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Incidence and Temporal Dynamics of Combined Infections in SARS-CoV-2-Infected Patients With Risk Factors for Severe Complications

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ABSTRACT

Background: Coronavirus disease 2019 (COVID-19) is a newly emerged infectious disease that needs further clinical investigation. Characterizing the temporal pattern of combined infections in patients with COVID-19 may help clinicians understand the clinical nature of this disease and provide valuable diagnostic and therapeutic guidelines.
Methods: We retrospectively analyzed COVID-19 patients isolated in four study hospitals in Korea for one year period from May 2021 to April 2022 when the delta and omicron variants were dominant. The temporal characteristics of combined infections based on specific diagnostic tests were analyzed.
Results: A total of 16,967 COVID-19 patients were screened, 2,432 (14.3%) of whom underwent diagnostic microbiologic tests according to the clinical decision-making, 195 of whom had positive test results, and 0.55% (94/16,967) of whom were ultimately considered to have clinically meaningful combined infections. The median duration for the diagnosis of combined infections was 15 (interquartile range [IQR], 5–25) days after admission. The proportion of community-acquired coinfections (≤ 2 days after admission) was 11.7% (11/94), which included bacteremia (10/94, 10.63%) and tuberculosis (1/94, 1.06%). Combined infections after 2 days of admission were diagnosed at median 16 (IQR, 9–26) days, and included bacteremia (72.3%), fungemia (19.3%), cytomegalovirus (CMV) diseases (8.4%), *Pneumocystis jerovecii* pneumonia (PJP, 8.4%) and invasive pulmonary aspergillosis (IPA, 4.8%).
Conclusion: Among COVID-19 patients with risk factors for severe complications, 0.55% had laboratory-confirmed combined infections, which included community and nosocomial pathogens in addition to unusual pathogens such as CMV disease, PJP and IPA.

Keywords: COVID-19; Coinfection; Korea; Bacteremia; Opportunistic Infections

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The authors declare that they have no conflicts of interest.

Author Contributions
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INTRODUCTION

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has posed an enormous global threat and is expected to remain an endemic infection. The clinical presentation of COVID-19 is diverse, and its severity ranges from asymptomatic cases to critical conditions associated with mortality.[1,2] Risk factors associated with severe complications and fatality of COVID-19, such as age, obesity, smoking status and various underlying diseases, have been studied.[3] Combined infection by microorganisms other than SARS-CoV-2 in COVID-19 patients has also been reported to be associated with increased mortality.[4-6] COVID-19 renders infected patients vulnerable to infection by bacteria, fungi and other viruses due to impairment of the immune system by the infection itself and damage to the lung, in addition to the use of certain therapeutics, including steroids and antibiotics, for COVID-19 treatment.[7] The overall combined infection rate in COVID-19 patients has been reported to be 0.6–45%. This wide variation stems from the various types of infections and causative pathogens, as well as geographic and demographic factors, which differ between studies.[8] Coinfections at the initial presentation or secondary infectious complications during the clinical course are important in predicting and properly managing patients. Therefore, precisely defining the characteristics of combined infections in COVID-19 patients may improve the quality of care available for COVID-19 patients and determine the unique features of SARS-CoV-2 infection. This study aimed to characterize such combined infections in terms of their temporal sequence and type of infection by applying the most objective diagnostic methods in COVID-19 patients who had risk factors for severe complications and were hospitalized by national policy in South Korea.

METHODS

Study design and subjects

All patients who were aged ≥ 19 years with COVID-19, which was officially confirmed by SARS-CoV-2 real-time reverse transcription polymerase chain reaction (RT–PCR) or a rapid antigen assay, and who were hospitalized at four study hospitals (National Medical Center, Seoul Medical Center, Boramae Medical Center and Veterans Health Service Medical Center in Seoul, Korea) between May 1st, 2021, and April 30th, 2022, according to the government mandate (for patients who had severe COVID-19 at presentation or risk factors for severe complication such as underlying diseases and advanced age) were enrolled for screening. There were two Korean peak epidemics (4th and 5th waves) of COVID-19 during the study period, and the most prevalent variants were the delta and omicron variants, respectively. The clinical decision regarding patient care was made solely by the physicians in charge. Patients who underwent subsequent laboratory-based microbiologic tests within 3 months of hospitalization were screened among the initially enrolled patients, and the patients with positive test results were ultimately included in the final analysis. We excluded patients with a prior history of COVID-19 and those whose clinical course could not be followed because they were transferred from other hospitals at least 3 days after admission or because they were transferred to other hospitals during hospitalization. The tests used were blood culture, *Mycobacterium tuberculosis* tests (smear, culture and PCR), *Aspergillus* antigen assays, cytomegalovirus (CMV) PCR or antigenemia assays, and *Pneumocystis jirovecii* PCR.

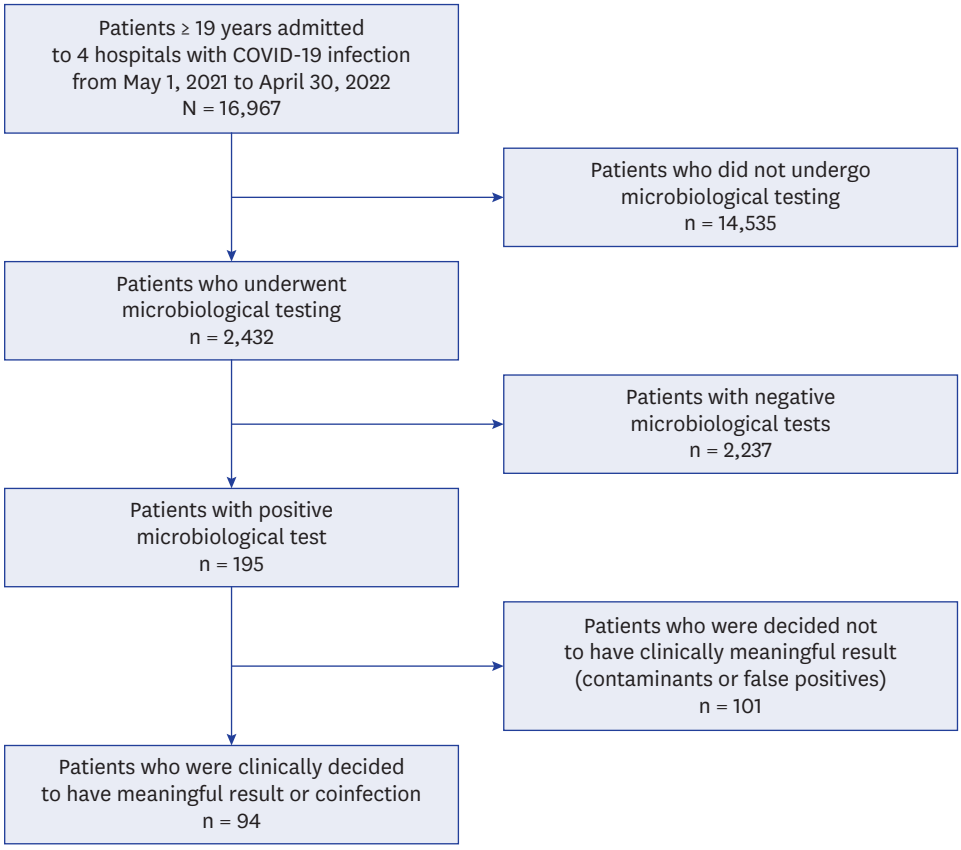

Fig. 1. Flow diagram of the patient selection.
COVID-19 = coronavirus disease 2019.

Data collection

All the data were retrospectively collected from medical records. A positive microbiological test was interpreted as a true positive if the physician decided that the test was significant, and the patient was offered specific therapy (**Fig. 1**). Demographics such as age, sex, underlying disease status, and temporal data regarding the onset of COVID-19 symptoms, hospitalization and discharge were collected. The specific or ancillary medications for COVID-19 treatment, including corticosteroids and other antimicrobial agents, were reviewed.

Definition

The 'combined infection' encompassed both the infectious disease(s) presenting together with COVID-19 at admission (coinfection), which indicates an independent dual presence, and secondary infectious complications during the clinical course in COVID-19 patients. Bacteremia was defined if the usual pathogenic bacteria were isolated from at least one pair of blood cultures. In the case of the isolation of common contaminants, true bacteremia was defined when the physicians in charge treated the patients as having clinically meaningful bacteremia. Tuberculosis (TB) was defined as a positive culture or nucleic acid amplification test for *M. tuberculosis* in samples from clinically compatible patients. CMV disease was defined as positive CMV antigenemia or quantitative CMV PCR tests resulting in the administration of anti-CMV antiviral agents. *P. jirovecii* pneumonia (PJP) was defined as a positive PCR test for *P. jirovecii* in patients treated with trimethoprim-sulfamethoxazole or alternatives due to clinically suspected PJP. Invasive pulmonary aspergillosis (IPA) was

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defined as a positive aspergillosis antigen assay (galactomannan, GM) with an optical density ≥ 0.5 in blood sample combined with clinically suspected aspergillosis and compatible radiological findings, leading to the therapeutic administration of antifungal agents. The diagnostic criteria largely used Biomarkers-based Aspergillosis in Intensive Care Unit (ICU) diagnostic algorithm (BM-AspICU), but the cut-off of GM index in blood sample was 0.5 rather than 1.0.[9] The diagnostic date of the coexisting infections was defined as the date when the sample with diagnostic value was obtained. The coinfections were categorized into three groups—community-acquired (≤ 2 days), early hospital-onset (> 2 and ≤ 30 days) and late hospital-onset (> 30 and ≤ 90 days)—regarding the date of hospital admission. The anti-COVID-19 drugs included nirmatrelvir/ritonavir, molnupiravir, remdesivir, regdanvimab, tocilizumab and baricitinib, which were available and permitted for use during the study period in South Korea.

Statistical analysis

For the statistical analysis, Student's *t*-test was used for continuous variables, and the χ^2 test or Fisher's exact test was used for categorical variables. The distribution of coinfections was analyzed using a box plot (IBM SPSS Statistics for Windows, version 26; IBM Corp., Armonk, NY, USA). All tests were two-tailed, and a *P* value < 0.05 was considered to indicate statistical significance.

Ethics statement

This study was approved by the Institutional Review Boards of Boramae Medical Center (No. 20-2021-53) and the other participating centers. The requirement for informed consent was waived because of the retrospective nature of this investigation and the minimal risk to the study subjects. Personal identifiers were removed before data processing, and this study complied with the tenets of the Declaration of Helsinki.

RESULTS

Study subjects

A total of 16,967 patients with confirmed COVID-19 were hospitalized for one year during the study period at the four study hospitals. Among them, 2,432 (14.3%) patients underwent the specified microbiological tests according to the clinical decisions of the physicians in charge, 195 patients had positive test results, and 0.55% (94/16,967) of patients had clinically meaningful infections; consequently, these patients were administered specific antimicrobial treatment (**Fig. 1**) and were included in the final analysis. The median age was 71.5 (interquartile range [IQR], 61.75–78) years, and at least one comorbidity was present in 92.6% of the patients (**Table 1**). The severity scores showed that the median National Early

Table 1. Baseline characteristics of COVID-19 patients with combined infections during hospitalization

Variables	Total (n = 94)	Fungemia (n = 17)	Bacteremia (n = 70)	Tuberculosis (n = 5)	CMV (n = 7)	PJP (n = 7)	IPA (n = 4)
Age, yr	71.5 (61.8–78)	75 (68.5–78.5)	73 (63–79)	63 (52–86.5)	66 (60–76)	55 (49–62)	59 (34.8–75.8)
Male sex	57 (60.6)	13 (76.5)	31 (44.3)	2 (40)	4 (57.1)	5 (71.4)	1 (25)
BMI	23.3 (20.5–26.4)	23.3 (21.9–24.5)	23.5 (20.5–26.7)	17.6 (12.9–25.1)	20.8 (19.6–25.7)	23.2 (21.6–26.1)	24.4 (21.5–25.4)
Comorbidity ≥ 1	87 (92.6)	17 (100)	64 (91.4)	4 (80)	6 (85.7)	7 (100)	4 (100)
Hypertension	51 (54.3)	8 (47.1)	37 (52.9)	3 (60)	4 (57.1)	4 (57.1)	2 (50)
Diabetes mellitus	33 (35.1)	4 (23.5)	26 (37.1)	0	3 (42.9)	4 (57.1)	2 (50)

(continued to the next page)

Table 1. (Continued) Baseline characteristics of COVID-19 patients with combined infections during hospitalization

Variables	Total (n = 94)	Fungemia (n = 17)	Bacteremia (n = 70)	Tuberculosis (n = 5)	CMV (n = 7)	PJP (n = 7)	IPA (n = 4)
Diabetes mellitus with complication	4 (4.3)	0	3 (4.3)	1 (20)	0	0	1 (25)
Congestive heart disease	4 (4.3)	2 (11.8)	3 (4.3)	0	0	0	0
Myocardial infarction	11 (11.7)	1 (5.9)	10 (14.3)	0	0	1 (14.3)	0
Peripheral artery disease	1 (1.1)	0	1 (1.4)	0	0	0	0
Cerebrovascular accident	15 (16.0)	2 (11.8)	12 (17.1)	0	1 (14.3)	2 (28.6)	0
Hemiplegia	5 (5.3)	1 (5.9)	5 (7.1)	0	0	0	0
Dementia	14 (14.9)	2 (11.8)	13 (18.6)	0	0	0	0
Chronic obstructive pulmonary disease	2 (2.1)	1 (5.9)	1 (1.4)	0	0	0	0
Connective tissue disease	5 (5.3)	1 (5.9)	3 (4.3)	0	0	1 (14.3)	1 (25)
Chronic liver disease							
Mild	2 (2.1)	1 (5.9)	2 (2.9)	0	0	0	0
Severe	3 (3.2)	0	3 (4.3)	0	0	0	0
Chronic kidney disease	6 (6.4)	2 (11.8)	4 (5.7)	0	0	1 (14.3)	0
End stage renal disease	2 (2.1)	0	1 (1.4)	0	0	1 (14.3)	0
Solid organ cancer							
Localized	10 (10.6)	4 (23.5)	6 (8.6)	0	0	0	0
Metastatic	3 (3.2)	1 (5.9)	3 (4.3)	0	0	0	0
Hematologic malignancy	5 (5.3)	1 (5.9)	5 (7.1)	0	0	0	0
HIV	1 (1.1)	0	0	0	0	1 (16.7)	0
Receiving immunomodulating agents	13 (13.8)	5 (29.4)	9 (12.9)	0	1 (14.3)	1 (14.3)	1 (25)
CCI	4 (3–6)	5 (2–7)	4 (3–6)	4 (1–4)	3 (2–3)	3 (2–5)	2 (2–3.5)
COVID-19 severity: NEWS2	6 (3–10)	6 (3.5–9.5)	6.5 (3.75–11)	1 (0.5–6)	6 (2–13)	2 (1–9)	7.5 (5.3–12)
COVID-19 severity: NIH scale							
1	3 (3.2)	0	2 (2.9)	1 (20)	0	0	0
2	11 (11.7)	0	7 (10)	2 (40)	0	2 (28.6)	0
3	10 (10.6)	1 (5.9)	9 (12.9)	0	0	1 (14.3)	1 (25)
4	10 (10.6)	0	7 (10)	1 (20)	1 (14.3)	1 (14.3)	0
5	60 (63.8)	16 (94.1)	45 (64.3)	1 (20)	6 (85.7)	3 (42.9)	3 (75)
COVID-19 therapy							
None	16 (17.0)	1 (5.9)	12 (17.1)	2 (40)	1 (14.3)	0	1 (25)
Nirmatrelvir/ritonavir	3 (3.2)	0	3 (4.3)	0	0	0	0
Remdesivir	74 (78.7)	16 (94.1)	54 (77.1)	3 (60)	6 (85.7)	7 (100)	3 (75)
Regdanvimab	4 (4.3)	0	3 (4.3)	0	1 (14.3)	1 (14.3)	0
Tocilizumab	10 (10.6)	2 (11.8)	9 (12.9)	0	0	0	0
Baricitinib	9 (9.6)	2 (11.8)	7 (10)	0	4 (57.1)	1 (14.3)	2 (50)
Dexamethasone[a], mg							
None	17 (18.1)	0	13 (18.6)	4 (80)	0	0	1 (25)
6	27 (28.7)	6 (35.3)	22 (31.4)	0	2 (28.6)	2 (28.6)	1 (25)
> 6	50 (53.2)	11 (64.7)	35 (50)	1 (20)	5 (71.4)	5 (71.4)	2 (50)
Duration of dexamethasone use	11 (8–18)	13 (10–20.5)	11 (8–18.5)	11.5 (8–18)	10 (10–21)	10 (7–15)	10 (N/A)
Duration from admission to coinfection diagnosis, days	15 (5–25)	24 (16.5–37.5)	8.5 (1–18.3)	3 (0–8.5)	32 (19–35)	31 (15–33)	16.5 (10.8–17)
Community-acquired (≤ 2 days)	11 (11.7)	0	10 (14.3)	1 (20.0)	0	0	0
Early hospital-onset (> 2 & ≤ 30 days)	68 (72.3)	10 (58.8)	54 (77.1)	4 (80.0)	3 (42.9)	3 (42.9)	4 (100)
Late hospital-onset (> 30 & ≤ 90 days)	15 (16.0)	7 (41.2)	6 (8.6)	0	4 (57.1)	4 (57.1)	0
Duration of hospitalization, days	24 (10–48.3)	35 (28–88)	23 (11.8–42.5)	19 (6–51)	73 (21–112)	10 (8–57)	111 (62–118.8)
30-Day mortality							
Survival	35 (37.2)	7 (41.2)	25 (35.7)	3 (60)	2 (28.6)	4 (57.1)	1 (25)
Death	41 (43.6)	8 (47.1)	32 (45.7)	1 (20)	4 (57.1)	2 (28.6)	2 (50)
Unknown	18 (19.1)	2 (11.8)	13 (18.6)	1 (20)	1 (14.3)	1 (14.3)	1 (25)
In-hospital mortality	44 (46.8)	11 (64.7)	35 (50)	1 (20)	3 (42.9)	1 (14.3)	2 (50)

Data are presented as the median (interquartile range) or number (%).
COVID-19 = coronavirus disease 2019, CMV = cytomegalovirus, PJP = *Pneumocystis jirovecii* pneumonia, IPA = invasive pulmonary aspergillosis, BMI = body mass index, HIV = human immunodeficiency virus, CCI = Charlson Comorbidity Index score, NEWS2 = National Early Warning Score 2, NIH = National Institutes of Health, N/A = not applicable.
[a]Dexamethasone or equivalent dose of steroids.

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Warning Score 2 (NEWS2) score at admission was 6 (IQR, 3–10), and the National Institutes of Health (NIH) severity scale score was above moderate for 85.0% of the patients, while 63.8% of the patients were critically ill. At least one anti-COVID-19 drug was administered to 83.0% of the patients, and dexamethasone 6 mg or an equivalent dose of other steroids was used in 81.9% of the patients. The in-hospital mortality rate was 46.8% (44/94). The 30-day mortality rate was 43.6% (i.e., 41 of the 76 patients followed). The 30-day mortality rate for the patients who had positive tests but were considered not to have clinically meaningful combined infections categorized in the study was 17.8% (18/101) which was lower than that of the study patients (46.8%, 44/94; $P < 0.01$).

Combined infections

The infections concurrently diagnosed in the COVID-19 patients at admission or during the hospital course included 70 cases of bacteremia (74.5%), 17 cases of fungemia (18.1%), 7 cases of CMV disease (18.1%), 7 cases of PJP (7.4%), 5 cases of TB (5.3%) and 4 cases of IPA (4.3%) (**Table 1**). Two or more coinfections were diagnosed in 12 (12.8%) patients. The proportions of patients with community-acquired (≤ 2 days), early hospital-onset (> 2 & ≤ 30 days), and late hospital-onset (> 30 & ≤ 90 days) infections were 11.7% (11/94), 72.3% (68/94) and 16.0% (15/94), respectively. The median duration from admission to the diagnosis of combined infections was 15 (IQR, 5–25) days.

TB and bacteremia began to be identified in the early stages of hospitalization (**Fig. 2**). The median time from admission to TB diagnosis was 4 (IQR, 0–8.5) days. Only pulmonary TB was confirmed. Compared to the other combined infections, the TB group had a lower body mass index (mean 18.53, $P = 0.027$), lower NEWS2 score (mean 2.8, $P = 0.041$) and a greater percentage of patients with a low (asymptomatic to mild) NIH score ($P = 0.028$) at admission (**Table 1**). The median time from admission to the onset of the 1st bacteremia episode was 9 (IQR, 1–19) days, and 77.1% (54/70) of the bacteremia cases were categorized as early

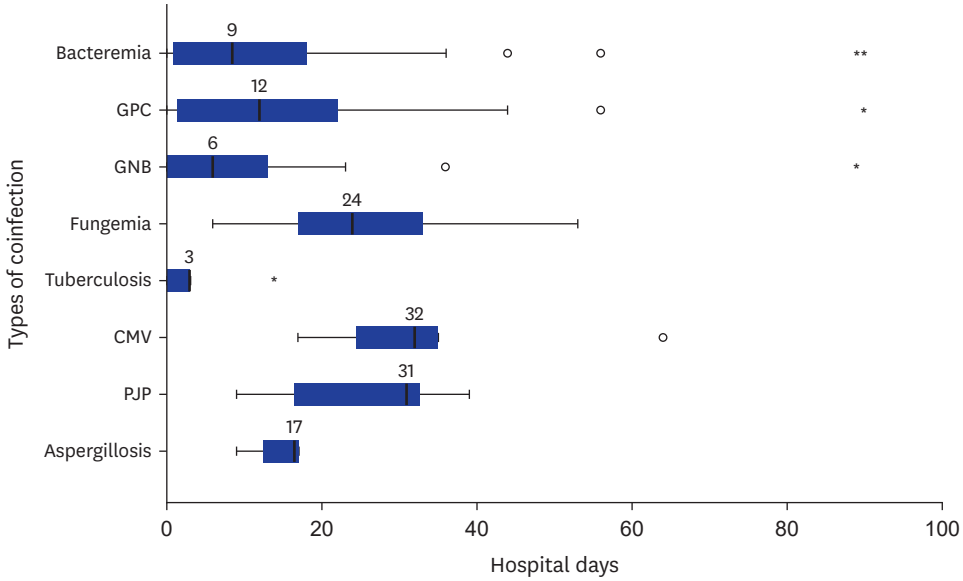

Fig. 2. Timelines of the diagnosis of combined infections in coronavirus disease 2019 patients after hospitalization. '*' denotes an outlier value, and 'o' represents an extreme value. The number above the vertical line within the box indicates the median value.
GPC = gram-positive cocci, GNB = gram-negative bacilli, CMV = cytomegalovirus, PJP = *Pneumocystis jirovecii* pneumonia.

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Table 2. Causative microorganisms of bloodstream infections in coronavirus disease 2019 patients according to the length of hospitalization

Types	Community-acquired (≤ 2 days)		Early hospital-onset (> 2 & ≤ 30 days)		Late hospital-onset (> 30 & ≤ 90 days)	
	Pathogens	No. (%)	Pathogens	No. (%)	Pathogens	No. (%)
Fungemia (n = 17)			*Candida albicans*	7 (70)	*Candida albicans*	4 (57.1)
			Candida glabrata	1 (10)	*Candida parapsilosis*	2 (27.6)
			Candida tropicalis	1 (10)	*Candida tropicalis*	1 (14.3)
			Cryptococcus neoformans	1 (10)		
Bacteremia (n = 70)	CNS	6 (28.6)	CNS	8 (19.0)	CNS	4 (57.1)
	Escherichia coli	6 (28.6)	*Enterococcus* spp.	7 (16.7)	*Enterococcus* spp.	2 (27.6)
	ESBL producing	3 (14.3)	Vancomycin resistant	3 (7.1)	Vancomycin resistant	2 (27.6)
	MSSA	3 (14.3)	*Klebsiella pneumoniae*	7 (16.7)	MRSA	1 (14.3)
	Klebsiella pneumoniae	3 (14.3)	Carbapenem-resistant	4 (9.5)	*Escherichia coli*	1 (14.3)
	Enterococcus spp.	2 (9.5)	ESBL producing	1 (2.4)	Non-ESBL producing	1 (14.3)
	Pseudomonas aeruginosa	2 (9.5)	*Pseudomonas aeruginosa*	6 (14.3)	*Acinetobacter baumannii*	1 (14.3)
	Stenotrophomonas maltophilia	1 (4.8)	Carbapenem-resistant	1 (2.4)	Carbapenem-resistant	1 (14.3)
	Rothia dentocariosa	1 (4.8)	*Acinetobacter baumannii*	5 (11.9)		
	Citrobacter freundii	1 (4.8)	Carbapenem-resistant	5 (11.9)		
	Proteus mirabilis	1 (4.8)	MSSA/MRSA	1 (2.4)/4 (9.5)		
			Escherichia coli	4 (9.5)		
			Carbapenem-resistant	1 (2.4)		
			ESBL producing	1 (2.4)		
			Stenotrophomonas maltophilia	1 (2.4)		
			Bacteroides fragilis	1 (2.4)		
			Corynebacterium spp.	1 (2.4)		
			Enterobacter cloacae	1 (2.4)		
			Enterobacter aerogenes	1 (2.4)		

CNS = coagulase-negative staphylococci, ESBL = extended-spectrum beta-lactamase, MSSA = methicillin-sensitive *Staphylococcus aureus*, MRSA = methicillin-resistant *Staphylococcus aureus*.

hospital-onset (> 2 & ≤ 30 days) (**Table 2**). The infection foci of bacteremia were identified as primary bacteremia (26 cases, 37.1%), central line associated bloodstream infection (BSI, 21 cases, 30.0%), pneumonia (12 cases, 17.1%), urinary tract infection (UTI, 8 cases, 11.4%), intraabdominal infection (3 cases, 4.3%) and bone & joint infection (2 cases, 2.9%). No significant difference from the other combined infection groups in terms of patient characteristics, severity or COVID-19 treatment regimen was observed at admission (**Table 1**). Commonly isolated bacteria included coagulase-negative staphylococci (22%), *Escherichia coli* (13.4%), enterococci (13.4%), *Klebsiella pneumoniae* (12.2%), *Staphylococcus aureus* (11.0%), *Pseudomonas aeruginosa* (9.8%) and *Acinetobacter baumannii* (7.3%) in the order of frequency. Among the gram-negative bacteria, 41.5% (17/41) were multidrug resistant, and 12.2% (5/41) were carbapenem-resistant *Enterobacterales*. The proportion of multidrug-resistant gram-negative bacteria was 18.8% (3/16) in the community-acquired group, 56.5% (13/23) in the early hospital-onset group and 50% (1/2) in the late hospital-onset group. The were 3 cases having subsequent 2nd episode of bacteremia which were 1st methicillin-resistant *S. aureus* (MRSA) to 2nd methicillin-sensitive *S. aureus*, 1st *Enterococcus* to 2nd MRSA and 1st *K. pneumoniae* to 2nd vancomycin-sensitive *Enterococcus* respectively.

The other combined infections tended to occur in the later phase of hospitalization (**Fig. 2**). Fungemia consisted of mostly candidemia (16 cases) and one case of *Cryptococcus neoformans* (**Table 2**). The earliest onset of fungemia occurred on the 6th day of hospitalization, and the median time from hospitalization to fungemia onset was 24 (IQR, 16.5–37.5) days. There were no significant differences in the characteristics of patients or the severity of COVID-19 or COVID-19 specific treatment regimens between patients with fungemia and those with other combined infections (**Table 1**). The median time from hospitalization to CMV disease diagnosis was 32 (IQR, 19–35) days. Compared with the other combined infection groups, the CMV group had a greater percentage of patients who used baricitinib for COVID-19 treatment

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(57.1%, $P < 0.001$) and a longer total hospital stay (mean 66.6 days, $P = 0.018$). The median time from hospitalization to PJP diagnosis was 31 (IQR, 15–33) days. Compared with the other combined infection groups, the PJP group had a lower mean age (52.7 years, $P = 0.024$) and included one human immunodeficiency virus (HIV) patient ($P < 0.001$) and one end stage renal disease patient ($P = 0.021$). The median time from hospitalization to IPA diagnosis was 16.5 (IQR, 10.8–17) days. Compared with those who received other combined infections, the percentage of patients who received baricitinib for COVID-19 treatment was greater (50%, $P = 0.005$), and the mean hospital stay was longer (97.3 days, $P = 0.033$).

DISCUSSION

This was a multicenter study involving four major public referral hospitals dedicated to the care of a large volume of COVID-19 patients during the pandemic in South Korea and with the capability of intensive care. Our study revealed that among the study patients who had severe COVID-19 at presentation or who were minimally symptomatic but had risk factors for severe complications, such as underlying disease and advanced age, 14.3% of the patients needed further investigation for BSIs, TB, CMV disease, PJP and IPA, and clinically meaningful coinfections were diagnosed and treated in 0.55% of the patients. The combined infections were diagnosed within 2 days in 11.7% of the patients, between 2 and 30 days in 72.3% of the patients, and between 1 and 3 months in 16.0% of the patients.

Bacteremia was a main issue of infection in our study. Several studies reported a bacteremia rate of 1.6% or 1.7% in COVID-19 patients, which was higher than that in COVID-19-negative patients.[10,11] The incidence of bacteremia may be influenced by several factors, such as differences in severity or the presence of different risk factors in the study population.[12] Community-acquired (10 cases, 14.3%) and early hospital-onset (54 cases, 77.1%) comprised 91.4% of the 70 bacteremia cases in our study. The source of bacteremia was assessed as primary bacteremia (26 cases, 37.1%), central line associated BSI (21 cases, 30.0%), pneumonia (12 cases, 17.1%), UTI (8 cases, 11.4%), intraabdominal infection (3 cases, 4.3%) and bone & joint infection (2 cases, 2.9%). Old age (median 71.5 years), presence of comorbidity (92.6%) and NIH severity above moderate at admission (85.0%) suggested that combined symptomatic infection of community origin with COVID-19 might lead to early hospital visit. However, the large proportion of primary bacteremia (26 cases, 37.1%) at admission pointed out that the clinicians need more effort to appropriately evaluate the diagnosis. The antibiotics resistance in each temporal stage might reflect the status of the community or of individual hospitals. Extended-spectrum beta-lactamase (ESBL)-producing *E. coli* bacteremia diagnosed within 2 days of hospitalization may reflect the ESBL-producing *E. coli* proportion of 24.6% among community-acquired UTI cases in South Korea.[13,14] Early hospital-onset (< 2 & ≤ 30 days) bacteremia included antibiotic-resistant pathogens such as MRSA, vancomycin-resistant enterococci and multidrug-resistant gram-negative bacteria, which may be related with the length of hospitalization.[15] In this study, the proportion of multidrug-resistant organisms (MDRO) increased with the duration of hospitalization. Witt et al.[16] attribute this to factors such as increased use of medical devices, overuse of antibiotics and the strain on healthcare systems, which led to lapses in standard infection control practices and inadequate MDRO screening. These challenges have been reported as significant contributors to the rise in MDRO infections observed during and after the COVID-19 pandemic. The incidence of fungemia in COVID-19 patients also varies greatly from 0.14% to 34.9% according to the study population.[17,18] Our study revealed no cases

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of fungemia within 48 hours of admission, and the mean time to onset of fungemia was 26.8 days after admission. This finding is consistent with previous studies indicating the correlation of fungemia with an increasing length of hospitalization.[15] One case of cryptococcal fungemia was observed in the early-onset period of our study. Considering the quarantined hospitalization of the patient, COVID-19 itself or the related treatment might have triggered this overt presentation.

TB and COVID-19 markedly differ in the chronicity of the pathogenesis. There is no evidence that TB enhances SARS-CoV-2 infection, and vice versa. The combined presence of active TB with COVID-19 is known to be a risk factor for increased mortality.[19] TB has also been diagnosed simultaneously with or subsequent to a COVID-19 diagnosis.[20,21] While some studies have reported increased severity of known active TB before COVID-19,[21-23] there is controversy regarding whether TB diagnosed simultaneously with or subsequent to COVID-19 infection is a risk factor for severe complications.[20,24] In our study, 20% (1/5) of pulmonary TB cases were diagnosed simultaneously (within 2 days) with COVID-19, and the others were diagnosed a median of 4 days after admission. The TB incidence in five of the 16,967 enrolled patients in the general population in South Korea was close to the total TB incidence. Our data indicate that coincidental occurrence of TB in COVID-19 patients is not unusual, but vigilant suspicion of TB is needed to avoid a missed diagnosis.

Reactivation of CMV in COVID-19 patients may be due to direct injury to cellular immunity caused by SARS-CoV-2 infection as well as the use of immunosuppressive treatment.[25] The use of corticosteroids for more than 15 days or the use of high-dose corticosteroids in COVID-19 was a risk factor for CMV reactivation/disease during ICU stays.[26] In our study, the mean duration of steroid use in CMV-treated patients was 15.6 days, and 71.4% of CMV-treated patients received ≥ 6 mg dexamethasone. Univariate analysis showed that 57.1% of CMV-treated patients received baricitinib ($P < 0.001$). CMV disease was reported to be related to the use of baricitinib in rheumatoid arthritis patients. Baricitinib has been known to be associated with serious infections as the mechanism of pharmacologic action implies, and CMV disease and IPA were such examples.[27] However, the real-world data of baricitinib related infections are awaiting further investigations. Combined use of other immunosuppressive agents such as steroids and severe viral infection itself in COVID-19 must be considered in the interpretation of CMV disease or IPA under baricitinib use. The longer hospital stay in our patients with CMV disease or IPA might be related to the indication of baricitinib in COVID-19 which implies critical severity.

The risk of PJP is known to be greater in patients with cancer, organ or hematopoietic stem cell transplant recipients, patients receiving treatment for rheumatoid disease or patients with impaired cell-mediated immunity.[28] In non-HIV patients, the use of glucocorticoids is a well-known risk factor for PJP.[29] In our study, all patients coinfected with PJP not only received corticosteroids for COVID-19 treatment but also included patients with HIV or solid organ transplant recipients. Chong et al.[30] reported that the overall mortality in COVID-19 patients with PJP was 41.6%, whereas it was 14.3% in our study. COVID-19 and PJP are difficult to differentiate due to their similar clinical presentations. Since we used PCR to detect *P. jirovecii*, we might have overestimated the rate of PJP, resulting in a lower mortality rate. The younger age of our patients in the univariate analysis might be biased due to their immunosuppressive underlying diseases such HIV, connective tissue disease and kidney transplantation in young patients.

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Viral infection itself can cause coinfection involving IPA, and influenza and severe fever with thrombocytopenia syndrome are such examples.[31,32] Current evidence indicates that SARS-CoV-2 infection is also associated with IPA.[33-36] One study reported that the prevalence of IPA was 0–34.3% among COVID-19 patients in the ICU, with a mean prevalence of 10%.[33] Black fungus or mucormycosis is also a key complication of COVID-19,[33] but our study did not collect relevant data.

Several studies on the combined infections in COVID-19 patients have been reported in South Korea. These studies included laboratory screening studies on combined respiratory pathogens in the same specimens, the evaluation of risk factors for MDRO in COVID-19 pneumonia, a case report of fatal fungal coinfection, bacterial coinfection in a single center (n = 367) and the analysis of risk factors for secondary infections (n = 348).[37-42] Our study had the largest study population and analyzed combined infections and their time-dependent relationship in a multicenter setting. Our study may provide clinicians with a useful predictive tool for serious coinfections in COVID-19 care in a time progressive manner. We included BSI, TB, CMV disease, IPA and PJP in the analysis combined with the final clinical decision of physicians in the real-world practice.

This study had a few limitations. First, we underestimated the overall incidence of combined infections in COVID-19 patients. However, our result for combined infection might represent the minimum value for each infection because we used the most objective diagnostic criteria. As we limited the number of target infections to five categories and used laboratory results as a diagnostic minimum, we underestimated the number of real combined infections, excluding other infections and clinically diagnostic infections. The diagnostic ambiguity and relatively low clinical significance of these methods in some infections led us to concentrate on several problematic infections. Both overestimation and underestimation are also possible for CMV, PJP and aspergillosis. As COVID-19 is not a classic host factor for these opportunistic infections, the current diagnostic criteria may not be applicable to COVID-19 patients. A physical barrier to performing timely relevant tests in patients who were strictly quarantined for COVID-19 was one of the clinical difficulties in the peak pandemic period. Therefore, our results need to be interpreted in the context of relative incidence. Second, the small number of our patients with positive combined infections led to insufficient statistical comparisons between the positive subgroups; consequently, our results were presented mostly descriptively. Nevertheless, most studies on combined infections in patients with COVID-19 have been case studies, and systematic analyses have only been published for a few types of combined infections. Our study has the advantage of being a multicenter study covering a large COVID-19 population.

In summary, 14.3% of hospitalized COVID-19 patients with risk factors for severe complications needed further laboratory evaluation for combined infections, and laboratory-confirmed combined infections were detected in 0.55% of the patients. The combined infections included common community and nosocomial pathogens in relation to the length of hospitalization and the epidemiology of the community or hospital in addition to unusual pathogens such as CMV disease, PJP and IPA. Predicting the causative organisms based on the timing of coinfection and conducting appropriate clinical evaluations could help reduce COVID-19-related complications.

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REFERENCES

1. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med* 2020;382(18):1708-20. PUBMED | CROSSREF
2. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72,314 cases from the Chinese Center for Disease Control and Prevention. *JAMA* 2020;323(13):1239-42. PUBMED | CROSSREF
3. Gao YD, Ding M, Dong X, Zhang JJ, Kursat Azkur A, Azkur D, et al. Risk factors for severe and critically ill COVID-19 patients: a review. *Allergy* 2021;76(2):428-55. PUBMED | CROSSREF
4. Abdoli A, Falahi S, Kenarkoohi A. COVID-19-associated opportunistic infections: a snapshot on the current reports. *Clin Exp Med* 2022;22(3):327-46. PUBMED | CROSSREF
5. Silva DL, Lima CM, Magalhães VCR, Baltazar LM, Peres NTA, Caligiorne RB, et al. Fungal and bacterial coinfections increase mortality of severely ill COVID-19 patients. *J Hosp Infect* 2021;113:145-54. PUBMED | CROSSREF
6. Clancy CJ, Nguyen MH. Coronavirus disease 2019, superinfections, and antimicrobial development: what can we expect? *Clin Infect Dis* 2020;71(10):2736-43. PUBMED | CROSSREF
7. Ripa M, Galli L, Poli A, Oltolini C, Spagnuolo V, Mastrangelo A, et al. Secondary infections in patients hospitalized with COVID-19: incidence and predictive factors. *Clin Microbiol Infect* 2021;27(3):451-7. PUBMED | CROSSREF
8. Lai CC, Wang CY, Hsueh PR. Co-infections among patients with COVID-19: the need for combination therapy with non-anti-SARS-CoV-2 agents? *J Microbiol Immunol Infect* 2020;53(4):505-12. PUBMED | CROSSREF
9. Hamam J, Navellou JC, Bellanger AP, Bretagne S, Winiszewski H, Scherer E, et al. New clinical algorithm including fungal biomarkers to better diagnose probable invasive pulmonary aspergillosis in ICU. *Ann Intensive Care* 2021;11(1):41. PUBMED | CROSSREF
10. Nakagawara K, Kamata H, Chubachi S, Namkoong H, Tanaka H, Lee H, et al. Diagnostic significance of secondary bacteremia in patients with COVID-19. *J Infect Chemother* 2023;29(4):422-6. PUBMED | CROSSREF
11. Sepulveda J, Westblade LF, Whittier S, Satlin MJ, Greendyke WG, Aaron JG, et al. Bacteremia and blood culture utilization during COVID-19 surge in New York City. *J Clin Microbiol* 2020;58(8):e00875-20. PUBMED | CROSSREF
12. Nori P, Cowman K, Chen V, Bartash R, Szymczak W, Madaline T, et al. Bacterial and fungal coinfections in COVID-19 patients hospitalized during the New York City pandemic surge. *Infect Control Hosp Epidemiol* 2021;42(1):84-8. PUBMED | CROSSREF
13. Kim WB, Cho KH, Lee SW, Yang HJ, Yun JH, Lee KW, et al. Recent antimicrobial susceptibilities for uropathogenic *Escherichia coli* in patients with community acquired urinary tract infections: a multicenter study. *Urogenit Tract Infect* 2017;12(1):28-34. CROSSREF
14. Colodner R, Rock W, Chazan B, Keller N, Guy N, Sakran W, et al. Risk factors for the development of extended-spectrum beta-lactamase-producing bacteria in nonhospitalized patients. *Eur J Clin Microbiol Infect Dis* 2004;23(3):163-7. PUBMED | CROSSREF
15. Kubin CJ, McConville TH, Dietz D, Zucker J, May M, Nelson B, et al. Characterization of bacterial and fungal infections in hospitalized patients with coronavirus disease 2019 and factors associated with health care-associated infections. *Open Forum Infect Dis* 2021;8(6):ofab201. PUBMED | CROSSREF
16. Witt LS, Howard-Anderson JR, Jacob JT, Gottlieb LB. The impact of COVID-19 on multidrug-resistant organisms causing healthcare-associated infections: a narrative review. *JAC Antimicrob Resist* 2023;5(1):dlac130. PUBMED | CROSSREF
17. Prigitano A, Blasi E, Calabrò M, Cavanna C, Cornetta M, Farina C, et al. Yeast bloodstream infections in the COVID-19 patient: a multicenter Italian study (FiCoV Study). *J Fungi (Basel)* 2023;9(2):277. PUBMED | CROSSREF
18. Colaneri M, Giusti EM, Genovese C, Galli L, Lombardi A, Gori A. Mortality of patients with candidemia and COVID-19: a systematic review with meta-analysis. *Open Forum Infect Dis* 2023;10(7):ofad358. PUBMED | CROSSREF
19. Centers for Disease Control and Prevention (US). Underlying medical conditions associated with higher risk for severe COVID-19: information for healthcare professionals. https://archive.cdc.gov/www_cdc_gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions.html. Updated 2023. Accessed May 26, 2024.
20. Tadolini M, Codecasa LR, García-García JM, Blanc FX, Borisov S, Alffenaar JW, et al. Active tuberculosis, sequelae and COVID-19 co-infection: first cohort of 49 cases. *Eur Respir J* 2020;56(1):2001398. PUBMED | CROSSREF

21. Motta I, Centis R, D'Ambrosio L, García-García JM, Goletti D, Gualano G, et al. Tuberculosis, COVID-19 and migrants: preliminary analysis of deaths occurring in 69 patients from two cohorts. *Pulmonology* 2020;26(4):233-40. PUBMED | CROSSREF

22. TB/COVID-19 Global Study Group. Tuberculosis and COVID-19 co-infection: description of the global cohort. *Eur Respir J* 2022;59(3):2102538. PUBMED | CROSSREF

23. Sarkar S, Khanna P, Singh AK. Impact of COVID-19 in patients with concurrent co-infections: a systematic review and meta-analyses. *J Med Virol* 2021;93(4):2385-95. PUBMED | CROSSREF

24. Visca D, Ong CW, Tiberi S, Centis R, D'Ambrosio L, Chen B, et al. Tuberculosis and COVID-19 interaction: a review of biological, clinical and public health effects. *Pulmonology* 2021;27(2):151-65. PUBMED | CROSSREF

25. Kim JY, Ragusa M, Tortosa F, Torres A, Gresh L, Méndez-Rico JA, et al. Viral reactivations and co-infections in COVID-19 patients: a systematic review. *BMC Infect Dis* 2023;23(1):259. PUBMED | CROSSREF

26. Yamamoto Y, Shiroyama T, Hirata H, Kuge T, Matsumoto K, Yoneda M, et al. Prolonged corticosteroid therapy and cytomegalovirus infection in patients with severe COVID-19. *J Med Virol* 2022;94(3):1067-73. PUBMED | CROSSREF

27. Winthrop KL, Harigai M, Genovese MC, Lindsey S, Takeuchi T, Fleischmann R, et al. Infections in baricitinib clinical trials for patients with active rheumatoid arthritis. *Ann Rheum Dis* 2020;79(10):1290-7. PUBMED | CROSSREF

28. Torres HA, Chemaly RF, Storey R, Aguilera EA, Nogueras GM, Safdar A, et al. Influence of type of cancer and hematopoietic stem cell transplantation on clinical presentation of *Pneumocystis jiroveci* pneumonia in cancer patients. *Eur J Clin Microbiol Infect Dis* 2006;25(6):382-8. PUBMED | CROSSREF

29. Hughes WT, Feldman S, Aur RJ, Verzosa MS, Hustu HO, Simone JV. Intensity of immunosuppressive therapy and the incidence of *Pneumocystis carinii* pneumonitis. *Cancer* 1975;36(6):2004-9. PUBMED | CROSSREF

30. Chong WH, Saha BK, Chopra A. Narrative review of the relationship between COVID-19 and PJP: does it represent coinfection or colonization? *Infection* 2021;49(6):1079-90. PUBMED | CROSSREF

31. Kim MJ, Kim MK, Kang CK, Jun KI, Bang JH, Park SW, et al. A case of acute cerebral aspergillosis complicating influenza A/H1N1pdm 2009. *Infect Chemother* 2013;45(2):225-9. PUBMED | CROSSREF

32. Bae S, Hwang HJ, Kim MY, Kim MJ, Chong YP, Lee SO, et al. Invasive pulmonary aspergillosis in patients with severe fever with thrombocytopenia syndrome. *Clin Infect Dis* 2020;70(7):1491-4. PUBMED | CROSSREF

33. Kariyawasam RM, Dingle TC, Kula BE, Vandermeer B, Sligl WI, Schwartz IS. Defining COVID-19-associated pulmonary aspergillosis: systematic review and meta-analysis. *Clin Microbiol Infect* 2022;28(7):920-7. PUBMED | CROSSREF

34. Ryu BY, Shin EJ, Kim NY, Kim DH, Lee HJ, Kim AR, et al. Severity of COVID-19 associated with SARS-CoV-2 variants circulating in the republic of Korea. *Public Health Wkly Rep* 2022;15(47):2873-95. CROSSREF

35. Huang SF, Wu AYJ, Lee SSJ, Huang YS, Lee CY, Yang TL, et al. COVID-19 associated mold infections: review of COVID-19 associated pulmonary aspergillosis and mucormycosis. *J Microbiol Immunol Infect* 2023;56(3):442-54. PUBMED | CROSSREF

36. Segrelles-Calvo G, Araújo GR, Llopis-Pastor E, Carrillo J, Hernández-Hernández M, Rey L, et al. Prevalence of opportunistic invasive aspergillosis in COVID-19 patients with severe pneumonia. *Mycoses* 2021;64(2):144-51. PUBMED | CROSSREF

37. Roh KH, Kim YK, Kim SW, Kang ER, Yang YJ, Jung SK, et al. Coinfections with respiratory pathogens among COVID-19 patients in Korea. *Can J Infect Dis Med Microbiol* 2021;2021:6651045. PUBMED | CROSSREF

38. Son HJ, Kim T, Lee E, Park SY, Yu S, Hong HL, et al. Risk factors for isolation of multi-drug resistant organisms in coronavirus disease 2019 pneumonia: a multicenter study. *Am J Infect Control* 2021;49(10):1256-61. PUBMED | CROSSREF

39. Kim JH, Kim M, Lim S, Park SY, Jegal Y, Lee T, et al. A fatal case report of invasive pulmonary aspergillosis and mucormycosis coinfection in an immunocompetent patient with coronavirus disease 2019 in Korea. *Acute Crit Care* 2023;38(3):382-8. PUBMED | CROSSREF

40. Jeong S, Lee N, Park Y, Kim J, Jeon K, Park MJ, et al. Prevalence and clinical impact of coinfection in patients with coronavirus disease 2019 in Korea. *Viruses* 2022;14(2):446. PUBMED | CROSSREF

41. Lee J, Chang E, Jung J, Kim MJ, Chong YP, Kim SH, et al. Bacterial co-infection and empirical antibacterial therapy in patients with COVID-19. *J Korean Med Sci* 2023;38(4):e37. PUBMED | CROSSREF

42. Na YS, Baek AR, Baek MS, Kim WY, Kim JH, Lee BY, et al. Clinical outcomes of and risk factors for secondary infection in patients with severe COVID-19: a multicenter cohort study in South Korea. *Korean J Intern Med* 2023;38(1):68-79. PUBMED | CROSSREF