Secondary Infections in Critical Patients with COVID-19 Associated ARDS in the ICU: Frequency, Microbiologic Characteristics and Risk Factors

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ABSTRACT

Objective: To determine frequency, microbiologic characteristics and risks of secondary infections in patients with Coronavirus disease 2019 (COVID-19) associated acute respiratory distress syndrome (ARDS).

Study Design: An Observational study.

Place and Duration of Study: COVID-19 intensive care unit (ICU), University of Health Sciences, Diskapı Yildirim Beyazit Research and Training Hospital, Turkey, from July 2020 to January 2021.

Methodology: Demographic data of the COVID-19 patients with ARDS, was collected with reference to (age, gender), comorbidities, illness scores, ICU management modalities, hospital, and ICU stay durations and ICU outcomes. Secondary infections [bloodstream infection (BSI), possible lower respiratory tract infection (pLRTI) or urinary tract infections (UTI)], microbiologic pathogens, and resistant patterns were recorded.

Results: A total of 205 COVID-19-related ARDS patients were included in this study. Out of them, 61 (29.8%) were diagnosed with secondary infection, 27 (13.1%) had at least one BSI, 20 (9.8%) had at least one pLRTI, and 34 (16.6%) had at least one UTI. Gram-negative pathogens were the most common cause of secondary infections (66/91, 72.5%). *Klebsiella* spp for BSI (10/19, 52.6%), *Acinetobacter baumannii* for pLRTI (10/18, 55.6%), and *Escherichia coli* for UTI (29/40, 72.5%) were the main causative agents. Among all Gram-negative bacteria, Carbapenem resistant was 62.1% (41/66) and extended-spectrum beta-lactamases positivity was 22.7% (15/66). At multivariable analysis, application of mechanical ventilation (MV) longer than 48 h, central catheterisation longer than 72 h, ICU stay longer than 10 days, and the time from hospitalisation to admission to the ICU longer than 48 h were associated with secondary infections.

Conclusion: Patients with COVID-19 associated ARDS had a high rate of secondary infections. In order to reduce secondary infection in these patients, MV duration and ICU stay should be shortened and invasive catheters should be removed as soon as possible.

Key Words: *SARS-CoV-2, COVID-19, Acute respiratory distress syndrome, Secondary infections.*

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INTRODUCTION

The Coronavirus disease 2019 (COVID-19) disease is a multisystemic disease, and as such its symptoms are mostly nonspecific and comprise several organs, tissues, and functions of the body.

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As of 7 August 2022, there are nearly 581.8 million cases worldwide with 6.4 million deaths.[1] It was initially viewed as primarily a respiratory disease, in some cases progressing to viral pneumonia.[2,3] It is now recognised as a complex, potentially lethal systemic disease that affects many organ systems, and it often progresses to a severe course that requires hospitalisation especially intensive care unit (ICU) support.[4] The severe complications associated with non-survival in patients with COVID-19 were primarily acute respiratory distress syndrome (ARDS), septic shock, metabolic acidosis, coagulation dysfunction, and multiple organ failure. *SARS-CoV-2* can lead to ARDS by causing an exaggerated immune response in the immune phase.[5]

Effective treatment of severe COVID-19 cases usually requires the reduction of inflammation and control of thrombosis.

Immunosuppressive agents, which are widely used to prevent virus-related immune system disorder and cytokine release syndrome, predispose to secondary infections.[6] In addition, frequent use of invasive procedures such as endotracheal intubation, central venous catheterisation, and tracheostomy in critically ill COVID-19 patients also pave the way for secondary infections.[7] In the recent studies, critically ill COVID-19 patients, admission to the ICU, the presence of ARDS, and prolonged mechanical ventilation were found to be associated with increased risk of secondary infections.[7-9]

The aim of this study was to determine the frequency, microbiological characteristics, and risk-factors of secondary infections in COVID-19 associated acute respiratory distress syndrome (ARDS) patients during ICU stay.

METHODOLOGY

The patients who tested positive for *SARS-CoV-2* based on real--time reverse transcriptase polymerase chain reaction (RT-PCR) from a nasopharyngeal swab, had the diagnosis of ARDS and followed up in the COVID-19 ICU of the University of Health Sciences, Diskapi Yildirim Beyazit, Research and Training Hospital, Turkey, between 1 July 2020 and 15 January 2021 were included. Patients younger than 18 years of age, possible COVID-19 patients with negative RT-PCR, without ARDS, growth in surveillance cultures upon admission to ICU, patients who were lost or discharged from ICU within 48 hours of admission, pregnant patients and post-operative patients were excluded.

Demographic data of the patients (age, gender), comorbidities, acute physiology and chronic health evaluation score II (APACHE II), sequential organ failure assessment (SOFA) score, time from hospital admission to ICU admission, immunosupressive therapies, respiratory support therapies, secondary infection development times, secondary infection types and resistant patterns, hospital and ICU stay durations and ICU outcomes were recorded from the hospital information system manually by filling out the study forms.

The general health status and acute disease severity of the patients admitted to the ICU were evaluated with the APACHE II score, and the organ failure conditions were evaluated with the SOFA score.[10] All the patients received non-invasive mechanical ventilation (NIMV) with at least 5 cm H_2O positive end-expiratory pressure (PEEP). The Berlin criteria was used for the diagnosis of ARDS.[11]

Cultural data were recorded from the 48th hour of ICU admission. Secondary infection was defined as having at least one of the bloodstream infections (BSI), possible lower respiratory tract infections (pLRTI) or urinary tract infections (UTI). BSI was defined as a single positive blood culture for a likely pathogen or two or more positive blood cultures for common skin colonizers.[12] Positive follow-up blood culture (FUBC) is defined as bacteremia in which the FUBCs gave the same organism as the initial blood culture, as long as the FUBC was obtained at least 24 h after the initial blood culture. Any positive blood cultures obtained within 24 h of the initial positive culture were considered as the same episode.

Possible lower respiratory tract infection (pLRTI) was defined as a distal airway infection including either trachea, bronchi or lungs. pLRTI was determined microbiologically as the growth of a possible pathogenic microorganism in sputum and tracheal aspirate samples. Bartlett score was used to distinguish colonization/-contamination (C/C) and pathogen. Since the risk of oropharyngeal and oral C/C is high, *Candida* spp. growth was not considered as causative agents.

Urinary tract infections (UTI) was accepted as the possible growth of pathogenic microorganism in urine samples.[13] In order to distinguish between C/C and the causative agent, the presence of pus cells in urine analysis and the amount of growth in the culture were examined. *Candida spp*. growth was accepted as a pathogen of UTI if the same agent was grown after the urinary catheter was removed.

BacT/Alert aerobic/FA Plus and anaerobic/FN Plus (bioMérieux, USA) blood culture bottles were used for the investigation. Microorganism identification and antimicrobial susceptibility testings were performed with Vitek 2 Compact (BioMérieux) system and MALDI-TOF MS (Bruker, Germany). Patients for whom no microbiology specimens were requested were considered not to have secondary infections.

This study was conducted in accordance with the Declaration of Helsinki with the ethics guidelines. This retrospective study was approved by the institutional review board of the Hospital (Approval number: 107/15, 22/03/2021) and permission from the Ministry of Health of the Republic of Turkey was obtained.

Statistical analysis was performed using SPSS Statistics (Version 17.0, SPSS Inc). The normal distribution of the data was tested using the Shapiro-Wilk test. The study group was divided into two groups as group with secondary infection (with at least one secondary infection) and non-infection group (without secondary infection) and these groups were compared. Continuous variables were shown as mean ± standard deviation or median (25thand 75th percentiles) depending on the data distribution and compared using Student's t-test or Mann-Whitney U-test. Categorical variables are expressed as numbers (%) and compared using chi-square test or Fisher exact test. Multivariable model was performed to determine the independent risk--factors for secondary infection development. Level of statistical significance was considered as $p<0.05$.

RESULTS

Two hundred and five patients with a mean age of 68.4±13.1 years were included; 119 (58%) were males and 86 (42.0%) were females. The mean APACHE II score was 19.6±4.8, the SOFA score was 4.9±2.4 at the time of ICU admission. All the patients had at least one comorbidity. The most common comorbidities were hypertension with 62.4%, diabetes mellitus with 43.2%, and coronary artery disease with 24%.

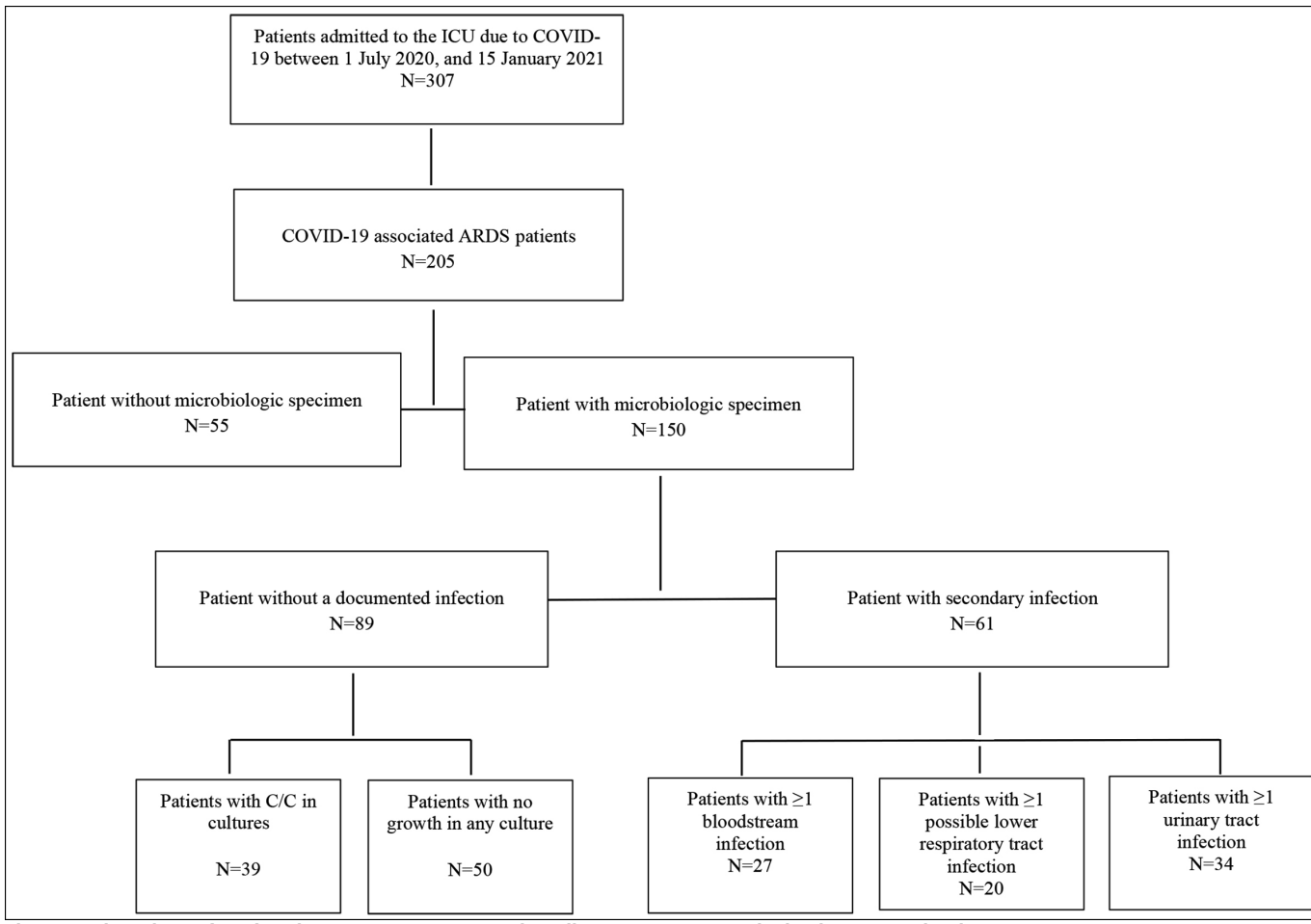

Figure 1: Flow-chart of study cohort. *COVID 19,* Coronavirus disease 2019; C/C, Colonization/Contamination.

The mean time from symptom onset to ICU admission was 8.2±5.8 days. Out of them, 54.1% of the patients were admitted to the ICU within 48 h of their hospital admission. At admission to the ICU, 187 patients (91.2%) were treated with at least one antibiotic. As immunosuppressive therapy, tocilizumab was given to 69 (33.2%) patients and pulse steroid therapy was given to 39 (19.1%) patients. Mechanical ventilation (MV) and central catheterisation were performed in a total of 91 (44.4%) patients.

A secondary infection was diagnosed in 61 patients (29.8%); 27 patients (13.2%) had BSI, 20 patients (9.8%) had pLRTI, and 34 patients (16.6%) had UTI (Figure 1). The mean time from ICU admission to the first BSI was 9.2±7.2 days; to the first pLRTI was 11.4±8.6 days; to the first UTI was 12.7±8.8 days. Common possible sources of BSI's were pneumonia (14/27, 51.9%), central catheter (7/27, 25.9%), and UTI (4/27, 14.8%). The source of BSI could not be determined in two patients.

Age, gender, APACHE II scores were similar in two groups (p>0.05). They had also similar comorbidity rates (86.8% *vs.*. 84%; p=0.584). SOFA score at ICU admission was higher in secondary infection group (p=0.04). There was no difference in the frequency of immunosuppressive treatment between the groups. Invasive MV rates were similar. The mean time from ICU admission to intubation was also similar (5.9±5.7 *vs.* 4.9±4.6 days; p=0.283). The rate of central catheterisation was higher in the group with secondary infection (54.1% *vs.* 40.3%; p=0.04). Total hospital stay and ICU stay were longer in the secondary infection group (p<0.01). Although there was no difference in the rate of patients who were admitted to a lower level ICU and died, more patients were discharged to the ward in the group without secondary infection (p=0.035, Table I).

At the time of ICU admission, mean white blood cell count (p=0.004), neutrophil count (p=0.015), lactate dehydrogenase (p=0.043), and lactate level (p=0.04) were higher in patients with secondary infection than in the group without secondary infection. Other laboratory findings were similar (Table II).

Microbiological sampling for culture was not requested from 55 of the patients (26.8%) during their ICU stay. The microorganisms were accepted as C/C in 39/150 (26%) patients for whom any sampling was requested. The number of patients whose blood culture was not performed was 85 (41.5%). When blood cultures with positive signals were evaluated, blood culture agents of 30/120 (25%) were evaluated as C/C (Figure 1). Most detected contaminant microorganisms were *Staphylococcus epidermidis* (n=18), *Staphylococcus hominis* (n=9) and *Corynebacterium striatum* (n=3).

Table I: Comparison of general characteristics of groups with and without secondary infection.

Characteristics	Group with secondary infection (N=61, %)	Group without secondary infection (N=144, %)	p
Age (years) (mean±SD)	70.4±10.5	67.5±13.9	0.104*
Gender (male)	31 (50.8)	88 (73.8)	0.216**
APACHE II score	19.6±6.5	19.1±2.8	0.685*
SOFA at ICU admission	4.9±1.9	4.8±2.8	0.04*
Time from hospital admission to ICU admission <48 hours	25 (41.0)	86 (59.7)	0.014**
Type of immunosuppressive drug			
Tocilizumab	20 (32.8)	48 (33.3)	0.537**
Pulse steroid[α]	12 (19.7)	27 (18.8)	0.519**
Invasive mechanical ventilation (Yes)	31 (50.8)	60 (41.7)	0.282**
Central catheterisation (Yes)	33 (54.1)	58 (40.3)	0.04**
ICU stay (days)	14.7±6.8	10.4±6.2	<0.001*
Total length of hospitalisation (days)	23.1±11.0	16.0±8.6	<0.001*
ICU outcomes (%)			
Transfer to ward	24 (39.3)	77 (53.5)	0.035**
Transfer to lower level ICU	4 (6.6)	4 (2.8)	0.136**
Exitus	32 (52.5)	63 (43.8)	0.161**

*[α]Prednisolone 250 mg once daily for 4 days (except for prednisolone 40 mg twice daily given to all patients) * Student's t-test, ** Chi-square test.*

Table II: Comparison of laboratory parameters of groups with and without secondary infection.

Laboratory parameters	Group with secondary infection (N=61)	Group without secondary infection (N=144)	p
White blood cells (per 10^3/L)$^{+}$	12.784±8.981	9.922±5.096	0.004*
Lymphocytes (per 10^3/L)$^{+}$	0.78±0.44	0.78±0.66	0.968*
Neutrophils (per 10^3/L)$^{+}$	10763±6.260	8.760±4.900	0.015*
Haemoglobin (g/dL)$^{+}$	12.2±2.1	12.5±2.2	0.365*
Platelets (per 10^3/L)$^{+}$	259.466±157.147	244.790±100.635	0.427*
Creatinine (mg/dL)$^{+}$	1.23±1.1	1.43±1.2	0.275*
Alanine aminotransferase (U/L)$^{++++}$	28 (18-50)	27 (18-47)	0.467**
Aspartate aminotransferase (U/L)$^{++++}$	37 (25-58)	38.5 (26-63)	0.766**
Lactate dehydrogenase (U/L)$^{++}$	612±514	597.7±278.3	0.043*
Ferritin (ng/mL)$^{++++}$	689 (380-1437)	735 (303-1277)	0.761**
Lactates (mmol/L)$^{++++}$	1.7 (1.3-2.4)	1.5 (1.2-2.0)	0.04**
D-dimer (mg/mL)$^{++++}$	1320 (740-2720)	1280 (623-2558)	0.496**
Fibrinojen (mg/dL)$^{+}$	552.2±177.6	570.6±183.1	0.517*
Prothrombin time (s)$^{++}$	14.3±15.9	12.2±6.7	0.194*
C-reactive protein (mg/L)$^{++}$	121±86	131±92.2	0.494*
Procalcitonin (ng/mL)$^{++++}$	0.3 (0.13-0.85)	0.35 (0.13-1.8)	0.290**
Creatinine kinase (U/L)$^{++}$	128 (53-258)	124 (62.3-355)	0.475**

*COVID 19, Coronavirus disease 2019; ARDS, Acute respiratory distress syndrome; ICU, Intensive care unit. [+]Mean±standard deviation, [++]Median (25-75 percentile), * Student's t-test, ** Mann-Whitney U-test.*

Table III: Multivariate analysis of the risk factors of secondary infections.

Baseline characteristics	Hazard ratio	95% confidence interval	p
ICU admission >48 hours from hospital admission, yes *vs.* no	1.77	1.1-3.35	0.004
Mechanical ventilation >48 hours, yes *vs.* no	1.86	2.1-7.7	0.012
Central catheterization >72 hours, yes *vs.* no	3.21	2.8-6.7	0.028
Intensive Care Unit (ICU) stay >10 days, yes *vs.* no	2.05	3.5-5.03	0.001

Gram-negative pathogens were the most common cause of BSI (19/30, 63.3%), pLRTIs (18/21 isolates, 85.7%), and UTIs (29/40 isolates, 72.5%). The main pathogens were *Klebsiella* spp. (10/19, 52.6%) for BSI, *Acinetobacter baumannii* (*A. baumannii*) (10/18, 55.6%) for pLRTIs, and *Escherichia coli (E. coli)* (15/29, 51.7%) for UTIs.

For BSI; resistance mechanisms were carbapenem resistant (CR) *Klebsiella* spp. 9/10 (90%), CR *A. baumannii* 7/7 (100%), extended spectrum beta-lactamases (ESBL) positive *E. coli*: 2/2 (100%), methicillin-resistant Coagulase Negative Staphylococcus (CoNS) 2/2 (100%). For pLRTI resistance mechanisms were CR *A. baumannii* 10/10 (100%), CR *Klebsiella* spp. 4/4 (100%), CR *Pseudomonas aeruginosa* 2/3 (66.7%), ESBL positive *E. coli* 1/1 (100%). For UTI; resistance mechanisms were ESBL positive *E. coli* 10/15 (66.7%), CR *Klebsiella* spp. 5/8 (62.5%), ESBL positive *Klebsiella* spp. 1/8 (12.5%), CR *A. baumannii* 3/3 (100%), CR *Enterobacter aerogenes* 1/2 (50%), ESBL positive *E. aerogenes* 1/2 (50%), methicillin-resistant *S. aureus* 1/ 1 (100%).

Among all Gram-negative bacteria, the ratio of CR was 62.1% (41/66) and the ratio of ESBL positivity was 22.7% (15/66). In this study, all members of Enterobacterales family bacteria had CR (19/439, 15/43 had ESBL, and non-fermenter bacteria had 22/23 CR).

Multivariate analysis revealed that if the time from hospital admission to ICU admission was longer than 48 h, if patient received MV longer than 48 h, if central catherisation duration was longer than 72 h and if ICU stay was longer than 10 days increased the hazard of developing secondary infection and these factor indepently related with secondary infection (Table III).

DISCUSSION

In this study, the secondary infection rate was 29.8%, and most of the pathogens were Gram-negative multi-drug resistant microorganisms. Long-term MV and central catheterisation and a long stay in the ICU were determined as independent risk-factors for the development of secondary infection.

In the study, Ripa *et al*. the secondary infection rate was found as 9.3% in hospitalised COVID-19 patients. At least one BSI was detected in 7.9% of patients, and pLRTI was detected in 3.0%. The 28-day cumulative incidence was 16.4%. Similar to the present study, *A. baumanii* and *E. coli* were the most common Gram-negative pathogens. Lower basal lymphocyte ratio, lower basal PaO_2/FIO_2 ratio and ICU admission in the first 48 h of hospitalisation were found to be the risk-factors for secondary infection.[6] In the present study, the secondary infection rate was 29.8%. The secondary infection rate seems to be higher. But compared to the study, the number of patients in Ripa *et al.'s* study was quite high with 731. In this study all of the patients were critical COVID-19-related ARDS patients and PaO_2/FIO_2 ratio of all of them had lower than 300 mmHg. It was shown that the need of ICU and the high number of invasive interventions in critical COVID-19 patients increase the risk of developing secondary infections.[14]

Yu *et al*. investigated the secondary infection rate in 226 critically ill COVID-19 patients and secondary infection rate was 21.7%.[15] Zhang *et al*. found 57.89% secondary infection in 38 critical and severe COVID-19 patients.[16] In both of those studies, as in this study, UTIs were included in secondary infection, and the COVID-19 patients included in their study were serious or critical, not all of them were critically ill. The high rate in the study of Zhang *et al*. may be attributed to the low number of their patients. In this study, all patients were critical and ARDS patients, nearly half of them were intubated and had central catheterisation.

It was proposed that COVID-19 infected patients were more likely to develop BSI compared to those without COVID-19 infection.[17] There was a significant increase between pre--pandemic and pandemic BSI rates. Pasquini *et al*. reported that BSI was higher than in the pre-pandemic period in their multicentre study from Italy in the first 6 months of the pandemic. BSI was higher in patients with COVID-19 (8.19 episodes per 1000 patient-day *vs.* 2.72 episodes per 1000 patient-day). They also stated that the diagnosis of BSI was delayed (16.0 *vs.* 5 days) compared to patients without COVID-19. Similar to the present study, BSIs frequently caused by multi-drug resistant pathogens.[18]

Bhatt *et al*. evaluated 375 critically ill COVID-19 patients in a multicentre prospective cohort study. The rate of BSI was 34.1% and the most common three agents were *S. epidermidis*, *S. aureus*, *Enterococcus faecalis.*[7] Rothe *et al*. found the rate of BSI as 29.7% in 154 COVID-19 patients followed in the ICU. The most common agents were Enterobacterales, CoNS and *Enterococcus faecium.*[19] In this study, BSI rate was 13.1%. Gram-negative pathogens were the most common causative agents, while Gram-positive pathogens were less common than other studies. Since follow-up blood cultures were not obtained from most of the patients whose blood cultures had skin colonizers, these pathogens were considered as C/C. Therefore, the rate of Gram-positive bacteria as an BSI causative agent in the study seems to be found lower than in other studies.

Buehler *et al*. found the bacterial pulmonary superinfection rate 42.2%. (19/45) critical COVID-19 patients with ARDS. In this study, *Enterococcus* spp. was the most common causative pathogen. Bacteremia was detected more frequently in these patients. In this study 88.9% of the patients were treated with MV, bacterial growth rate was 34.1% in the blood cultures. BSI was detected more frequently in the group of patients with pulmonary superinfection (47.4% *vs.*. 7.7%; p=0.004).[20]

In Mumcuoglu *et al*.'s study, the rate of secondary bacterial respiratory tract infection rate was 19.7% (7684/1513) in critical COVID-19 patients followed in the ICU. The most common causative pathogen was *A. baumannii*. This study did not have any data on disease severity and respiratory support treatments such as MV, 65.9% of patients with SBI died.[21] In this study, the rate of laboratory-proven pLRTI was 9.9%, and the most common causative pathogen was *A. baumannii*.

In this study, no blood culture samples were taken from 41.5% of the patients. The C/C ratio was 25%. The rate of patients who were not requested any microbiological sampling (28.8%) and the total C/C ratio (26%) were very high. A decrease in microbiological sampling and sampling quality due to the increased healthcare burden during COVID-19 pandemic may be the underlying reason. A second reason might be the limits to exclude C/C when defining BSI and pLRTI in the study method. Compared to the previous studies, the lower rates of BSI and pLRTI in this study may be due to insufficient microbiological sampling and high accepted C/C rates.

Recent studies have shown the rapid spread of CR in ICU patients during the COVID-19 pandemic.[22,23] Similar to these findings Mumcuoglu *et al*. also detected high CR in their study [83.7% for *A. Baumannii*, 79.2% for *P. Aeruginosa*,

42.7% for *K. pneumoniae*).[21] In this study, CR was higher (81.8% for *Klebsiella* spp., 100% for *A. Baumanni*). This local difference in CR can be attributed to the different frequency of broad-spectrum antibiotic use in the study centre.

Recent data indicate that high CR rates in the critically ill COVID-19 patients may pose a very serious threat. To prevent this, more comprehensive surveillance strategies should be established and the potential abuse of empirical broad-spectrum antibiotics should be reduced in patients with COVID-19.[7,24,25]

This study had some limitations. The first and the most important limitation was its retrospective nature. This made it difficult to distinguish between C/C and actual infection. Secondly, none of the patients samples tested for the diagnosis of invasive asperigillosis. Therefore, the study did not contain the rate of invasive aspergillosis in patients with COVID-19 ARDS patients. Third, it was a single-centre study. Multicentre, prospective controlled studies are needed for the accurate determination of secondary infection rates in COVID-19 associated ARDS patients. The study also had some strengths. The strongest aspect was that all the study patients had ARDS associated with COVID-19, this is the first data obtained from Turkey. These data are important in terms of contributing to the demonstration of the current antibiotic resistance patterns of ICU during the COVID-19 pandemic.

CONCLUSION

Patients with COVID-19-associated ARDS had a high rate of secondary infections. In order to reduce secondary infection in these patients, MV duration, and ICU stay should be shortened and invasive catheters should be removed as soon as possible. The high rates of antimicrobial resistance of isolated bacteria require increased surveillance measures and careful empirical treatment choices in COVID-19 associated ARDS patients.

ETHICAL APPROVAL:

Ethics committee approval (Ethics committee for clinical investigations of Diskapi Yildirim Beyazit Training & Research Hospital—22 March 2021, no: 107/15) was obtained for the study prior to initiation of the research work.

PATIENTS' CONSENT:

Informed consent were obtained from the patients during this study.

COMPETING INTEREST:

All authors declared no competing interest relevant to this article.

AUTHORS' CONTRIBUTION:

MRT, FY: Planned, analysed, and wrote the study. FY also made the critical analysis of study. MS, HID, IS: Analysed and evaluated the results as well as contributed to writing the manuscript.

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