1.55–7.09)
Heart rate >90 bpm	99 (40.4)	28 (73.7)	71 (33.8)	<0.001	5.36 (2.47–11.67)
RR >20/min or PaO$_2$ <38 mmHg	107 (43.7)	34 (89.5)	73 (35.3)	<0.001	15.60 (5.33–45.70)
WBC >12,000 or <4,000×10^9/L or immature neutrophil >10%	64 (26.1)	20 (52.6)	44 (21.3)	<0.001	4.12 (2.01–8.44)
Radiographic findings					
Findings					
Characteristic	92 (37.6)	9 (23.7)	83 (40.1)	0.055	0.46 (0.21–1.03)
Non-specific					
Focal, unilateral	13 (5.3)	1 (2.6)	12 (5.8)	0.698	0.44 (0.06–3.48)
Ill-defined bibasilar opacities	72 (29.4)	7 (18.4)	65 (31.4)	0.106	0.49 (0.21–1.18)
Diffuse opacities	51 (20.8)	17 (44.7)	34 (16.5)	<0.001	4.12 (1.97–8.61)
Upper lobe predominant opacities	7 (2.9)	0 (0.0)	7 (3.4)	0.600	–
Mass-like opacities	8 (3.3)	4 (10.5)	4 (1.9)	0.022	5.97 (1.43–25.02)
Effusion	2 (0.8)	0 (0.0)	2 (1.0)	1.000	–
Brixia chest X-ray score	8 (5 to 11)	11 (8 to 15)	7 (4 to 11)	<0.001	1.24 (1.13–1.35)
Laboratory testing					
Hemoglobin (g/dL)	12.8±2	12.6±2	12.8±2	0.436	0.93 (0.79–1.11)
White blood cell count (×10^9/L)	6,524.2±3,010.2	8,720.3±5,153.1	6,121±2,216	0.004	1.0002 (1.0001–1.0004)
Absolute neutrophil count (×10^9/L)	4,060 (2,980 to 5,805)	5,955 (3,980 to 10,212.5)	3,970 (2,910 to 5,490)	<0.001	1.0003 (1.0002–1.0004)
D-dimer (ng/mL)	869 (503 to 1,596)	1,015 (635 to 3,127.5)	863 (489.3 to 1,539.5)	0.025	1.0001 (1.00001–1.0002)
C-reactive protein (mg/dL)	49.7 (15.7 to 88.1)	83.9 (58 to 126.4)	41.8 (9.8 to 79.2)	<0.001	1.01 (1.005–1.02)
Procalcitonin (ng/mL)	0.22 (0.09 to 0.54)	0.43 (0.19 to 1.58)	0.17 (0.08 to 0.36)	0.115	1.05 (0.99–1.12)

Data are presented as median (IQR) or n (%) or mean ± SD. bpm, beats per minute; CI, confidence interval; g/dL, grams per deciliter; HFNC, high-flow nasal cannula; ICU, intensive care unit; IQR, interquartile range; IMV, invasive mechanical ventilation; L, liters; mg/dL, milligrams per deciliter; ng/mL, nanograms per milliliter; PaO$_2$, partial pressure of oxygen in arterial blood; RR, respiratory rate; SIRS, systemic inflammatory response syndrome; SD, standard deviation; WBC, white blood cells.

Table 3 Hospital course and complications of patients in the early bacterial co-infection and unlikely early bacterial co-infection groups

Variables	Total (N=245)	Early bacterial co-infection (N=38)	Unlikely early bacterial co-infection (N=207)	P value	Odd ratio (95% CI)
Hospital course					
Worsening respiratory failure, n (%)	73 (29.8)	13 (34.2)	60 (29.0)	0.517	1.27 (0.61–2.66)
Length of hospital stays (days), median (IQR)	9 (5 to 14)	12.5 (8 to 16)	9 (5 to 14)	0.078	1.03 (0.997–1.07)
Length of ICU stays (days), median (min to max)	9 (5 to 15)	9 (5 to 17)	9 (5 to 15)	0.697	1.02 (0.96–1.09)
Days of mechanical ventilation (days), median (range)	9 (7 to 19.5)	13 (7.5 to 26.5)	8.5 (5.5 to 18.8)	0.472	1.02 (0.97–1.08)
Outcome, n (%)					
Discharge	170 (69.4)	24 (63.2)	146 (70.5)	–	1
Refer to other hospital	37 (15.1)	2 (5.3)	35 (16.9)	0.164	0.35 (0.08–1.54)
Death	38 (15.5)	12 (31.6)	26 (12.6)	0.012	2.81 (1.25–6.30)
Respiratory cause	35 (14.3)	11 (28.9)	24 (11.6)		
Other cause	3 (1.2)	1 (2.6)	2 (1.0)		
Complications, n (%)					
Pneumothorax	5 (2.0)	1 (2.6)	4 (1.9)	0.573	1.37 (0.15–12.62)
Pneumomediastinum	5 (2.0)	1 (2.6)	4 (1.9)	0.573	1.37 (0.15–12.62)
VAP/HAP	24 (9.8)	4 (10.5)	20 (9.7)	0.773	1.10 (0.35–3.42)
Nosocomial infection other than LRTI				0.918	
Urinary tract infection	5 (2.0)	1 (2.6)	4 (1.9)		
Catheter-related blood stream infection	2 (0.8)	0 (0.0)	2 (0.8)		
Bacteremia	7 (2.9)	2 (5.3)	5 (2.4)		
CMV colitis	1 (0.4)	0 (0.0)	1 (0.5)		

CI, confidence interval; CMV, cytomegalovirus, HAP, hospital-acquired pneumonia; ICU, intensive care unit; IQR, interquartile range; LRTI, lower respiratory tract infection; VAP, ventilator-associated pneumonia.

met the criteria for probable bacterial co-infection. The initial empirical antibiotics were prescribed in 25.3% (97.4% in the Early bacterial co-infection group and 12.1% in the Unlikely early bacterial co-infection group; P<0.001). The causative pathogens included methicillin-susceptible *Staphylococcus aureus* (n=2), *Pseudomonas aeruginosa* (n=2), and *Stenotrophomonas maltophilia* (n=2), *Haemophilus influenza* (n=1), *Klebsiella pneumoniae* (n=1), and *Enterobacter cloacae* (n=1).

When using the Brixia chest X-ray score cut-off at 8, patients with scores of more than 8 had more IMV use (20.2% and 5.1%, P<0.001) and ICU admission (24.8% and 6.6%, P<0.001). This group also had higher mortality when compared to the group with a lower Brixia chest X-ray score (22% and 10.3%, respectively; P=0.049) (*Table 4*).

When using the CRP level cut-off at 60 mg/dL, patients with CRP levels of at least 60 mg/dL had more IMV use (17.8% and 7.2%, P=0.012). Higher mortality was also observed in this group compared to those with lower CRP levels as shown in *Table 4*.

When using the PCT level cut-off at 0.5 ng/mL, there was no significant difference in the number of patients with worsening respiratory failure, length of hospital stays, invasive mechanical ventilator use, ICU admission, and all-cause mortality.

Univariate and multivariate analyses

All of the potential risk factors for early bacterial co-infection were assessed using univariate and multivariate

Table 4 Correlations between patient outcomes and Brixia chest X-ray score and serum biomarkers

Variables	Brixia chest X-ray score				CRP level (mg/dL)				PCT level (ng/mL)			
	>8 (N=109)	≤8 (N=136)	P value	Odd ratio (95% CI)	≥60 mg/dL (N=107)	<60 mg/dL (N=138)	P value	Odd ratio (95% CI)	≥0.5 ng/mL (N=37)	<0.5 ng/mL (N=109)	P value	Odd ratio (95% CI)
Worsening respiratory failure	31 (28.4)	42 (30.9)	0.678	0.89 (0.51–1.55)	34 (31.8)	39 (28.3)	0.551	1.18 (0.68–2.05)	11 (29.7)	31 (28.4)	0.881	1.07 (0.47–2.41)
Length of hospital stays (days)	10 (5 to 14)	9 (5 to 3)	0.211	1.02 (0.99–1.05)	10 (6 to 14)	8 (5 to 14)	0.07	1.02 (0.99–1.05)	12 (7 to 15)	9 (6 to 14)	0.257	1.01 (0.97–1.05)
Any invasive mechanical ventilator use during hospital course	22 (20.2)	7 (5.1)	<0.001	4.66 (1.91–11.38)	19 (17.8)	10 (7.2)	0.012	2.76 (1.23–6.23)	5 (13.5)	15 (13.8)	0.97	0.98 (0.33–2.91)
Any ICU admission during hospital course	27 (24.8)	9 (6.6)	<0.001	4.65 (2.08–10.38)	20 (18.7)	16 (11.6)	0.12	1.75 (0.86–3.58)	8 (21.6)	16 (14.7)	0.325	1.6 (0.62–4.13)
Outcome												
Discharge	77 (70.6)	93 (68.4)	–	1	76 (71.0)	94 (68.1)	–	1	27 (73.0)	85 (78.0)	–	1
Refer to other hospital	8 (7.3)	29 (21.3)	0.01	0.33 (0.14–0.77)	7 (6.5)	30 (21.7)	0.005	0.29 (0.12–0.69)	0 (0.0)	5 (4.6)	1	–
Death	24 (22.0)	14 (10.3)	0.049	2.07 (1.003–4.28)	24 (22.4)	14 (10.1)	0.042	2.12 (1.03–4.38)	10 (27.0)	19 (17.5)	0.261	1.66 (0.69–4.00)

Data are presented as median (IQR) or n (%). CI, confidence interval; CRP, C-reactive protein; ICU, intensive care unit; IQR, interquartile range; mg/dL, milligrams per deciliter; ng/mL, nanograms per milliliter; PCT, procalcitonin.

analyses as shown in *Table 5*. The analysis demonstrated that the CCI >4 (OR 2.99, 95% CI: 1.24–7.19, P=0.014), the use of HFNC (OR 22.21, 95% CI: 4.69–105.13, P<0.001), the use of IMV (OR 63.69, 95% CI: 9.9–413.06, P=0.002), diffuse opacities on chest X-ray (OR 3.23, 95% CI: 1.31–7.97, P=0.011), and mass-like opacities on chest X-ray (OR 21.31, 95% CI: 2.47–183.85, P=0.005) were independent factors associated with early bacterial co-infection.

Discussion

The prevalence of early bacterial co-infection in COVID-19 pneumonia widely varies depending on the patient population and diagnostic criteria, ranging from 0–46% (2,22-25). The microbiological tests in the present study were infrequently performed which was similar to the previous report that might reflect the real-world situation (1). The present study reported a prevalence of 15.5% which included the patients who had a microbiological confirmation and patients with probable early bacterial co-infection. In the pandemic situation, the collection of respiratory specimens cannot be performed in all patients because of the risk of the virus spreading to healthcare providers and other patients. Therefore, the use of clinical data combining with chest X-ray features and other laboratory tests might be helpful. The present study demonstrated that higher CCI, the use of a high level of respiratory support, diffuse opacities, and mass-liked opacities on chest X-rays were independent factors associated with early bacterial co-infection consistently with previous reports (8,9,22,26,27). A large multicenter study identified the characteristics of patients at risk for developing early bacterial co-infection, comprising of higher targeted real-time early warning score, higher CRP level, and higher ferritin level. Moreover, it also showed that the high-grade fever, purulent sputum, leukocytosis, need for supplementary oxygen, and specific chest radiographic findings including consolidation, infiltration, and interstitial opacities, were found more in patients with early bacterial co-infection (8). Another observation cohort study found that combining the white blood cell count of more than $8.8×10^9$ cells/L, absolute neutrophil count of more than $6.9×10^9$ cells/L, and CRP level of more than 119.8 mg/dL can predict the early bacterial co-infection with very high negative predictive values (9).

Chest X-ray is commonly used and plays an important role in monitoring COVID-19 pneumonia patients to assess the severity and extent of lung involvement,

Table 5 Univariate and multivariate analyses of the factors associated with early bacterial co-infection

Factors	Univariate analysis		Multivariate analysis	
	Odd ratio (95% CI)	P value	Odd ratio (95% CI)	P value
Male	0.42 (0.21–0.88)	0.018		
Charlson Comorbidity Index ≥4	2.39 (1.19–4.83)	0.013	2.99 (1.24–7.19)	0.014
Coronary artery disease	4.63 (1.82–11.80)	0.002		
Chronic kidney disease, without RRT	4.07 (1.25–12.22)	0.013		
Shortness of breath	3.64 (1.60–8.32)	0.001		
Mode of respiratory support in the first 48 hours				
HFNC	16.47 (4.59–59.14)	<0.001	22.21 (4.69–105.13)	<0.001
IMV	54.60 (11.17–266.88)	<0.001	63.96 (9.9–413.06)	0.002
Initial ICU admission	8.96 (3.40–23.61)	<0.001		
Vasopressors use	12.06 (2.13–68.41)	0.006		
Chest X-ray findings, n (%)				
Diffuse opacities	4.12 (1.97–8.61)	<0.001	3.23 (1.31–7.97)	0.011
Mass-like opacities	5.97 (1.43–25.02)	0.022	21.31 (2.47–183.85)	0.005
Brixia chest X-ray score >8	4.36 (2.01–9.40)	<0.001		
CRP level ≥60 mg/dL	5.30 (2.4–11.85)	<0.001		

CI, confidence interval; CRP, C-reactive protein; HFNC, high-flow nasal cannula; ICU, intensive care unit; IMV, invasive mechanical ventilation; mg/dL, milligrams per deciliter; RRT, renal replacement therapy.

identify complications, and treatment guidance (28). The characteristic chest X-ray finding, including bilateral patchy and/or confluent, bandlike ground-glass opacity or consolidation, peripheral and mid to lower lung zone distribution, was more likely to be found in the Unlikely early bacterial co-infection group. The present study confirmed the usefulness of chest X-ray in determining the severity and monitoring the disease. The presence of early bacterial co-infection should be considered in patients who had diffuse or mass-liked opacities on chest X-ray and Brixia chest X-ray score of more than 8. However, these radiological features can overlap and cannot be totally distinguished from COVID-19 pneumonia, combining with the clinical data and other laboratory tests would be necessary to consider microbiological tests to confirm the presence of early bacterial co-infection. The previous study has reported the severity scoring system of chest X-ray, the Brixia chest X-ray score, which the higher score was associated with mortality in COVID-19 pneumonia patients (20). Consistently, we found that the Brixia chest X-ray score of more than 8 was associated with more severe

disease and higher mortality.

Several studies found that the elevation of CRP and PCT levels were associated with worse clinical outcomes (29-34). Data on the use of these biomarkers to predict early bacterial co-infection in COVID-19 pneumonia is limited. The present study found that early bacterial co-infection was associated with higher CRP levels but there was no correlation with PCT levels. Consistently with previous studies, baseline PCT level should be interpreted with caution to exclude early bacterial co-infection but a rising of PCT level might be useful in the detection of acquired bacterial infection during hospitalization (35).

We did not perform microbiological tests in all patients because of the followings: (I) The present study was a retrospective study. We did not have a routine protocol for collecting respiratory specimens in all patients with COVID-19 pneumonia, and (II) there was a limitation in respiratory specimen collection due to the risk of spreading the virus to healthcare providers and other patients. These appear to be real-life situations in the pandemic era in which the rate of respiratory specimen collection was

low (1). The most common causative pathogens included *S.aureus*, *H.influenzae*, and *S.pneumoniae* while gram-negative organisms were more reported in nosocomial infection (3,11,36). However, gram-negative organisms have also been reported as the causative pathogens in early bacterial co-infection with variable prevalence, including *K.pneumoniae* (3.4%), *P.aeruginosa* (9.3%), and *E.coli* (7.6%) (1,26). In the present study, two patients had *S.maltophilia* mixed with *K.pneumoniae* and MSSA on their sputum cultures. Therefore, the authors included these patients in the early bacterial co-infection group.

In the present study, the initial empirical antibiotics were prescribed in 25.3% which was lower than that in the previous studies (37,38). However, the role of empirical antibiotics in COVID-19 pneumonia patients is controversial. There have been studies demonstrating that inappropriate use of antibiotics may lead to increased morbidity and mortality in patients with COVID-19 (37-39). Furthermore, overuse of antibiotics results in antibiotic-related side effects and the development of resistant nosocomial bacterial and fungal pathogens. Despite the low reported prevalence of bacterial co-infection, one study showed that more than half of hospitalized COVID-19-infected patients were empirically treated with antibiotics at hospital admission. Most of these patients were elderly, had severe disease symptoms, had lobar infiltrates from chest X-rays, or were admitted to the for-profit hospital (37). The National Institutes of Health (NIH) guideline stated that there was insufficient evidence to give any recommendation either for or against empirical antibiotics in the absence of another indication. The recent surviving sepsis campaign guideline recommended prescribing empirical antibiotics only in patients with respiratory failure requiring mechanical ventilation (40). According to the results of the present study, the initial empirical antibiotics may be considered in COVID-19 pneumonia patients with higher comorbidities, diffuse or mass-liked opacities on chest X-ray, and receiving a high level of respiratory support while waiting for confirmation from microbiological tests.

The present study has some limitations. Firstly, it is a single-center, retrospective cross-sectional study. Some data collection might be limited. Secondly, we did not routinely perform microbiological tests in all patients. These might result in underdiagnosis of bacterial co-infection if microbiological confirmation is the only criteria for diagnosis. Therefore, we included the patient with probable bacterial co-infection by carefully reviewing the criteria of categorization to minimize bias.

Conclusions

The prevalence of early bacterial co-infection in hospitalized patients with COVID-19 pneumonia was low. There is insufficient evidence to support the empirical use of antibiotics in patients with COVID-19 pneumonia. A further prospective study is required to confirm the results of the present study.

Acknowledgments

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-1681/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-1681/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and approved by the Institutional Review Board of the Faculty of Medicine Siriraj Hospital (COA No. SI901/2564). Informed consent was waived due to the retrospective nature of the study.

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