



## Original Article

# Bacterial co-infection and secondary infection in critically ill patients with acute respiratory failure of coronavirus disease 2019

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## ABSTRACT

**Objectives:** The objective of the study is to understand the prevalence of bacterial co-infection and secondary infection in severe coronavirus disease 2019 (COVID-19) pneumonia in a tertiary hospital intensive care unit (ICU), the spectrum of pathogens, and the impact of these infections on clinical outcomes. **Materials and Methods:** Retrospective analysis of all patients with COVID-19 with acute hypoxemic respiratory failure who were admitted to the ICU requiring invasive mechanical ventilation (IMV) or high-flow nasal cannula (HFNC) from January 2021 to August 2022. **Results:** Of the 123 cases, 59.3% had culture-confirmed bacterial co-infection, mostly lower respiratory tract infections (LRTIs). Patients with bacterial co-infection had higher 30-day mortality (28.8% vs. 12%, hazard ratio [HR] = 2.96, %95 confidence interval [CI] = 1.1–7.99; adjusted HR [aHR] = 1.34, %95 CI = 0.43–4.17). *Klebsiella pneumoniae*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa* were the most common co-infection pathogens. Of the 108 cases who stayed in the ICU for >2 days, 34 (31.5%) cases developed secondary bacterial infections within 30 days, of whom all cases had LRTI, 4 had bacteremia, and 8 had urinary tract infections. IMV users had a higher 1-month incidence of secondary bacterial infections than HFNC users (47.5% vs. 8.9%,  $P < 0.0001$ ). Patients with secondary bacterial infections had higher 60-day mortality (32.4% vs. 11.2% HR = 3.45, 95% CI = 1.27–9.4; aHR = 2.29, %95 CI = 0.8–6.67). The most common secondary infection pathogens were *Acinetobacter* species, *P. aeruginosa*, *Stenotrophomonas maltophilia*, and *K. pneumoniae*. At the 30-day follow-up, 54 events of ICU-acquired secondary bacterial LRTI were noted in 34 patients, 18 (33.3%) events, and 15 (44%) patients were infected by carbapenem-resistant Gram-negative bacilli. **Conclusion:** The high incidence of bacterial co-infection and secondary infection in critically ill patients with COVID-19 might associated with increased mortality. Infection by drug-resistant pathogens may develop during the treatment course.

**KEYWORDS:** Acute respiratory failure, Bacterial co-infection, Coronavirus disease 2019, Secondary infection

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## INTRODUCTION

It has been over 4 years since the World Health Organization (WHO) declared coronavirus disease 2019 (COVID-19) a public health emergency of international concern (PHEIC) on January 30, 2020. Thereafter, the pandemic has caused over 7.7 trillion cases and 7 million deaths [1,2]. Although the WHO lifted its PHEIC declaration on May 5, 2023, COVID-19 continues to pose a significant global health risk [3]. The mortality and morbidity of COVID-19 are still much higher than seasonal influenza. The evolution of prevalent virus variants is rapid, making vaccine effectiveness limited. The substantial post-COVID-19 condition (also known as

long COVID-19) threatens human well-being continuously. Most patients with COVID-19 are asymptomatic or become symptomatic with only mild-to-moderate symptoms that spontaneously recover within days to weeks. Age, underlying comorbidities, immunity following a previous COVID-19 infection, and vaccination status are risk factors for severe and critical illness. The rate of critical illness among infected patients decreases as individuals develop immunity-to-severe

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acute respiratory syndrome coronavirus 2 (SARS-CoV-2) through vaccination, natural infection, and through the evolution of less virulent SARS-CoV-2 variants [4]. However, several patients require hospitalization, intensive care unit (ICU) admission, or other specialized medical care.

The use of concurrent antibiotics is a challenge in treating COVID-19. The bacterial co-infection prevalence is approximately 2%–10% and 23%–88% among hospitalized and ICU/critically ill patients with COVID-19, respectively [5-7]. Secondary infection, also known as hospital-acquired infection, is another challenge not only due to its impact on increased ICU stays and mortality but also due to the potential problem of drug-resistant organisms. Critically ill patients with COVID-19 have been reported to have a secondary infection prevalence of 57%–63% [8,9]. Co-infection and secondary infection rates significantly vary depending on the medical system and population characteristics.

This study aimed to determine the prevalence of bacterial co-infection and secondary infection in severe COVID-19 pneumonia in a tertiary hospital ICU, the spectrum of pathogens, and the impact of these infections on clinical outcomes.

## MATERIALS AND METHODS

### Study population

This is a retrospective cohort study of patients with COVID-19 admitted to the medical ICU of Hualien Tzu Chi Hospital, a tertiary referral center, between January 2021 and August 2022. This ICU was set in response to the pandemic, with the policy that all critically ill patients with COVID-19 who needed intensive care in Eastern Taiwan would be transferred to this ICU. This study was conducted in accordance with the Declaration of Helsinki. This study was reviewed and approved by the Research Ethics Committee of Hualien Tzu Chi Hospital. The requirement for written informed consent was waived (decision number: IRB112-142-B; date: July 1, 2023).

All patients had a confirmed diagnosis of SARS-CoV-2 infection by polymerase chain reaction testing of respiratory tract specimens. This study included patients with pneumonia and acute hypoxemic respiratory failure who needed invasive mechanical ventilation (IMV) or high-flow nasal cannula (HFNC) to support breathing in the first 24 h of ICU stay. This study excluded patients with hospital-acquired COVID-19, those with chronic respiratory failure, and those who were hospitalized for >24 h before ICU admission. Patient demographics, laboratory, pertinent medications, life-support interventions, and outcomes were abstracted by manual chart review from medical records.

### Outcome measurements

The definition of bacterial co-infection was based on clinician-driven microbiological tests performed in the first 24 h of ICU stay, including cultures of blood, tracheal aspirate, qualified sputum and urine, urinary antigen tests for *Legionella pneumophila* serogroup 1, serum *Mycoplasma pneumoniae* antibody, and sputum mycobacterial cultures.

Qualified sputum specimen was defined as >25 white blood cells (WBCs) per average low-power field (LPF) and <10 squamous epithelial cells/LPF. Urinary tract infection was defined as a urine culture with >100,000 colonies/mL.

Patients who stayed in the ICU for >48 h were included in the analysis for secondary infection, which was also defined using clinician-driven microbiological tests.

The primary outcome for all enrolled patients with COVID-19 with acute respiratory failure was 30-day mortality. ICU and hospital days, mechanical ventilation duration, ICU and hospital mortality, and secondary infection rate comprised other outcomes. For patients who stayed in the ICU for >48 h, the development of secondary infection within 30 days and their 60-day mortality were the outcome measures.

### Statistics

Demographic and clinical characteristics were calculated using descriptive statistics. Between-group comparisons were performed using the Chi-square test of independence for categorical variables and the Mann–Whitney *U*-test for discrete variables. Logistic regression was used to adjust the Acute Physiology and Chronic Health Evaluation (APACHE)-II score ( $\geq 25$  vs.  $< 25$ ) in the analysis of bacterial infection as a risk factor for mortality. Time-to-event analyses were performed using the log-rank test and depicted using Kaplan–Meier curves. A two-sided  $P < 0.05$  was considered statistically significant. All analyses were performed using IBM Statistical Package for the Social Sciences Statistics version 27 (Armonk, New York, USA).

## RESULTS

Of the 290 critically ill patients with COVID-19 admitted to the ICU in the study period, 154 received IMV or HFNC in the first 24 h of ICU stay. After applying the exclusion criteria, 123 patients were included in this study. The 108 patients who stayed in the ICU for >48 h were included in the analysis for secondary infection [Figure 1].

During the first 24 h of ICU admission, most patients underwent blood, sputum, and urine cultures and urine antigen tests for *L. pneumophila* serogroup 1 [Supplementary Table 1]. Of the 123 patients, 73 (59.3%) had confirmed bacterial co-infection. There were 63 (51.2%), 15 (12.2%), and 23 (18.7%) patients who had clinically significant culture results in sputum, blood, and urine cultures, respectively. Two cases had pulmonary tuberculosis co-infection [Supplementary Table 1].

The demographic data and blood test results at ICU admission are listed in Table 1. Compared with patients who had no bacterial co-infection (BC[−] group), critically ill patients with COVID-19 with bacterial co-infection at ICU admission (BC[+] group) were older (mean age,  $70.3 \pm 12.3$  vs.  $62.1 \pm 13.7$  years,  $P = 0.0009$ ) and thinner (body mass index [BMI],  $21.9 \pm 5.1$  vs.  $26.5 \pm 6.5$  kg/m<sup>2</sup>,  $P < 0.0001$ ). The BC (+) group had higher APACHE-II score ( $27.8 \pm 7.6$  vs.  $22.1 \pm 8.9$ ,  $P < 0.0001$ ), higher Charlson comorbidity index ( $5.9 \pm 2.9$  vs.  $4.2 \pm 2.7$ ,  $P = 0.0013$ ), and higher proportions of stroke history status (39.7% vs. 14%,

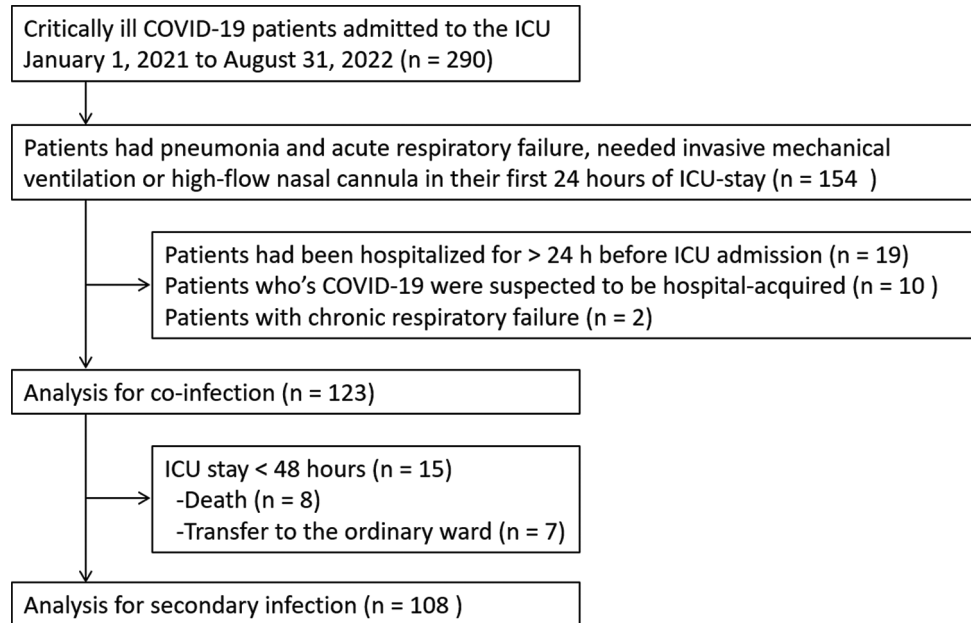


Figure 1: Flowchart of patients enrolled for analysis. COVID-19: Coronavirus disease 2019, ICU: Intensive care unit

Table 1: Patient characteristics at intensive care unit admission

	All patients (n=123)	No co-infection (n=50)	Bacterial co-infection (n=73)	P
Age (years)	67.0±13.4	62.1±13.7	70.3±12.3	0.0009
Sex (male)	81 (65.9)	30 (60)	51 (69.9)	0.3333
BMI (kg/m <sup>2</sup> )	23.8±6.1	26.5±6.5	21.9±5.1	<0.0001
APACHE-II	25.5±8.6	22.1±8.9	27.8±7.6	<0.0001
Charlson comorbidity index	5.2±2.9	4.2±2.7	5.9±2.9	0.0013
SARS-CoV-2 vaccine doses before admission	1 (0-3)	2 (0-3)	1 (0-3)	0.4303
Current smoker	27 (22.0)	11 (22.0)	16 (21.9)	>0.9999
Hypertension	71 (57.7)	31 (62.0)	40 (54.8)	0.4618
Diabetes	55 (44.7)	26 (52.0)	29 (39.7)	0.1787
COPD	17 (13.8)	4 (8.0)	13 (17.8)	0.154
Heart failure	15 (12.2)	9 (18.0)	6 (8.2)	0.1035
Liver disease	24 (19.5)	11 (22.0)	13 (17.8)	0.5645
Chronic kidney disease	24 (19.5)	13 (26)	11 (15.1)	0.4646
Malignancy	28 (22.8)	8 (16)	20 (27.4)	0.1892
Stroke history	36 (29.3)	7 (14)	29 (39.7)	0.0021
Bedridden status	38 (30.9)	2 (4)	36 (49.3)	<0.0001
Nursing home resident	27 (22.0)	3 (6)	24 (32.9)	0.0003
Blood tests				
PaO <sub>2</sub> /FiO <sub>2</sub> (mmHg)	203 (107-362)	204 (116-384)	176 (104-355)	0.3574
WBC (×10 <sup>3</sup> /μL)	9.00 (5.87-12.51)	9.16 (6.57-12.50)	8.41 (5.65-12.59)	0.3765
Segmented neutrophil (% of WBC)	73.1 (55.0-82.9)	74.9 (65.5-84.9)	70.0 (47.5-79.8)	0.0202
Band neutrophil (% of WBC)	2.0 (0-19.0)	0 (0-7.0)	7.0 (0-32.5)	0.0001
Lymphocyte (% of WBC)	10.0 (6.0-16.0)	10.9 (6.2-19.9)	9.7 (5.3-15.0)	0.3361
Hb (g/dL)	12.0 (9.8-13.5)	11.4 (8.9-13.5)	12.1 (10.2-13.6)	0.2588
PLT (×10 <sup>3</sup> /μL)	202 (124-268)	204 (126-270)	194 (122-259)	0.7573
Creatinine (mg/dL)	1.21 (0.74-1.87)	1.23 (0.83-1.72)	1.17 (0.73-2.02)	0.987
CK (IU/L)	223 (100-583)	269 (111-7038)	197 (87-571)	0.4825
CRP (mg/dL)	8.5 (2.1-13.4)	6.2 (1.1-12.4)	8.8 (2.7-16.2)	0.0601
Procalcitonin (ng/mL)	1.36 (0.31-10.23)	0.44 (0.17-2.24)	6.51 (0.55-13.87)	0.0026

Values are expressed as *n* (%) or medium (quantiles). Chronic kidney disease is defined as a serum creatinine level of >3 mg/dL or on dialysis. BMI: Body mass index, COPD: Chronic obstructive pulmonary disease, WBC: White blood cell, APACHE-II: Acute physiology and chronic health evaluation-II, SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2, Hb: Hemoglobin, PLT: Platelet count, CRP: C-reactive protein, CK: Creatine kinase

$P = 0.0021$ ), bedridden status (49.3% vs. 4%,  $P < 0.0001$ ), and nursing home resident (32.9% vs. 6%,  $P = 0.0003$ ). The

BC(+) and BC(-) groups had median dose numbers of the SARS-CoV-2 vaccine before admission of 1 (0-3) and 2 (0-3),

respectively, without statistical significance. The BC(+) and BC(-) groups showed no differences in PaO<sub>2</sub>/FiO<sub>2</sub>, peripheral WBC count, platelet count, hemoglobin, creatinine, creatine kinase, and C-reactive protein levels. The BC(+) group had a higher band neutrophil proportion and a higher serum procalcitonin level [Table 1]. In the BC(+) group, 41 (56.2%) patients were mechanically ventilated, whereas that in the BC(-) group was 31 (62%), with no statistical difference.

The 30-day mortality of the BC(+) group was 28.8%, which was significantly higher than 12% in the BC(-) group (hazard ratio [HR] = 2.96, %95 confidence interval [CI] = 1.1–7.99,  $P = 0.029$ ) [Supplementary Figure 1a]. After adjustment by APACHE-II score, there was no statistical difference between groups (adjusted HR [aHR] = 1.34, %95 CI = 0.43–4.17,  $P = 0.609$ ). Both groups showed no differences in hospital, ICU, mechanical ventilation, and HFNC days. The incidence of secondary bacterial infections within the following month and the 60-day mortality was not different [Table 2].

Of the 108 patients who stayed in the ICU for >48 h, 63 (58.3%) received mechanical ventilation, and 45 (41.7%) used HFNC without mechanical ventilation. Thirty-four (31.5%) cases developed secondary bacterial infections within 30 days (BS[+] group), of whom all cases had lower respiratory tract infection (LRTI), 4 had bacteremia with pathogens different from those identified in the respiratory tract, and 8 had urinary tract infections. Patients who received IMV had a significantly higher risk of developing secondary infections than HFNC users (47.6% vs. 8.9%, log-rank test:  $P < 0.0001$ ) [Supplementary Figure 2].

The BS(+) group was older and had higher APACHE-II scores than the BS(-) group. Both groups had similar proportions of bacterial co-infection and hyperglycemia events. The BS(+) group had a more frequent use of mechanical ventilation, new initiation of hemodialysis, prone therapy, continuous intravenous cisatracurium, and vasopressor infusion than the BS(-) group. No differences in the use of remdesivir, systemic steroids, tocilizumab, and antibiotics were observed between the groups [Table 3].

The BS(+) group had higher 60-day mortality (32.4% vs. 11.2%, HR = 3.45, 95% CI = 1.27–9.4,  $P = 0.017$ ),

longer hospital stays (30 [18–47] vs. 12 [7–17] days,  $P < 0.0001$ ), and longer ICU stays (13.5 [7–18] vs. 4 [3–6],  $P < 0.0001$ ). After adjustment by APACHE-II score, the mortality difference between groups was insignificant (aHR = 2.29, %95 CI = 0.8–6.67,  $P = 0.129$ ). Among the patients who were mechanically ventilated at ICU admission, the BS(+) group had longer mechanical ventilation days (10 [6–20] vs. 3 [2–5] days,  $P < 0.0001$ ) than the BS(-) group [Supplementary Table 2 and Supplementary Figure 1b].

The most frequent pathogens identified by bacterial culture in critically ill patients with COVID-19 with co-infection and secondary infection are presented in Supplemental Table 3. *Klebsiella pneumoniae*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa* were the top three bacteria identified in patients with lower respiratory tract co-infection. *Acinetobacter species*, *P. aeruginosa*, and *Stenotrophomonas maltophilia* were the top three pathogens in patients with secondary bacterial lower respiratory infections.

Of the 106 isolates from 63 patients with lower respiratory tract bacterial co-infections, only one carbapenem-resistant Gram-negative bacillus (CR-GNB) (*Acinetobacter pittii*) isolate was identified. Of the 34 patients with the first event of secondary LRTI, 15 and five patients developed the second and third events of LRTI, respectively. There were 11, 4, and 3 isolates of CR-GNB noted in 8 (23.5%), 4 (26.7%), and 3 (60%) patients' sputum from the first, second, and third events of ICU-acquired LRTI cases, respectively. CR-GNB in secondary LRTIs included CR-*Acinetobacter species*, *S. maltophilia*, and CR-*P. aeruginosa* [Figure 2].

## DISCUSSION

This study identified that the bacterial co-infection rate at ICU admission in critically ill patients with COVID-19 who needed IMV or HFNC support was 59.3%, and 86.3% of co-infections were LRTIs. The recent meta-analysis showed the prevalence of bacterial co-infection in critically ill COVID-19 patients was 57.7% (95% CI = 29.6%–81.6%) [7]. The incidence of ICU-acquired bacterial secondary infection within 1 month was 31.5%; all cases had LRTIs, 23.5% had urinary tract infections, and 11.8% had bloodstream infections. At

**Table 2: Clinical outcomes**

	All patients (n=123)	No co-infection (n=50)	Bacterial co-infection (n=73)	P
Hospital days	12 (5–24)	12 (6–26)	12 (4–22)	0.6897
ICU days	5 (3–9)	5 (3–7)	5 (3–11)	0.8037
IMV days in IMV patients (n=72)	5 (2–10)	4 (1–9)	5 (2–10)	0.5955
HFNC days in HFNC without IMV (n=51)	3 (2–4)	3 (2–4)	3 (2–4.75)	0.8638
ICU mortality	25 (20.3)	6 (12.0)	19 (26.0)	0.0697
Hospital mortality	31 (25.2)	8 (16.0)	23 (31.5)	0.0594
30-day mortality	27 (22.0)	6 (12.0)	21 (28.8)	0.029
60-day mortality	32 (26)	9 (18.0)	23 (31.5)	0.1004
Secondary infection within 1 month	34 (27.6)	13 (26.0)	21 (38.8)	0.8383
Secondary LRTI	34 (27.6)	13 (26.0)	21 (28.8)	0.8383
Secondary BSI	4 (3.3)	2 (4.0)	2 (2.7)	>0.9999
Secondary UTI	8 (6.5)	4 (8.0)	4 (5.5)	0.0623
Secondary infection with CR pathogen	15 (12.2)	5 (10.0)	10 (13.7)	0.5885

IMV: Invasive mechanical ventilation, HFNC: High-flow nasal cannula, BSI: Bloodstream infection, UTI: Urinary tract infection, CR: Carbapenem-resistant, LRTI: Lower respiratory tract infection

**Table 3: Risk factors for secondary bacterial infection**

	All (n=108)	No secondary infection within 1 month (n=74)	Secondary infection within 1 month (n=34)	P
Patient characteristics				
Age (years)	66.4±12.8	64.8±12.6	69.9±12.8	0.0393
Sex (male)	71 (65.7)	50 (67.6)	21 (61.8)	0.6631
BMI	23.9±2.3	24.0±6.8	23.7±5.1	0.7953
APACHE-II	24.2±18.7	22.6±7.1	27.6±7	0.0006
Charlson comorbidity index	5.1±2.9	5.1±2.9	5.3±2.8	0.604
SARS-CoV-2 vaccine doses before admission	1 (0-3)	2 (0-3)	1 (0-3)	0.328
Current smoker	24 (22.2)	16 (21.6)	8 (23.5)	0.8084
Hypertension	64 (59.3)	42 (56.8)	22 (64.7)	0.5286
Diabetes mellitus	51 (47.2)	36 (48.6)	15 (44.1)	0.6838
COPD	13 (12.0)	9 (12.2)	4 (11.8)	>0.9999
Heart failure	13 (12.0)	8 (10.8)	5 (14.7)	0.5423
Liver disease	21 (19.4)	14 (18.9)	7 (20.6)	>0.9999
Chronic kidney disease	20 (18.5)	14 (18.9)	6 (17.6)	>0.9999
Malignancy	20 (18.5)	16 (21.6)	4 (11.8)	0.2906
Stroke history	31 (28.7)	22 (29.7)	9 (26.5)	0.821
Bedridden status	33 (30.6)	21 (28.4)	12 (35.3)	0.5048
Nursing home resident	24 (22.2)	17 (23.0)	7 (20.6)	>0.9999
Clinical course and treatment				
Co-infection at ICU admission	62 (57.4)	42 (56.8)	20 (58.8)	>0.9999
Hyperglycemia	32 (29.6)	18 (24.3)	14 (41.2)	0.1112
IMV	63 (58.3)	33 (44.6)	30 (88.2)	0.0009
HFNC without requiring IMV	45 (41.7)	41 (55.4)	4 (11.8)	<0.0001
New initiation of hemodialysis	6 (5.6)	1 (1.4)	5 (14.7)	0.0115
Prone therapy ≥16 h	5 (4.6)	1 (1.4)	4 (11.8)	0.0333
Vasopressor ≥24 h	46 (42.6)	25 (33.8)	21 (61.8)	0.0113
Remdesivir ≥5 days	87 (80.6)	59 (79.7)	28 (82.4)	>0.9999
Systemic steroid ≥5 days	54 (50.0)	36 (48.6)	18 (52.9)	0.8361
Tocilizumab	12 (11.1)	8 (10.8)	4 (11.8)	>0.9999
Continuous cisatracurium ≥1 day	7 (7.4)	1 (1.4)	7 (20.6)	0.0038
Exposure to cephalosporin ≥2 days	37 (34.3)	28 (37.8)	9 (26.5)	0.2817
Exposure to BI/BLI ≥2 days	54 (50)	35 (47.3)	19 (55.9)	0.5346
Exposure to carbapenems ≥2 days	24 (22.2)	15 (20.3)	9 (26.5)	0.4671
Exposure to fluoroquinolones ≥2 days	10 (9.3)	8 (10.8)	2 (5.9)	0.5
Exposure to anti-ORSA ≥2 days	30 (27.8)	18 (24.3)	12 (35.3)	0.2549
Exposure to any antibiotics ≥2 days	106 (98.1)	74 (100)	32 (94.1)	0.0971

Values are expressed as *n* (%) or medium (quantiles). Hyperglycemia is defined as blood glucose levels of >300 mg/dL in ≥2 days. Chronic kidney disease is defined as a serum creatinine level of >3 mg/dL or on dialysis. COPD: Chronic obstructive pulmonary disease, BMI: Body mass index, IMV: Invasive mechanical ventilation, HFNC: High-flow nasal cannula, ORSA: Oxacillin-resistant *Staphylococcus aureus*, BI/BLI: β-lactam/β-lactamase inhibitor, APACHE-II: Acute physiology and chronic health evaluation-II, ICU: Intensive care unit

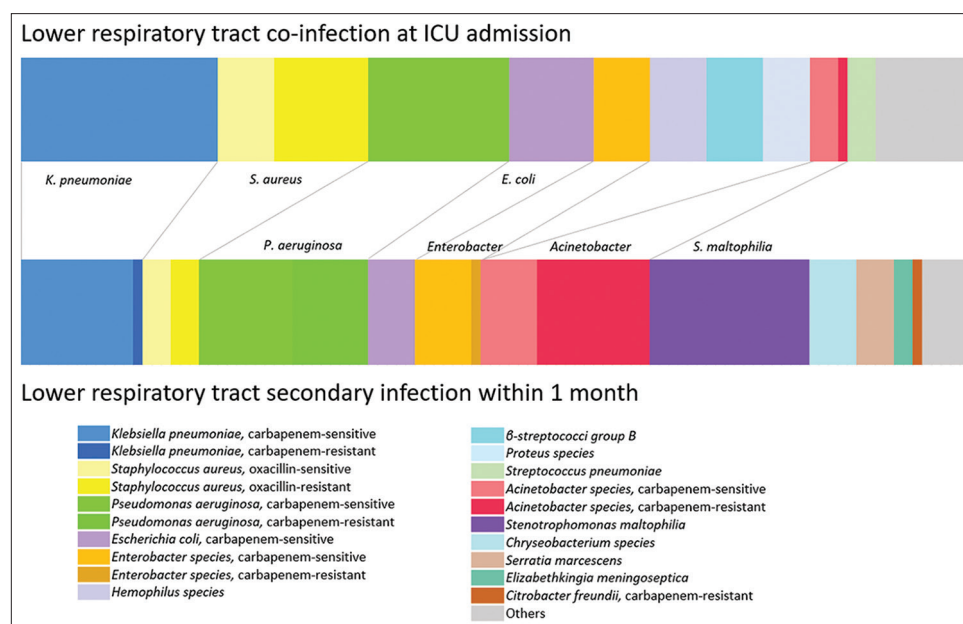
ICU admission, drug-resistant pathogens were uncommon but became substantial in secondary infection pathogens. Patients with bacterial co-infection had higher 30-day mortality, whereas those with secondary infection had higher 60-day mortality. However, after adjustment by the APACHE-II score, these mortality differences were not statistically different.

Old age, low BMI, high severity scores, and underlying comorbidities, especially bedridden status, are factors associated with higher co-infection rates. Bandemia and elevated procalcitonin levels may increase the suspicion of bacterial co-infection. In critically ill patients with COVID-19, the SARS-CoV-2 vaccination status was not associated with bacterial co-infection.

The dysregulation of the immune system in aging is an important risk factor for severe COVID-19. Immunosenescence

involves impaired innate and adaptive immunities, and inflammaging, which represents the attendance of systemic inflammatory mediators in the body of the elderly, causes more turbulences to the immune system, and strengthens many persistent diseases of them [10]. Low body weight and sarcopenia may aggravate inflammaging through a complicated causal relationship map [11].

Early in 2022, the Omicron variant began to dominate globally, including in Taiwan. This variant was highly transmissible and had several mutations in its spike protein, leading to immune evasion. In March 2021, Taiwan officially launched the SARS-CoV-2 vaccination program. Owing to limited supply and vaccine hesitancy, the initial rollout was slow. Before the end of 2021, with more vaccines arriving and the approaching community outbreaks, second doses were



**Figure 2:** Bacterial pathogens identified in critically ill patients with coronavirus disease 2019 with lower respiratory bacterial co-infection and secondary infection. ICU: Intensive care unit

being widely administered, particularly for frontline workers, older adults, and those with underlying health conditions. Among the enrolled 123 patients, 50 (40.7%) never received SARS-CoV-2 vaccine, and 60 (48.8%) received at least two vaccine doses. Although SARS-CoV-2 vaccines can effectively reduce the progression of COVID-19 to severe disease, once the infected patients become critically ill, vaccination status does not protect against bacterial infection.

Old age, high APACHE-II scores, mechanical ventilation use, and receiving hemodialysis, neuromuscular blockers, paralysis therapy, prone therapy, and vasopressors are risk factors for secondary bacterial infection. Counterintuitively, the prolonged use of systemic steroids for  $\geq 5$  days and the use of tocilizumab as anti-inflammatory therapies in patients with severe COVID-19 were not associated with secondary bacterial infection development; however, the limited case numbers may make the results inconclusive. Therapy with tocilizumab reduced the mortality of hospitalized COVID-19 patients. The meta-analysis included 10,930 patients in 27 trials. It showed no statistical difference in secondary infection rate by 28 days between patients treated with immunoglobulin (IL)-6 antagonist and those treated with usual care or placebo [12]. Similar finding was found in systemic steroids; compared with no glucocorticoids, systemic steroids significantly improved clinical outcomes without increasing secondary infections [13-15]. The severity of COVID-19 pneumonia and the host's immunity may more significantly influence secondary infection occurrence. Viruses increase bacterial infection by the following mechanisms: impairing the host's immune response, disrupting epithelial barrier integrity and the expression of surface receptors and adhesion proteins, direct binding of the virus to bacteria, altering nutritional immunity, and affecting the bacterial biofilm [16]. A study on mice reported that coronavirus limits the bacterial killing ability of macrophages by impairing lysosomal acidification

and fusion with engulfed bacteria, and lysosomal dysfunction further promotes pyroptotic cell death and IL-1  $\beta$  release [17]. Additionally, IMV may increase the risk of secondary bacterial infections in patients with COVID-19 by either directly breaching the host defense or through coronavirus-impaired host immunity [18].

Despite the confirmed viral pneumonia, almost all patients received antibiotic treatment for  $\geq 2$  days. Antibiotic overuse can cause the development of subsequent infections due to drug-resistant pathogens. For physicians dealing with patients with severe viral pneumonia and for the high co-infection incidence among patients with severe COVID-19, wisely selecting empirical antibiotics is crucial.

This study had some limitations. First, the single-center retrospective study design hindered the extrapolation of its results to patients from other settings. Second, differentiating the severity of LRTIs as pneumonia, bronchitis, tracheitis, or just bacterial colonization was not performed. Distinguishing between viral and bacterial pneumonia on the basis of symptoms or chest radiographs was challenging. To overcome this shortcoming, we only used culture results from qualified sputum specimens and conservatively used the term "LRTI" instead of "pneumonia." Third, due to the limited number of patients and the retrospective study design, we did not analyze the impact of polymicrobial results of sputum culture on the outcomes. A prospective study design with routine and repeated sampling of bronchoalveolar lavage fluid for culture may be needed to derive a reliable result on the impact of mixed infection.

## CONCLUSION

The high bacterial co-infection and secondary infection incidence among critically ill patients with COVID-19 is associated with increased mortality, but the impact was not

significant after adjustment of disease severity. Older adult patients with high illness severity, multiple comorbidities, frailty, bacteremia, and elevated procalcitonin levels should be more closely monitored for co-infections. The most common co-infection bacterial pathogens, especially in LRTIs, are *K. pneumoniae*, *S. aureus*, and *P. aeruginosa*. Patients requiring IMV have a high incidence of secondary LRTI. Infections due to drug-resistant bacteria may develop during the treatment course; secondary LRTIs due to carbapenem-resistant *Acinetobacter* species, *Pseudomonas*, and *K. pneumoniae* are potential threats.

#### Data availability statement

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

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Nil.

#### Conflicts of interest

There are no conflicts of interest.

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**SUPPLEMENTARY MATERIAL**

**Supplementary Table 1: Clinician-driven microbiological tests within the first 24 h of intensive care unit admission among all study participants**

Laboratory tests	Tested cases	Tested rate (%)	Positive results	Positivity rate among 123 cases (%)
Tracheal aspirate or sputum culture	106	86.2	63	51.2
Blood culture	112	91.1	15	12.2
Urine culture	81	65.9	23	18.7
<i>S. pneumoniae</i> antigen	94	76.4	25	20.3
<i>L. pneumophila</i> antigen	94	76.4	0	0.0
<i>Mycoplasma</i> IgG	66	53.7	2	1.6
<i>Mycoplasma</i> IgM	69	56.1	0	0.0
Sputum TB culture	44	35.8	2	1.6

TB: Tuberculosis, ICU: Intensive care unit, Ig: Immunoglobulin. *S. pneumoniae*: *Streptococcus pneumoniae*, *L. pneumophila*: *Legionella pneumophila*

**Supplementary Table 2: Clinical outcomes of patients with >48-h intensive care unit stay**

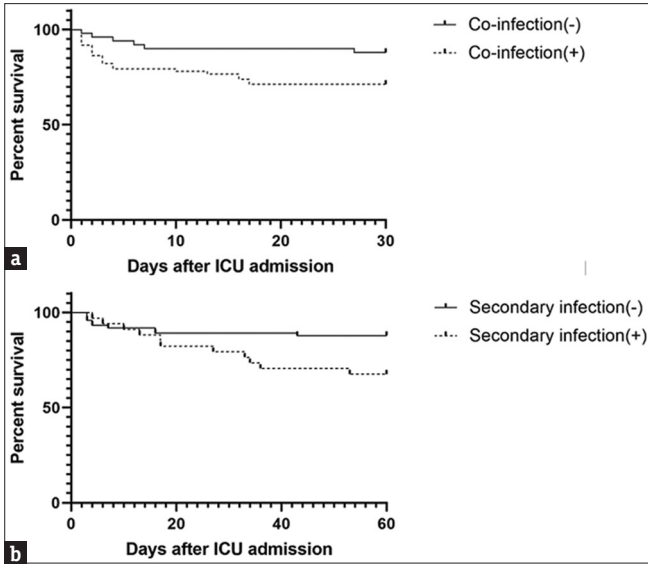
	All (n=108)	No secondary infection within 1 month (n=74)	Secondary infection within 1 month (n=34)	P
Hospital days	14 (8–26)	12 (7–17)	30 (18–47)	<0.0001
ICU days	6 (4–10)	4 (3–6)	13.5 (7–18)	<0.0001
IMV days in patients receiving IMV (n=62)	5 (3–10)	3 (2–5)	10 (6–20)	<0.0001
HFNC days in HFNC without IMV (n=45)	3 (2–5)	3 (2–5)	4.5 (2–13)	0.3621
ICU mortality	13 (12.0)	7 (9.5)	6 (17.6)	0.3387
Hospital mortality	19 (17.6)	9 (12.2)	10 (29.4)	0.0539
30-day mortality	15 (13.9)	8 (10.8)	7 (20.6)	0.2307
60-day mortality	20 (18.5)	9 (12.2)	11 (32.4)	0.0169

HFNC: High-flow nasal cannula, IMV: Invasive mechanical ventilation, ICU: Intensive care unit

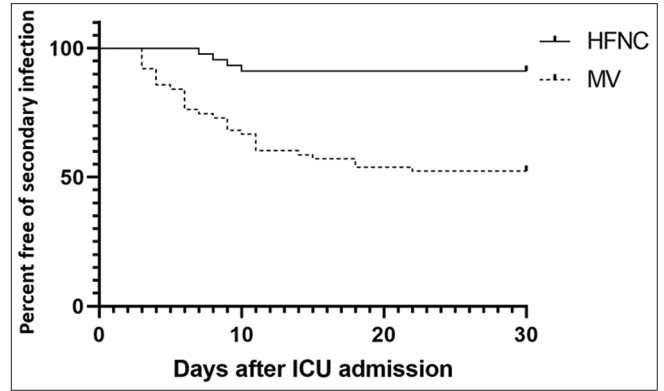
**Supplementary Table 3: Most frequent pathogens identified by bacterial culture in critically ill patients with coronavirus disease 2019 with co-infection and secondary infection**

Co-infection		Secondary infection	
Pathogen	Count of isolates	Pathogen	Count of isolates
<b>LRTIs</b>			
106 isolates from 63 patients		79 isolates in 53 events of 34 patients	
<i>K. pneumoniae</i>	22	<i>Acinetobacter</i> species	14
<i>S. aureus</i>	17	<i>P. aeruginosa</i>	14
<i>P. aeruginosa</i>	16	<i>S. maltophilia</i>	13
<i>E. coli</i>	10	<i>K. pneumoniae</i>	10
<i>Enterobacter</i> species	6	<i>Enterobacter</i> species	6
<b>Urinary tract infection</b>			
37 isolates from 23 patients		12 isolates in 11 events of 8 patients	
<i>E. coli</i>	8	<i>Candida</i> spp.	7
<i>E. faecalis</i>	8	<i>E. faecium</i>	2
<i>K. pneumoniae</i>	4	<i>K. pneumoniae</i>	1
<i>P. aeruginosa</i>	4	<i>E. cloacae</i>	1
<i>M. morgani</i>	3	<i>P. aeruginosa</i>	1
<b>Bacteremia</b>			
19 isolates from 15 patients		4 isolates in 4 events of 4 patients	
<i>E. coli</i>	3	<i>C. tropicalis</i>	1
<i>K. pneumoniae</i>	3	<i>E. faecalis</i>	1
<i>P. aeruginosa</i>	2	<i>E. aerogenes</i>	1
<i>Staphylococcus</i> spp.	2	<i>K. pneumoniae</i>	1
<i>Streptococcus</i> spp.	2		

*K. pneumoniae*: *Klebsiella pneumoniae*, *S. aureus*: *Staphylococcus aureus*, *P. aeruginosa*: *Pseudomonas aeruginosa*, *E. coli*: *Escherichia coli*, *S. maltophilia*: *Stenotrophomonas maltophilia*, *E. faecalis*: *Enterococcus faecalis*, *E. faecium*: *Enterococcus faecium*, *M. morgani*: *Morganella morgani*, *E. cloacae*: *Enterobacter cloacae*, *C. tropicalis*: *Candida tropicalis*, *E. aerogenes*: *Enterobacter aerogenes*, LSTIs: Lower respiratory tract infection



**Supplemental Figure 1:** Kaplan–Meier curve for cumulative mortality. (a) Patients with bacterial co-infection at intensive care unit admission have significantly higher 30-day mortality (log-rank test:  $P = 0.0269$ ). (b) Patients with secondary infection have significantly higher 60-day mortality (log-rank test:  $P = 0.0266$ ). ICU: Intensive care unit



**Supplemental Figure 2:** Time to secondary infection development. Patients who have experienced mechanical ventilation have a significantly higher risk of developing secondary infections (log-rank test:  $P < 0.0001$ ). IMV: Invasive mechanical ventilation, HFNC: High-flow nasal cannula, ICU: Intensive care unit