Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Risk factors for isolation of multi-drug resistant organisms in coronavirus disease 2019 pneumonia: A multicenter study

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Objectives: Superimposed multi-drug resistant organisms (MDROs) co-infection can be associated with worse outcomes in patients with severe coronavirus disease 2019 (COVID-19), even if these patients were managed with strict airborne and contact precautions. Identifying risk factors for isolation of MDROs is critical to COVID-19 treatment.

Methods: All eligible adult patients with confirmed COVID-19 pneumonia from 10 hospitals in the Republic of Korea between February 2020 and May 2020 were retrospectively enrolled. Using this cohort, epidemiology and risk factors for isolation of MDROs were evaluated.

Results: Of 152 patients, 47 with microbial culture results were included. Twenty isolates of MDROs from 13 (28%) patients were cultured. *Stenotrophomonas maltophilia* (5 isolates) was the most common MDRO, followed by methicillin-resistant *staphylococcus aureus* (4 isolates). MDROs were mostly isolated from sputum samples (80%, 16/20). The median time from hospitalization to MDRO isolation was 28 days (interquartile range, 18-38 days). In-hospital mortality was higher in patients with MDRO isolation (62% vs 15%; $P = .001$). Use of systemic corticosteroids after diagnosis of COVID-19 (adjusted odds ratio [aOR]: 15.07; 95% confidence interval [CI]: 2.34-97.01; $P = .004$) and long-term care facility (LTCF) stay before diagnosis of COVID-19 (aOR: 6.09; 95% CI: 1.02-36.49; $P = .048$) were associated with MDRO isolation.

Conclusions: MDROs were isolated from 28% of COVID-19 pneumonia patients with culture data and 8.6% of the entire cohort. Previous LTCF stay and adjunctive corticosteroid use were risk factors for the isolation of MDROs. Strict infection prevention strategies may be needed in these COVID-19 patients with risk factors.

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INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the cause of coronavirus disease 2019 (COVID-19), first appeared in China at the end of 2019. It is constantly spreading over the world.[1] Clinical presentation of COVID-19 ranges from asymptomatic to severe cases requiring mechanical ventilation.[2] The fatality rate of COVID-19 is approximately 1.4%.[3] Remdesivir and dexamethasone might be helpful for certain patients. However, because drugs with proven therapeutic effects are limited, supportive treatment and prevention of secondary infections are important as well

It is well-known that respiratory viral diseases will make patients vulnerable to bacterial infections. Bacterial infections of *S. aureus* and *S. pneumonia* following influenza infection have been reported.[4] There is also a concern of superimposed bacterial infection after SARS-CoV-2 infection. Patients with severe COVID-19 are often indistinguishable from bacterial co-infection based on signs, symptoms, physical findings, and radiographic findings.[5] Bacterial co-infections occur more often in patients requiring intensive care unit and mechanical ventilation with increased disease severity.[5-10] They are known to be associated with worse outcomes of patients with COVID-19 pneumonia.[11] Understanding the epidemiology and risk factors of MDROs in COVID-19 patients is very important for establishing strategies to treat COVID-19 and prevent infection by MDROs. Although, several studies reported MDRO isolation and antimicrobial stewardship challenges in patients in COVID-19,[12-14] only few studies have dealt with risk factors of MDRO isolation in patients with COVID-19.[15] Therefore, the aim of this study was to evaluate incidences of and risk factors for isolation of MDROs in COVID-19 patients.

MATERIALS AND METHODS

Patients and study design

All eligible adult patients with confirmed COVID-19 pneumonia at 10 hospitals in the Republic of Korea between February 2020 and May 2020 were retrospectively evaluated. COVID-19 was diagnosed by real-time reverse transcriptase polymerase chain reaction (RT-PCR) for SARS-CoV-2 using a PowerChekTM 2019-nCoV Real-time PCR Kit (Kogenebiotech, Seoul, Korea) and an Allplex 2019-nCoV Assay (Seegene, Seoul, Korea) to determine virus using envelope (E) gene and RNA-dependent RNA polymerase (RdRp) gene as two genetic markers. Patients were excluded if cultures for bacteria and fungi were not done (Fig 1). Cases were defined as patients with culture-confirmed MDRO and controls were defined as patients who underwent culture tests, but with negative results or isolated non-MDRO. Data about age, gender, underlying diseases, history of medical institution visit, antibiotics use, isolation of MDROs before admission due to SARS-COV2 infection, types of rooms during hospitalization after admission due to SARS-CoV2 infection, intensive care unit stay, use of systemic corticosteroids, antibacterial agents, and in-hospital mortality were collected. Risk factors for isolation of MDROs were then evaluated. COVID-19 pneumonia was defined when patients with COVID-19 had radiologically relevant findings of SARS-CoV2 infection on chest radiograph or computed tomography.[16]

Definition of MDRO and microbiological methods

MDROs were defined as seven antibiotic-resistant organisms, including methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), extended-spectrum beta-lactamase (ESBL) producing enterobacteriaceae, carbapenem-resistant enterobacteriaceae (CRE), carbapenem-resistant *Acinetobacter baumannii* (CRAB), carbapenem-resistant *Pseudomonas aeruginosa* (CRPA), and *Stenotrophomonas maltophilia*.[17] Microbiological test was performed at the judgment of the attending clinician. Microorganism identification was performed using standard methods at each hospital in which quality control of microbiological tests had passed the evaluation of accredited institutions. Susceptibility testing was done using microdilution method and results were interpreted according to the National Committee for Clinical Laboratory Standards guidelines.[18]

Statistical analysis

Categorical variables were compared using $\chi 2$ test or Fisher's exact test as appropriate. Continuous variables were compared using

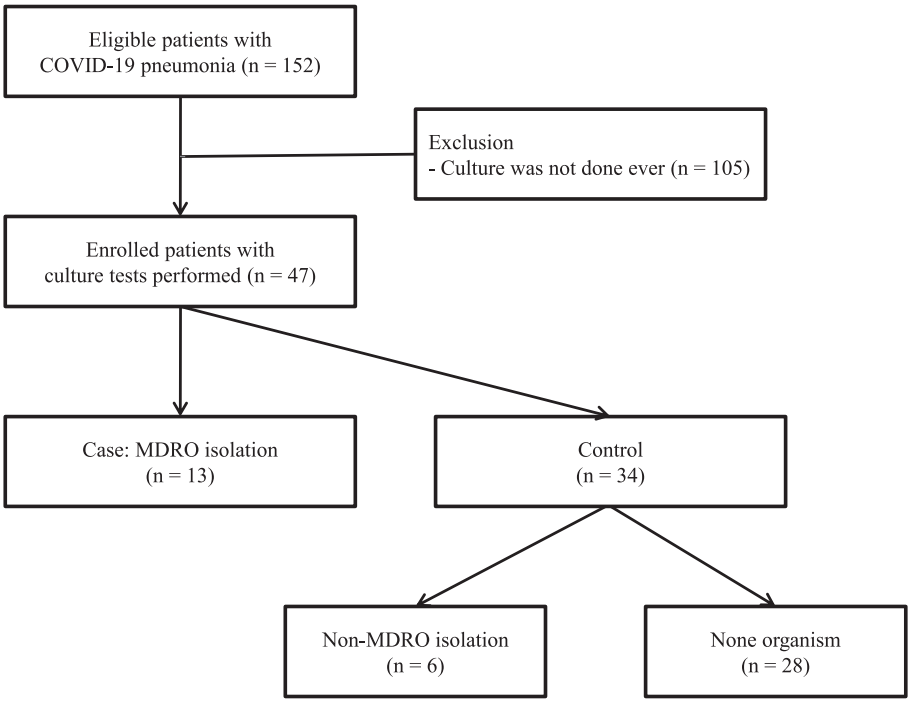

Fig. 1. Study flowchart.

Student's t-test or Mann-Whitney U-test as appropriate. All tests of significance were two-tailed and *P* values < .05 were considered statistically significant. A univariate analysis was performed using a logistic regression to determine independent risk factors associated with isolation of MDROs. Subsequently, multiple logistic regression analysis was performed for variables with a *P* value < .1 in the univariate analysis based on the backward stepwise selection method. Two variables, the use of urinary tract catheter and the use of antibacterial agent after diagnosis of COVID-19, were excluded from the logistic regression analysis as their occurrence was 100%. Results are reported as odds ratio (OR) with 95% confidence interval (CI). All statistical analyses were performed with SPSS for Windows, version 26 (SPSS Inc., Chicago, IL, USA).

Ethical approval

This study was approved by the Institutional Review Board (IRB) of Soonchunhyang University Seoul Hospital (IRB No. 2020-06-012). Informed consent was waived by the IRB because no intervention was involved and no patient-identifying information was included.

RESULTS

Patient characteristics

A total of 152 patients with COVID-19 pneumonia were identified during the study period. Patients without a culture study (n = 105) were excluded. Clinical characteristics of the entire cohort including patients without a culture study is described in Supplementary Table 1. A total of 47 patients with microbial culture data according to the doctor's judgement were included in the final analysis (Fig 1). Clinical characteristics of enrolled patients with COVID-19 pneumonia are described in Table 1. The median age of these patients was 68 years (interquartile range [IQR]: 62-77 years). Of these patients, 26 (55%) were males. Diabetes mellitus (23%, 11/47) was the most common underlying disease, followed by neurologic disease (19%, 9/47) and chronic lung disease (17%, 8/47). Twelve (26%) patients stayed in LTCF within 90 days before admission due to COVID-19. A total of 34 (72%) patients stayed in negative pressured single room after admission due to COVID-19. Two (4%) patients developed bacteremia and two (4%) developed candidemia and all these patients were included in MDRO group. Twenty-two (47%) patients received antibacterial agents and 36 (77%) received systemic corticosteroids. In-hospital mortality was 28% (13/47).

Description of patients with isolation of multi-drug resistant microorganisms

MDROs were detected from 28% (13/47) among patients with culture data and 8.6% (13/152) of the entire cohort. A total of 20 isolates of MDROs were cultured from 13 patients. The median time from COVID-19 diagnosis to MDRO isolation was 28 days (IQR: 18-38 days) (Table 2, Fig 2). Characteristics of these 13 patients with MDRO isolation are summarized in Table 2. Eleven (85%) patients had visited or

Table 1
Clinical characteristics of patients with coronavirus disease 2019 pneumonia

Characteristic of patients	MDRO (n=13)	Control (n =34)	Total (n = 47)	*P* value
Age (IQR)	73 (65-77)	64 (50-76)	68 (62-77)	.18
Male gender	8 (62)	18 (53)	26 (55)	.60
Underlying disease/condition				
Diabetes	5 (39)	6 (18)	11 (23)	.13
Neurologic disease	3 (23)	6 (18)	9 (19)	.69
Chronic lung disease	3 (23)	5 (15)	8 (17)	.67
Chronic kidney disease	2 (15)	4 (12)	6 (13)	.99
Cardiovascular disease	3 (23)	3 (9)	6 (13)	.33
Chronic liver disease	2 (15)	0 (0)	2 (4)	.07
Malignancy	2 (15)	1 (3)	3 (6)	.18
Corticosteroid use	0 (0)	1 (3)	1 (2)	.99
Human immunodeficiency virus infection	0 (0)	1 (3)	1 (2)	.99
Before admission due to SARS-CoV2 infection				
Medical institution visit within 90 d				
None (community acquired)	2 (15)	9 (27)	11 (23)	.70
LTCF	6 (46)	6 (17)	12 (26)	.045
Hospital	4 (31)	16 (47)	20 (43)	.35
Outpatient clinic visit	4 (33)	19 (56)	23 (50)	.31
Hemodialysis clinic	1 (8)	0 (0)	1 (2)	.26
Antibiotic use within 90 d	2/6 (33)	1/18 (6)	3/24 (13)	.14
MDRO isolation within 180 d	1/3 (33)	0/14 (0)	1/17 (6)	.18
After admission due to SARS-CoV2 infection				
Types of rooms during hospitalization				
General single room	1 (8)	0 (0)	1 (2)	.28
Negative pressured single room	6 (46)	28 (82)	34 (72)	.01
Negative pressured shared room	6 (46)	6 (18)	12 (26)	.045
Have been out of the hospital room for CT scan	6 (46)	14 (41)	20 (43)	.76
Intensive care unit	10 (77)	16 (47)	26 (55)	.10
Quick SOFA score ≥ 2 points	3 (23)	4 (12)	7 (15)	.38
Medical devices				
Urinary tract catheter	13 (100)	16 (47)	29 (62)	.001
Central venous catheter	11 (85)	12 (35)	23 (49)	.003
Mechanical ventilation	9 (69)	9 (27)	18 (38)	.02
Bacteremia	2 (14)	0 (0)	2 (4)	.08
Candidemia	2 (14)	0 (0)	2 (4)	.08
Use of systemic corticosteroids	11 (85)	11 (32)	22 (47)	.002
Use of antibacterial agent	13 (100)	23 (68)	36 (77)	.02
In hospital mortality	8 (62)	5 (15)	13 (28)	.001

NOTE. Data are presented as number of patients (with the corresponding percentage shown in parentheses) unless otherwise specified.
CT, computed tomography; *IQR*, interquartile range; *LTCF*, long-term care facility; *MDRO*, multi-drug resistant organism; *SOFA*; sequential organ failure assessment

Table 2
Description of patients whose clinical specimens had multi-drug resistant microorganism

Patient number	Age/gender	Setting	Previous colonization	Types of specimen	Microorganism	Days from diagnosis to pathogen isolation	In hospital mortality
Patient 1	73/F	Outpatient clinic visit	No	Sputum	CRE (*E. coli*)	18	Died
				Urine	*C. glabrata*	39	
Patient 2	72/F	Community	Unknown	Sputum	CRAB	7	Alive
				Sputum	ESBL *K. pneumoniae*	22	
				Urine	CRPA	49	
Patient 3	75/M	Hospital	Unknown	Sputum	CRAB	30	Died
Patient 4	92/M	LTCF	Unknown	Sputum	CRAB	12	Died
				Blood	VRE	43	
				Sputum	MRSA	43	
Patient 5	65/M	Dialysis clinic	Unknown	Blood	VRE	19	Alive
				Sputum	MRSA	25	
				Sputum	*C. albicans*	19	
Patient 6	75/F	LTCF	No	Sputum	*S. maltophilia*	0	Died
Patient 7	83/F	Hospital	Unknown	Sputum	MRSA	38	Died
Patient 8	64/M	Community	Unknown	Blood	*C. parapsilosis*	38	Died
				Sputum	*S. maltophilia*	45	
Patient 9	58/M	LTCF	Unknown	Sputum	*S. maltophilia*	56	Alive
				Sputum	CRPA	80	
Patient 10	65/F	Hospital	ESBL E. coli	Urine	ESBL *E. coli*	19	Alive
Patient 11	77/M	Hospital	Unknown	Blood	*C. albicans*	44	Died
				Sputum	MRSA	28	
				Sputum	*S. maltophilia*	55	
Patient 12	71/M	LTCF	Unknown	Sputum	*S. maltophilia*	46	Died
Patient 13	81/M	Hospital	Unknown	Sputum	CRPA	53	Alive
				Stool	*C. difficile*	24	

CRAB, carbapenem-resistant Acinetobacter baumannii; *CRE*, carbapenem-resistant enterobactericeae; *CRPA*, carbapenem-resistant Pseudomonas aeruginosa; *ESBL*, extended-spectrum beta-lactamase; *LTCF*, long-term care facility;
MRSA, methicillin-resistant Staphylococcus aureus; *VRE*, vancomycin-resistant enterococci.

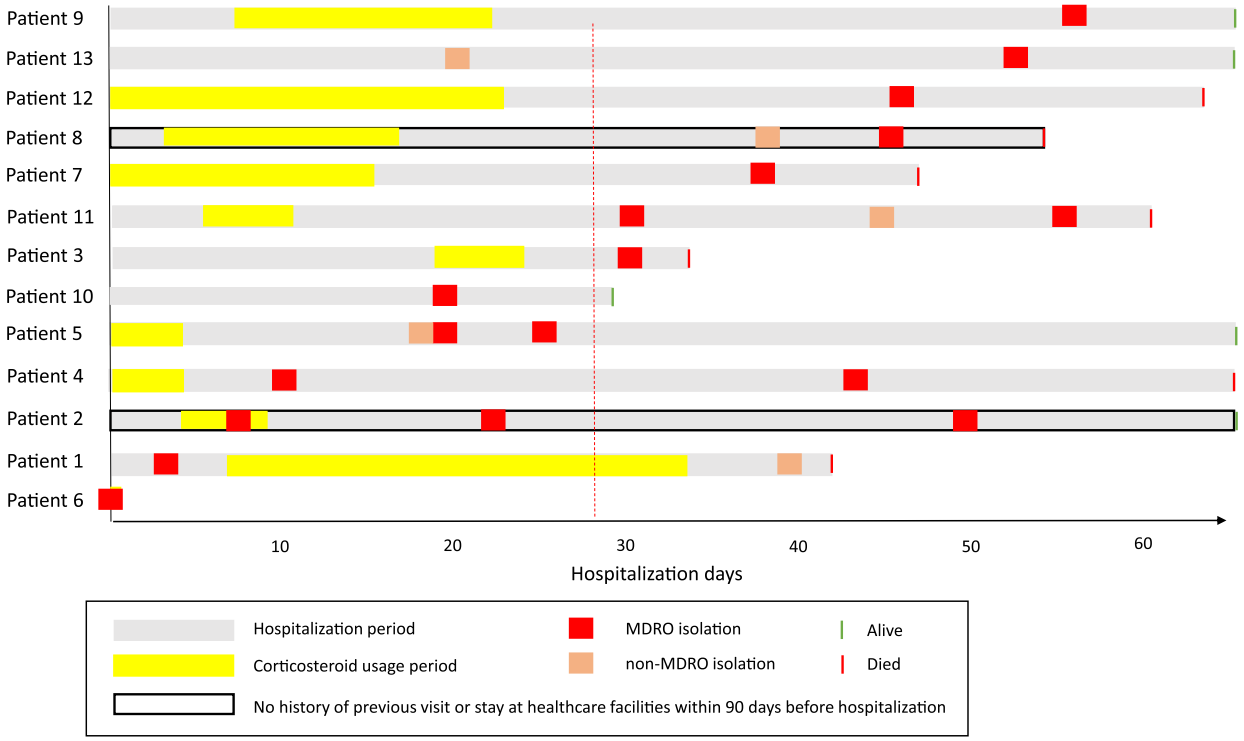

Fig. 2. Timelines of 13 patients with coronavirus disease 2019 and isolation of multi-drug resistant microorganism.The median time from COVID-19 diagnosis to MDRO isolation was 28 days (IQR: 18-38 days) (red dash line). All patients except patients 10 and 13 received adjunctive corticosteroid. Patient 6 received only 2 days of corticosteroid because she died two days after admission. All patients with MDRO isolation received antibiotics during hospitalization before MDRO isolation.

stayed at any type of healthcare facilities within 90 days before hospitalization. All patients with isolation of MDROs received antibacterial agents and 85% (11/13) used systemic corticosteroids. The number of identified MDRO was as follows: five *Stenotrophomonas maltophilia*, 4 MRSA, 3CRAB, 3 CRPA, 2 ESBL enterobacteriaceae, 2 VRE, and one CRE. Most bacteria were isolated from sputum (16 isolates). Two MDRO isolates were identified from blood and urine, respectively. In-hospital mortality of patients with MDRO isolation was 62% (8/13).

Candida was isolated from four patients with MDRO and polymicrobial non-MDRO was isolated from one patient. A total of 6 patients with monomicrobial non-MDRO isolates, 3 had non-MDRO isolation from sputum, 2 had non-MDRO isolation from urine, and 1 had non-MDRO isolation from sputum and urine. Types of non-MDRO were as follows: two candida species, 1 *klebsiella pneumonia*, 1 *Escherichia coli*, 1 *Enterococcus faecalis*, 1 *Rahnella aquatilis*, and 1 nontuberculous mycobacteria. The median time from COVID-19 diagnosis to non-MDRO isolation was 17 days (IQR: 6-34 days). In-hospital mortality in the non-MDRO group 33% (2/6) (Supplementary Table 2).

Risk factors for isolation of multi-drug resistant organisms

Significant variables in univariate analysis were LTCF admission before diagnosis of COVID-19 (OR: 4.00, 95% CI: 0.98 - 16.26, P = .05), single room stay after diagnosis of COVID-19 (OR: 0.25, 95% CI: 0.06 -1.02, P = .05), having central venous catheter (OR: 10.08, 95% CI: 1.91 - 53.18, P = .01), mechanical ventilation (OR: 6.25, 95% CI: 1.54 - 25.42, P = .01), and use of systemic corticosteroids after diagnosis of COVID-19 (OR: 11.50, 95% CI: 2.17 - 61.04, P = .004). All significant variables in univariate analysis and age were included in the multivariate analysis. Multivariate analysis indicated that the use of systemic corticosteroids after COVID-19 diagnosis (aOR: 15.07, 95% CI: 2.34-97.01, P = .004) and LTCF stay before diagnosis of COVID-19 (aOR: 6.09, 95% CI: 1.02-36.49, P = 0.048) were independent risk factors for MDRO isolation (Table 3). Risk factors for MDRO isolation from the entire cohort including patients without culture data were also evaluated. Not only LTCF stay and receipt of corticosteroids but also mechanical ventilation revealed to be a risk factor of MDRO isolation (Supplementary Table 3).

DISCUSSION

The COVID-19 pandemic has highlighted the need for monitoring the use of excess antibiotics and multi-drug resistance.[19] Knowing the epidemiology and risk factors of MDROs in COVID-19 patients can help establishing strategies to treat COVID-19 and preventing infection by MDROs. In this multi-centered retrospective study, MDROs were isolated from 13 (28%) of 47 patients. All patients with MDRO isolation received previous antibacterial agents. Risk factors of MDRO isolation in patients with COVID-19 pneumonia were the use of corticosteroids after hospitalization due to COVID-19 and LTCF stay before diagnosis of COVID-19.

Antimicrobial resistance in bacterial pathogens has become one of the most important threats to public health around the world. The Republic of Korea is also experiencing challenges with antimicrobial resistance. The recent nationwide surveillance system report by the Korea Centers for Disease Control and Prevention stated that MRSA is common (66% of *S. aureus*), and among tested *Acinetobacter baumannii* and *Pseudomonas aeruginosa* isolates collected from 16 general hospitals, 85% and 35% were imipenem-resistant.[20,21] In response to the COVID-19 pandemic, healthcare systems have rapidly adapted infection control policies to hinder the spread of COVID-19. However, the pandemic has also mitigated measures to prevent the spread of MDROs, such as screening, surveillance and antimicrobial stewardship.[12] A number of MDRO outbreaks and infections are now linked to breakdowns in infection prevention practices due to strains imposed by the pandemic.[22,23] Maintaining and monitoring a robust infection prevention practices is very important because the spread of MDRO might pose a long-term serious threat to public health.

Interestingly, despite application of enhanced standard precautions (hand hygiene policy and respiratory hygiene), the use of personal protective equipment, and appropriate environmental disinfection procedures, MDROs were still isolated from 13 (28%) patients of 47 patients who had culture test. Elderly patients with comorbidities requiring prolonged hospitalization with mechanical ventilation might have promoted the transmission of MDROs.[24] However, endogenous factors might also be important. The source of organism might be microbiota of the respiratory tract or intestine carried by patients themselves before they developed COVID-19, especially for those with previous hospitalization and those who were receiving broad-spectrum antibiotics. Indeed, most of patients with isolation of MDRO in our study had history of visiting or staying at any type of healthcare facilities.

In our study, more MDRO tended to be isolated from patients who stayed at the LTCF before COVID-19 diagnosis. Clusters of COVID-19 in LTCF have been widely reported.[25,26] Patients in LTCF are usually the elderly who have many underlying diseases.[26] They are also at higher risk of antibiotic resistance and more likely to have MDRO colonizations.[27] With this background, the possibility of getting MDRO secondary infection rapidly increases when a patient in LTCF gets COVID-19. Therefore, close monitoring of secondary MDRO infections is required for COVID-19 outbreak in LTCF.

SARS-CoV-2 can cause immune dysregulation due to increased production and circulation of cytokines, leading to hyper-inflammation and defects of lymphoid function.[28,29] Dexamethasone, a corticosteroid, is strongly recommended as it has been shown to improve survival outcomes for inpatients who require oxygen supplementation.[30,31] However, the use of corticosteroids for treating COVID-19 might have unintended consequences. The use of corticosteroids is known to be associated with secondary bacterial infection, invasive pulmonary aspergillosis, osteonecrosis of femoral head, and delayed viral clearance in other viral infections. High-dose corticosteroids potentially delayed viral shedding of patients with COVID-19.[32] Our finding that steroid use may promote MDRO infection has great implications. Even during therapeutic use of corticosteroids, it is necessary for clinicians to proceed with caution and steroids should only be given for the shortest recommended duration.

Previous studies have found that fewer than 10% of patients with COVID-19 experience co-infections and over 70% receive

Table 3
Risk factors for multi-drug resistant organism isolation in patients with coronavirus disease 2019 pneumonia

Risk factor	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value
Age	1.05 (0.99 - 1.11)	.10		
LTCF stay before diagnosis of COVID-19	4.00 (0.98 - 16.26)	.05	6.09 (1.02 - 36.49)	.048
Single room stay after diagnosis of COVID-19 vs. shared room	0.25 (0.06 - 1.02)	.05		
Central venous catheter	10.08 (1.91 - 53.18)	.01		
Mechanical ventilation	6.25 (1.54 - 25.42)	.01		
Use of systemic corticosteroids	11.50 (2.17 - 61.04)	.004	15.07 (2.34 - 97.01)	.004

NOTE. The model fitted data well in terms of discrimination (C-statistic = 0.83) and calibration (Hosmer-Lemeshow goodness of fit statistic = 2.18, P = .34).
CI, confidence interval; *LTCF*, long-term care facility; *OR*, odds ratio.

antibiotics.[7,11,19,33-35] In the present study, the rate of antibiotic use was 113/152 (74%). Despite a low rate of bacterial co-infection reported in patients with COVID-19, high rates of antimicrobial prescribing have been reported.[5,34,35] It is not unreasonable to treat bacterial pneumonia in unwell patients empirically with antimicrobials. However, frequent use of broad-spectrum antibiotics in a hospital setting is a risk factor for hospital-acquired infections by MDROs because these antibiotics will alter microbiota and select naturally resistant bacteria.[6,17] Previous studies have reported an increase in MRSA after SARS in 2003 and the gaining of antimicrobial-resistance in Gram-negative bacilli after COVID-19 pandemics.[19,36] One study reported that 100% of COVID-19 patients with MDRO infections received preceding antibiotics.[19] This was also observed in our study. Since administration of antibiotics to COVID-19 patients is heavily dependent on the judgement and experience of frontline clinicians,[37] caution is needed when using empirical antibiotics in patients with COVID-19. Stewardship will play a crucial role in limiting unnecessary antimicrobial use and antimicrobial-resistance.

Our study has several limitations. First, this study does not give information on MDRO infection, because positive cultures of MDRO may represent disease or colonization. Although it would be more useful to discriminate MDRO infections from colonization, we assume that understanding the MDRO co-detection in COVID-19 patients is also worthwhile. Second, this study was from the early months of the COVID-19 pandemic, and incidence, microbiology and resistance patterns may differ as the pandemic unfolded and patient management evolved. Third, culture samples were not available for all patients and information about previous bacterial colonization was not known for many patients. Culture implementation was limited due to safety and biosafety of medical staff in a laboratory. Fourth, a retrospective study with a low number of patients included in our analysis might limit the generalizability of our findings. Thus, results of this study should be interpreted cautiously owing to potential bias and confounding factors from an observational study. Furthermore, it would be helpful to perform risk-score stratification with more data and successive internal and external validation for further understanding of MDRO isolation and secondary infection prevention.

In conclusion, MDROs were isolated in the significant number of patients with COVID-19. Previous LTCF stay and therapeutic use of corticosteroids were important risk factors for the isolation of MDROs. In-hospital mortality was higher in patients with MDRO isolation. Thus, infection control management, antibiotic stewardship, and surveillance culture to monitor secondary MDRO infection are necessary, especially for patients with COVID-19 outbreak in a long term care facility. Owing to the risk of MDRO infection, corticosteroid usage should be carefully considered only for patients with indication.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.ajic.2021.06.005.

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