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Secondary infections in COVID-19 patients: A two-centre retrospective observational study

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Abstract

Introduction: We sought to evaluate secondary infections (SIs) in patients admitted to the intensive care unit (ICU) for COVID-19 with respect to incidence, causative pathogens, and clinical outcomes.

Methodology: In this two-centre retrospective study, we analysed 146 patients (96 males, 50 females; median age, 64 years) admitted to the ICU with COVID-19 between March 26 and December 31, 2020. Inclusion criteria were an ICU admission for at least 48 hours and age beyond 18 years. Patients with and without SIs were compared and the impacts of SIs and carbapenem resistance on mortality were analysed.

Results: During ICU admission, 84 episodes of SIs developed in 58 patients (39.7%). A total of 104 isolates were recovered, with Gram-negative bacteria most frequent accounting for 74%. At least one carbapenem-resistant pathogen (n = 61) was recovered in 41 patients (70.1%). In multivariate analysis, the use of ECMO and an elevated procalcitonin level were significantly associated with the development of SIs. The mortality rate and the incidence of carbapenem resistance did not differ significantly in COVID-19 patients with and without SIs ($p = 0.059$ and $p = 0.083$, respectively).

Conclusions: The incidences of SIs and carbapenem resistance among COVID-19 patients were alarming, emphasizing stricter infection control measures in the ICU setting.

Key words: COVID-19; secondary infections; carbapenem resistance; intensive care unit infections.

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Introduction

An outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causing coronavirus disease 2019 (COVID-19) first appeared in December 2019 in Wuhan, Hubei Province, China. Since then, it has affected our lives globally, infecting more than 158 million people and claiming more than three million lives [1].

Secondary infections (SIs) are a major complication of viral infections, associated with serious consequences. Bacterial pathogens have been implicated to play a major role in deaths in earlier pandemics [2]. Similarly, in the first months of the COVID-19 pandemic, SIs were observed in at least half of the patients who died from COVID-19 [3,4]. The reported incidences of SIs vary widely (12-57.9%) in patients admitted to the intensive care unit (ICU) with severe or critical COVID-19 [5–12]. This wide range may result from different patient profiles, varying diagnostic procedures including molecular tests and use of invasive interventions. However, reports on SIs among critically ill patients with COVID-19 have been limited to sporadic cases, with few or no data on the pathogenic spectrum of SIs. In the current study, we aimed to determine the incidence, microbiological aetiologies and consequences of SIs in patients receiving intensive care for COVID-19.

Methodology

We performed a two-centre retrospective study of COVID-19 patients admitted to the ICU between March 26 and December 31, 2020. The study was approved by the institutional review board and conformed to the Declaration of Helsinki.

Study settings

The two study centres were: a) university ICU of the Department of Internal Medicine, and b) cardiovascular ICU of a dedicated tertiary centre for both cardiovascular diseases and extracorporeal membrane oxygenation (ECMO) procedures. Although both centres do not serve as a main pandemic centre, the ICUs of both centres have been allocated to COVID-19 patients when necessary.

Study patients

A total of 183 consecutive patients were admitted to the ICU due to COVID-19. Inclusion criteria were an ICU admission for at least 48 hours and age beyond 18 years. The vast majority of patients (n = 175) were hospitalized with a COVID-19 diagnosis confirmed by reverse transcriptase polymerase chain reaction (RT-PCR) testing. All patients displayed radiological pulmonary manifestations of COVID-19. Patients who had been admitted to the ICU for causes other than COVID-19 and had an ICU stay exceeding five days with the likelihood of previously acquired SIs and those who had been found to have colonization of carbapenem-resistant bacteria before the diagnosis of COVID-19 were excluded. The final analysis included 146 patients.

Data collection and definitions

Demographic, clinical, and laboratory data of the patients were retrospectively retrieved from the hospital registry system and infection visit charts. Laboratory parameters included white blood cell (WBC) and lymphocyte counts and levels of C-reactive protein (CRP) and procalcitonin. In this regard, the parameters obtained on the day of positive cultures were taken into account in patients with SIs, whereas the highest values, with the exception of the lowest lymphocyte count, were taken into account in patients without SIs.

At ICU admission, Sepsis-related Organ Failure Assessment (SOFA) and Acute Physiology and Chronic Health Evaluation (APACHE) II scores were determined, with identification of septic shock and /or severe acute respiratory distress syndrome (ARDS).

Empirical use of antibiotics, duration of invasive mechanical ventilation (IMV), use of central venous catheters and ECMO and length of ICU stay as well as use of steroids and convalescent plasma therapies were recorded. Tocilizumab was the only interleukin-6 inhibitor used in both centres. Conditions associated with immune incompetence included chronic diabetes, active malignancies, organ transplantations, rheumatologic disorders and chronic use of immunosuppressive agents. Overweight and obesity were defined as having a body mass index (BMI) of 25 to < 30 and ≥ 30, respectively. BMI is calculated as weight in kilograms divided by the square of the height in meters.

Microbiological data

The diagnosis of SIs was based on the criteria of the European Centre for Disease Prevention and Control. Secondary infections were defined as the growth of pathogens in cultures of blood, endotracheal aspiration/bronchoalveolar lavage and/or urine after 48 hours of admission, in the presence of clinical manifestations including fever or hypothermia, purulent respiratory tract secretions, radiologically new or progressive chest infiltration as well as an increased need for oxygenation and/or inotropic agents [13].

Respiratory and urine samples were cultured in blood agar and eosin methylene blue agar and blood samples in blood culture bottles. Isolates were identified by the VITEK 2 (BioMérieux, Marcyl'Étoile, France) or Phoenix (Becton Dickinson, USA) automated systems. Antibiotic susceptibilities were determined according to the EUCAST criteria. Carbapenem resistance was defined as the resistance of pathogens to at least one carbapenem class of antibiotics (ertapenem, meropenem or imipenem) excluding intrinsic carbapenem-resistant bacteria [14].

Statistical analysis

Demographic, clinical, and laboratory data of the patients with and without SIs were compared. Data were processed using SPSS Statistics 20. For descriptive analysis, medians with the interquartile range (IQR) were used. The nonparametric Mann-Whitney U-test was used for comparison of numerical data, and Fisher's exact test was used for comparison of categorical data. The effects of variables on mortality and development of SIs were evaluated using univariate and multivariate analyses. For logistic regression analysis, odds ratios (OR) and 95% confidence intervals (CI) were calculated. A p value of less than 0.05 was considered significant.

Results

During the study period, a total of 183 patients with COVID-19 were hospitalized in both centres. A total of 37 patients were excluded because of shorter ICU stay of fewer than 48 hours (n = 33), colonization of carbapenem-resistant pathogens before the diagnosis of COVID-19 infection (n = 3), and insufficient records from the transferring centre (n = 1). A total of 146 patients (96 males, 50 females) were eligible for the study (Table 1). The median age was 64 years (IQR, 56-72.5). Diabetes (38.4%) and hypertension (35.6%) were the most common comorbidities. Eighty-one patients were immunocompromised. On the day of admission to the ICU, ARDS was present in 59.6% of patients and septic shock in 34.9%. Invasive mechanical ventilation was required in 116 patients (79.5%) (Table 1). The diagnosis of COVID-19 was based on both RT-PCR testing and CT findings in 128 patients. The remaining

18 patients had radiological pulmonary involvement of COVID-19.

Source of infection and microbiology

Blood, lower respiratory tract, and urine cultures were obtained at admission from 110 (75%), 14 (10%) and 30 (21%) patients, respectively, and from 81 (55%), 43 (29%), and 46 (32%) patients during the ICU stay, respectively. A total of 84 episodes of SIs developed in 58 patients (39.7%). Overall, 104 isolates were recovered. Gram-negative bacteria accounted for 74% of all isolates, including *Acinetobacter* spp. (n = 27, 26%), *Klebsiella* spp. (n = 26, 25%) and *Pseudomonas* spp. (n = 9, 9%). The remaining pathogens included Gram-positive bacteria (n = 20, 19%), *Candida* spp. (n = 7, 6.7%) and other Gram-negative bacteria (Table 2).

Of 58 patients with SIs, at least one carbapenem-resistant pathogen (n = 61) was recovered in 41 patients (70.1%), including *Acinetobacter* spp. (n = 26, 4 also resistant to colistin), *Klebsiella* spp. (n = 24, 13 also resistant to colistin), *Pseudomonas* spp. (n = 7, one also resistant to colistin) and others.

Risk factors for the development of SIs

In univariate analysis, the development of SIs was significantly associated with the following: younger age (median 59.5 years), overweight or obesity, use of tocilizumab or/and convalescent plasma, the presence of septic shock at admission, a reduced P_aO_2/F_iO_2 ratio on the first day of mechanical ventilation, longer ICU stay, duration of central catheters or IMV, use of ECMO and use of cytokine filters (Table 3).

In multivariate analysis, the use of ECMO (OR 22.7, 95% CI 2.6, 199.2, $p = 0.005$), and an elevated procalcitonin level (OR 1.1, 95% CI 1.0, 1.1, $p = 0.030$) were significantly associated with the development of SIs (Table 3).

Mortality and outcome

In univariate analysis, mortality and the presence of carbapenem resistance did not differ significantly in ICU patients with and without SIs ($p = 0.059$ and $p = 0.083$, respectively). The distribution of bacterial pathogens was also similar in survived and deceased patients.

In multivariate analysis, the predictors of mortality were older age (median 65 years) (OR 1.062, 95% CI 1.015, 1.11, $p = 0.009$), the presence of congestive heart failure (OR 41.458, 95% CI 1.689, 1017.446, $p = 0.02$) and use of IMV (OR 29.436, 95% CI 5.368, 161.422, $p = 0.000$) (Table 4).

Table 1. Demographic, clinical and laboratory characteristics of COVID-19 patients.

Parameters	n (%) or median [IQR]
Age, years	64 [56–72.3]
Gender, M/F	96 (65, 8) / 50 (34.2)
Body mass index, kg/m^2	25.1 [24.1–28]
Comorbidities	
Diabetes mellitus	56 (38.4)
Arterial hypertension	
Chronic arterial disease	27 (18.5)
Chronic obstructive pulmonary disease	20 (13.7)
Malignant neoplasia	18 (12.3)
Chronic kidney disease	14 (9.6)
Congestive heart failure	13 (8.9)
Obesity	7 (4.8)
Cerebrovascular event	7 (4.8)
Thyroid diseases	5 (3.4)
Chronic liver disease	4 (2.7)
Rheumatic diseases	3 (2.1)
Sarcoidosis	2 (1.4)
Peripheral artery disease	1 (0.7)
Laboratory workup	
White blood cells, cells/mL	15.920 [12.287-22.010]
Lymphocytes, cells/mL	500 [287–800]
C-reactive protein, mg/L	171 [95–251.2]
Procalcitonin, ng/mL	2.1 [0.4-9.4]
Patients' condition at ICU admission	
APACHE II score	24 [17–31]
SOFA score	5 [3-9]
Septic shock	51 (34, 9)
Acute respiratory distress syndrome	87 (59.6)
P_aO_2/F_iO_2	100 [90–150]
ICU interventions/treatment	
Length of ICU stay (days)	10 [5–21.3]
Cytokine filter	23 (15.8)
Convalescent plasma	17 (11.6)
Tocilizumab	19 (13)
Steroids	118 (80.8)
Duration of central catheter (days)	10 [5–20]
ECMO	26 (17.8)
Duration of ECMO (days)	17, 5 [8.5–53.3]
Invasive mechanical ventilation	116 (79.5)
Duration of mechanical ventilation (days)	10 [4.3–20]
Secondary infections	58 (39.7)
Bloodstream infections	36 (24.7)
Lung infections	33 (22.6)
Urinary infections	2 (1.4)
Wound infections	1 (0.7)
Carbapenem resistance	41 (28.1)
Survived	50 (34.2)
Deceased	96 (65.8)

Table 2. Pathogens recovered from blood, lower respiratory tract and/or urine cultures.

Pathogens	Blood culture	Respiratory culture	Combined	Urine	Total patients
Gram-negative					
Klebsiella pneumoniae	13	7	6		26
Acinetobacter baumannii	2	12	13		27
Pseudomonas aeruginosa	2	2	5		9
Escherichia coli	2		1*	1	4
Enterobacter aerogenes	2				2
Serratia marcescens	1		1		2
Stenotrophomonas maltophilia	3	1			4
Sphingomona paucimobilis	1		1**		2
Providencia rettgeri			1		1
Gram-positive					
Staphylococcus aureus					
Methicillin-resistant	2	3	1		6
Methicillin-susceptible	2				2
Coagulase-negative staphylococci	6				6
Enterococci	6				6
Candida spp.	7				

*Urine and blood cultures; **Wound and blood cultures.

Table 3. Univariate and multivariate analysis of risk factors for the development of secondary infections.

Parameters	Nosocomial infections		Univariate analysis	Multivariate analysis
	Present n (%) or median [IQR]	Absent n (%) or median [IQR]	p^1	OR (95% CI) p^2
Age, years	59.5 [47.8-67.3]	67.0 [58.0-74.8]	0.001	
Gender, M/F	38 (65.5)/20 (34.5)	58 (65.9)/30 (34.1)	0.550	
Body mass index, kg/m^2	27.1 [24.2-33.0]	24.4 [24.1-26.9]	0.000	
Comorbidities				
Diabetes mellitus	23 (39.7)	33 (37.5)	0.464	
Arterial hypertension	13 (22.4)	39 (44.3)	0.005	
Chronic arterial disease	9 (15.5)	18 (20.5)	0.299	
COPD	8 (13.8)	12 (13.6)	0.582	
Malignant neoplasia	2 (3.4)	16 (18.2)	0.006	
Chronic kidney disease	3 (5.2)	11 (12.5)	0.116	
Obesity	6 (10.3)	1 (1.1)	0.016	
Procalcitonin, ng/mL	5.6 [1.4-10.8]	1.4 [0.2-8.4]	0.006	1.1 (1.0-1.1) 0.030
APACHE II score	24.0 [18.0-28.0]	24.0 [15.3-32.8]	0.296	
SOFA score	5.0 [2.8-8.0]	6.0 [3.0-10.0]	0.163	
Septic shock at ICU admission	15 (25.9)	36 (40.9)	0.045	0.4 (0.1-1.1) 0.074
Severe ARDS at ICU admission	37 (63.8)	50 (56.8)	0.253	
P_aO_2/F_iO_2 on the first day of IMV	100.0 [80.0-120.0]	120.0 [100.0-150.0]	0.003	1.0 (1.0-1.0) 0.329
Length of ICU stay (days)	23.0 [14.0-36.5]	7.0 [4.0-11.5]	0.000	
Days from diagnosis to discharge/death	27.0 [18.0-47.8]	11.5 [7.3-16,8]	0.000	
Cytokine filter	17 (29.3)	6 (6.8)	0.000	
Convalescent plasma	13 (22.4)	4 (4.5)	0.001	2.3 (0.4-13.1) 0.357
Tocilizumab	13 (22.4)	6 (6.8)	0.007	2.3 (0.4-13.1) 0.357
Steroids	48 (82.8)	70 (79.5)	0.398	
Duration of central catheter (days)	23.0 [13.5-36.0]	6.0 [4.0-10.0]	0.000	
ECMO	25 (43.1)	1 (1.1)	0.000	22.7 (2.6-199.2) 0.005
Duration of ECMO (days)	19.0 [9.5-54.5]	6.0 [6.0-6.0]	0.308	
Invasive mechanical ventilation	55 (94.8)	61 (69.3)	0.000	
Duration of mechanical ventilation (days)	20.0 [11.0-35.0]	5.0 [3.0-11.0]	0.000	

[1] Mann-Whitney U-test for numerical variables; Fisher's exact test for categorical variables. [2] Logistic regression analysis. COPD: Chronic obstructive pulmonary disease; ARDS: Acute respiratory distress syndrome; IMV: Invasive mechanical ventilation.

Use of antibiotics

In the current study, antibiotics were used in the vast majority of patients (91%), with piperacillin/tazobactam (n = 77) most frequently administered, followed by antibiotics against methicillin-resistant Gram-positive organisms (n = 62), carbapenem derivatives (n = 52) and tigecycline (n = 51).

Carbapenem resistance

Patients with carbapenem resistance were found to have received carbapenem derivatives significantly more frequently than those without carbapenem resistance (58.5% vs. 17.6%; $p = 0.004$). In addition, carbapenem resistance was significantly higher in patients receiving convalescent plasma (29.3% vs. 4.8%; $p = 0.000$), tocilizumab (26.8% vs. 7.6; $p = 0.002$), ECMO (56.1% vs. 2.9%; $p = 0.0000$), and IMV (100% vs. 71.4%; $p = 0.000$).

Time to isolation of carbapenem-resistant microorganisms was significantly longer than that of carbapenem-susceptible microorganisms (median 14 vs. 10 days, $p = 0.006$).

The Impact of SIs on ICU parameters

The presence of SIs was significantly associated with a prolonged ICU stay and hospital stay, an increased need for ECMO and IMV, and prolonged use of IMV (Table 1).

Table 4. Univariate and multivariate analysis of risk factors for mortality.

Parameters	Patient outcome		Univariate analysis	Multivariate analysis
	Death n (%) or median [IQR]	Survival n (%) or median [IQR]	p[1]	OR (95% CI) p[2]
Age, years	65.0 [58.0-73.8]	59 [47.8-72]	0.010	1.062 (1.015-1.11) 0.009
Gender, M/F	64 (66.7) / 32 (33.3)	32 (64) / 18 (36)	0.443	
Body mass index, kg/m^2	24.7 [24.1-28.0]	25.7 [24.1-27.9]	0.580	
Comorbidities				
Diabetes mellitus	41 (42.7)	15 (30.0)	0.093	
Arterial hypertension	35 (36.5)	17 (34.0)	0.458	
Chronic arterial disease	22 (22.9)	5 (10.0)	0.043	3.174 (0.45-22.416) 0.247
COPD	12 (12.5)	8 (16.0)	0.364	
Malignant neoplasia	13 (13.5)	5 (10.0)	0.370	
Chronic kidney disease	12 (12.5	2 (4.0)	0.082	
Congestive heart failure	12 (12.5)	1 (2.0)	0.028	41.458 (1.689-1017.446) 0.02
Obesity	5 (5.2)	2 (4.0)	0.549	
Laboratory				
White blood cells, cells/mL	16685 [12758-24725]	13965 [11533-18168]	0.020	1 (1-1) 0.367
Lymphocytes, cells/mL	550 [308-800]	445 [278-788]	0.428	
C-reactive protein, mg/L	183 [109-270]	129.5 [70-222]	0.055	
Procalcitonin, ng/ml	4.7 [1.1-9.8]	0.93 [0.2-8.2]	0.001	1.038 (0.96-1.122) 0.352
APACHE II score	28 [22-32.8]	17.5 [12.8-21]	0.000	1.066 (0.993-1.144) 0.076
SOFA score	8 [3-10]	3 [2-4.3]	0.000	1.162 (0.929-1.452) 0.188
Septic shock at ICU admission	44 (45.8)	7 (14.0)	0.000	0.961 (0.184-5.034) 0.963
Severe ARDS at ICU admission	68 (70.8)	19 (38.0)	0.000	
P_aO_2/F_iO_2 on the first day of IMV	100 [90-150]	100 [85-150]	0.878	
Length of ICU stay (days)	12.0 [5.3-21.0]	9 [4.8-23]	0.372	
Days from diagnosis to discharge/ death	16.0 [11.0-26.8]	13 [8-25.3]	0.385	
Cytokine filter	17 (17.7)	6 (12.0)	0.259	
Convalescent plasma	11 (11.5)	6 (12.0)	0.561	
Tocilizumab	11 (11.5)	8 (16.0)	0.299	
Steroids	77 (80.2)	41 (82.0)	0.490	
Duration of central catheter (days)	12 [5.0-21.0]	9 [4.5-17]	0.217	
ECMO	19 (19.8)	7 (14. 0)	0.265	
Duration of ECMO (days)	10 [7-20]	60 [40-66]	0.000	
Invasive mechanical ventilation	91 (94.8)	25 (50.0)	0.000	29.436 (5.368-161.422) 0.000
Duration of mechanical ventilation (days)	10.0 [4.0-18.8]	13.5 [6-69.8]	0.089	
Nosocomial infection in the ICU	43 (44.8)	15 (30)	0.059	
Carbapenem-resistance	31 (32.3)	10 (20.0)	0.083	

[1] Mann-Whitney U-test for numerical variables; Fisher's exact test for categorical variables. [2] Logistic regression analysis. COPD: Chronic obstructive pulmonary disease; ARDS: Acute respiratory distress syndrome; IMV: Invasive mechanical ventilation.

Discussion

In this two-centre study, we found a high incidence of SIs among COVID-19 patients admitted to the ICU compared with the overall incidence of nearly 3.5% for ICU patients. In 58 patients (39.7%), 84 episodes were detected associated with 104 isolates, with Gram-negative bacteria being the most frequent pathogen accounting for 74% of all isolates. The most frequent pathogens were *Acinetobacter* spp. (n = 27, 26%), *Klebsiella* spp. (n = 26, 25%), and *Pseudomonas* spp. (n = 9, 9%). An alarmingly high rate of carbapenem resistance (69%) was also documented.

Reports on SIs in COVID-19 patients in the ICU are limited. Previous studies usually examined SIs among all hospitalised patients with COVID-19, with incidences ranging from 40.7 % to 86.6% [5,15,16].

At the beginning of the study, while collecting data and on the basis of previous reports and common beliefs, we presumed that both SIs and carbapenem resistance would significantly contribute to mortality, particularly in COVID-19 and ICU settings [17–19]. Contrary to our expectations, our analysis showed no significant effect of SIs or carbapenem resistance on mortality. Secondary infections accompanying COVID-19 have recently begun to receive attention. Most studies reported a significant association between SIs and mortality in critically ill COVID-19 patients [5,9,20,21]. A few studies found no significant effect of SIs and multidrug-resistant bacterial infections on mortality [8,11,16,22,23]. However, to our knowledge, no study has reported on the effect of carbapenem resistance on mortality. Notably, our findings showed a high incidence of carbapenem resistance among critically ill COVID-19 patients with SIs (n = 41/58, 70.1%). This worrisome aspect has not been addressed in the literature. In our series, the overall incidence of carbapenem resistance was 28% among ICU patients with COVID-19, accounting for one out of every four patients. We speculate that carbapenem resistance would be much more common, considering early mortality of ICU patients, particularly within the first week. Overall, the ICU stay was less than one week in 47 patients, of whom 30 died within the first week, and among the 17 survivors, only four developed SIs. Moreover, according to most studies, SIs usually occurs one week after admission to ICU; therefore, carbapenem resistance is likely to develop beyond this period [16,22,24,25]. In our series, the median duration for the detection of carbapenem resistance was 14 days.

Upon detection of a high incidence of SIs in the ICU settings, we reviewed possible and modifiable sources of contamination in three categories: treatment-related, facility/personnel-related, and patient-related. Treatment-related factors that raised concern included use of antibiotics (91%), steroids (80.8%), tocilizumab (13%) and catheters (100%) [8,11,25,26]. Facility/personnel-related factors required closer surveillance covering a broad range: non-effective hand hygiene, use of inappropriate gloves, lack of experience, lack of protective equipment, and increased patient load [27]. Finally, patient-related factors were those that were more likely to be associated with SIs and carbapenem resistance: comorbidities, ARDS, septic shock, viral mucosal invasion, immunocompromisation, and prolonged ICU need [26,27]. All ICU healthcare personnel were provided with additional training to improve adherence to hand hygiene practice. Moreover, indications for the use of antibiotics were narrowed.

Limitations

The main limitation to the present study is its retrospective design. A considerable portion of patients were those who were transferred from other centres for further interventions, particularly ECMO. In addition, some patients contracted COVID-19 during hospitalization for other conditions.

Conclusions

Secondary infections are an important challenge to both ICU patients and healthcare personnel, particularly when the main illness is COVID-19. The incidences of SIs and carbapenem resistance are alarming, as shown by the current study with 39.7% and 70.1%, respectively, emphasizing stricter infection control measures in the ICU setting.

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