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Coronavirus Pandemic

Clinical characteristics and risk factors associated with secondary bacterial pneumonia among COVID-19 patients in ICU

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Abstract

Introduction: COVID-19 and secondary infections developing during COVID-19 follow-up are one of the most important causes of morbidity and mortality in intensive care units (ICU). In this study, we aimed to determine the frequency, microbiology, risk factors, and outcomes of secondary bacterial pneumonia in hospitalized patients due to COVID-19.

Methodology: We studied all patients with bacterial pneumonia developed in patients with severe COVID-19 infection in the COVID-19 intensive care unit in a single-center hospital between March 16, 2020 and June 17, 2020.

Patients hospitalized and followed up in the ICU for respiratory failure were examined in terms of secondary infection affecting morbidity and mortality.

Results: Ninety-six (20%) of 471 patients had secondary bacterial pneumonia, respectively; of the leading pathogens were *Acinetobacter baumannii* (44.8%) and *Klebsiella pneumoniae* (39.6%), followed by *Pseudomonas aeruginosa* (4.2%), *Escherichia coli* (3.1%), *methicillin-resistant Staphylococcus aureus (MRSA)* (3.1%), *Streptococcus pneumoniae* (3.1%), and *Methicillin-susceptible Staphylococcus aureus (MSSA)* (1%). The mortality rate among infected (75% / 47.5%) was significantly higher than in uninfected patients. Associated with the development of secondary bacterial pneumonia in COVID-19 patients; corticosteroid therapy [odds ratio (OR) 6250, 95% confidence interval (CI) 1.383-28.571, $p = 0.017$), corticosteroid dose (OR 8.862 CI 2.299-70.258, $p= 0.006$), duration of mechanical ventilation (OR 1.199 CI) 1.088-1.322, $p< 0.001$).

Conclusions: Secondary bacterial pneumonia was found to be associated with the severity and survival of the disease in patients admitted to ICU due to COVID-19. Duration of mechanical ventilation and use of corticosteroids and high-dose corticosteroids are risk factors for secondary bacterial pneumonia.

Key words: Bacterial infections; co-infection; COVID-19; *K. pneumonia*.

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Introduction

The COVID-19 outbreak is an ongoing threat to global public health. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic has struck more than 500 million people worldwide as of April 24th, 2022, and over six million deaths have been reported globally [1]. The majority of COVID-19 cases can be observed with mild diseases.

However, a substantial percentage of patients can progress to critical illness with hypoxemic respiratory failure that may require respiratory support in up to 25% of the patients [2]. The prognosis is poor in patients on invasive mechanical ventilation and in ICU [3].

Hospitalized patients, especially critically ill, are at risk for secondary infections. The susceptibility to secondary bacterial infection is probably increased in COVID-19 due to both virus and drug-induced immunosuppression. Secondary bacterial infections occur in COVID-19 patients and lead to increased disease severity and mortality, especially in those requiring invasive mechanical ventilation. Pneumonia including ventilator-associated pneumonia (VAP) was reported to be the most common bacterial complication of COVID-19 [4]. *Enterobacteria spp, K. pneumoniae*, *Acinetobacter* spp., *Pseudomonas spp*., *Escherichia coli*, *Stenotrophomonas spp,* and *Staphylococcus spp*., are the most frequently detected causative pathogens among COVID-19 patients [5,6]. To develop new strategies for the prevention of secondary bacterial pneumonia, the identification of possible risk factors

associated with these infections is needed. We aimed to determine the frequency, microbiology, risk factors, and outcomes of secondary bacterial pneumonia, in patients admitted to the ICU with COVID-19.

Methodology

Study design and setting

We conducted a single-center retrospective cohort study with patients hospitalized for critical illness with COVID-19 in the intensive care unit of Sultan II. Abdulhamid Han Training and Research Hospital between March 16, 2020 - June 17, 2020.

The ethics committee of The Health Sciences University of Turkey approved this study (Ref.no: B.10.1.THK.4.34.H.GP.0.01/278). The data was collected from the medical records of the hospitalized patients, through a structured electronic format excluding the patient's identities. The need for informed consent was waived due to the retrospective nature of the study. This study is reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.

Patients older than 18 years of age with a positive SARS-CoV-2 real-time polymerase chain reaction (PCR) assay admitted to the ICU of our hospital, were included. Exclusion criteria were pregnancy, being younger than 18 years old, patients with negative SARS-CoV-2 test results, and patients who were discharged or died within 3 days of admission. In this period, a total of 512 patients with COVID-19 were admitted to the ICU. In the first 48 hours of these patients' admission to the ICU, 21 died and 11 were discharged. 9 patients had bacterial secondary infections at the time of admission to the ICU. 471 of these patients were included in the study.

Secondary bacterial pneumonia was defined as the development of VAP or nosocomial pneumonia. Bacterial pneumonia was identified with clinical symptoms, radiological, laboratory and microbiological data. Endotracheal aspirates or sputum cultures were collected in case of clinical suspicion with radiological and/or laboratory findings. Patients with no blood or samples of respiratory tract cultures were considered not to have secondary bacterial pneumonia.

The incidence and possible risk factors of secondary bacterial pneumonia were assessed as the primary outcome of the study. The secondary outcome was the impact of secondary bacterial pneumonia on mortality.

The age, sex, vital signs, test results, and comorbidities that influence the prognosis were analysed. In our study, disease severity was determined according to Acute Physiology and Chronic Health Assessment II (APACHE II) scores and Sequential Organ Failure Assessment (SOFA) scores. We also assessed the effect of secondary bacterial pneumonia on mortality.

Microbiological studies

In case of clinical suspicion with radiological and/or laboratory findings, endotracheal aspirates and blood cultures were collected. Patients with no blood or samples of respiratory tract cultures were considered not to have secondary infections. We checked for, clinically significant microorganisms based on the Centers for Disease Control and Prevention's (CDC) criteria in this study [7]. The identification and the minimum inhibitory concentrations (MIC) of the microorganisms were checked for and measured by an automated system (VITEK 2, Biomerieux, Marcy l'Etoile, France).

Statistical Analysis

Analyses were performed using SPSS Version 23.0 (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY). Characteristics of patients, as n (percent) or median (min-max) for categorical and continuous variables, respectively, were compared among treatment groups using chi-square or Mann-Whitney tests, as appropriate. The "Wilcoxon Test" was used to compare the laboratory parameters (Baseline vs onset time of infection) of the infected patient group. Logistic regression analysis was performed to determine the factors affecting the development of infection and mortality. A p -value less or equal to 5% was considered significant.

Results

A total of 471 patients with a median age of 70 (18-99) years were analyzed. Ninety-six (20%) of them had secondary bacterial pneumonia. The baseline characteristics of the 471 patients enrolled in this study are listed in Table 1. Overall, 187 (39.7%) of those patients with COVID-19 and secondary bacterial pneumonia were women. There was no significant difference based on the comorbidities between the two groups. The mortality rate was 53.1% (250/471). The mortality rate among infected (75%/47.5%) was significantly higher than uninfected patients.

Patients diagnosed with secondary bacterial pneumonia had a longer ICU stay ($p < 0.001$), and a longer need for mechanical ventilation ($p < 0.001$).

Table 1. Evaluation of demographic and clinical findings of patients with secondary bacterial pneumonia and non-secondary bacterial pneumonia.

Characteristics (n = 471)	non-secondary bacterial pneumonia (n = 375)	Secondary bacterial pneumonia (n = 96)	Total (n = 471)	*p* value
	Median (Min-Max) or n (%)	Median (Min-Max) or n (%)	Median (Min-Max) or n (%)	
Age, years	70 (18-96)	68 (26-99)	70 (18-99)	0.246
Gender				0.364
Female	145 (38.7)	42 (43.8)	187 (39.7)	
Male	230 (61.3)	54 (56.3)	284 (60.3)	
Applied Treatments, Corticosteroid usage	**205 (54.7)**	**69 (71.9)**	**274 (58.2)**	**0.002**
Corticosteroid dosage				**< 0.001**
No	**208 (55.5)**	**32 (33.3)**	**240 (51)**	
Low	**108 (28.8)**	**45 (46.9)**	**153 (32.5)**	
High (≥ 100 mg)	**59 (15.7)**	**19 (19.8)**	**78 (16.6)**	
Interleukin-6 Inhibitors usage	71 (18.9)	27 (28.1)	98 (20.8)	0.066
Interleukin-6 inhibitörs dosage				**0.037**
< 800 mg	**62 (87.3)**	**18 (66.7)**	**80 (81.6)**	
> 800 mg	**9 (12.7)**	**9 (33.3)**	**18 (18.4)**	
Colchicine usage	121 (32.3)	34 (35.4)	155 (32.9)	0.558
APACHE II score	26 (5-45)	27 (15-44)	26 (5-45)	0.431
SOFA score	4 (1-16)	4 (2-14)	4 (1-16)	0.181
Comorbidities	324 (86.4)	86 (89.6)	410 (87)	0.510
Lung disease	96 (25.6)	33 (34.4)	129 (27.4)	0.085
Coronary Arter Disease	86 (22.9)	25 (26)	111 (23.6)	0.613
Diabetes Mellitus	130 (34.7)	42 (43.8)	172 (36.5)	0.126
Congestive heart failure	65 (17.3)	12 (12.5)	77 (16.3)	0.323
Chronic kidney failure	60 (16)	9 (9.4)	69 (14.6)	0.140
Cancer	48 (12.8)	8 (8.3)	56 (11.9)	0.303
Hypertension	209 (55.7)	53 (55.2)	262 (55.6)	0.926
Neurological disease	81 (21.6)	22 (22.9)	103 (21.9)	0.889
Arrhythmia	35 (9.3)	8 (8.3)	43 (9.1)	0.845
Immunosuppression	22 (5.9)	3 (3.1)	25 (5.3)	0.416
Baseline Laboratory Results				
CRP (mg/L)	**36.2 (0.2-350)**	**79.6 (0.3-418)**	**41.5 (0.2-418)**	**0.015**
Procalcitonin (ng/mL)	**0.3 (0-80)**	**0.5 (0-76)**	**0.3 (0-80)**	**0.006**
Erythrocyte sedimentation rate mm/hour	62 (2-140)	62 (6-134)	62 (2-140)	0.443
Leukocyte count (× 10^9/L)	10 (0.8-206)	11.1 (0.3-50.9)	10.2 (0.3-206)	0.366
Neutrophil (10^9 /L)	8.6 (0.2-47.9)	9.7 (0.1-46.9)	8.7 (0.1-47.9)	0.244
Lymphocyte (× 10^9 /L)	**0.8 (0.1-39.9)**	**0.6 (0.1-11)**	**0.7 (0.1-39.9)**	**0.008**
Neutrophile / Lymphocyte ratio	**11 (0.1-142.6)**	**14.1 (0.2-107.6)**	**12.1 (0.1-142.6)**	**0.032**
Platelet (× 10^9 /L)	223.5 (15-1013)	211.5 (10-666)	218.5 (10-1013)	0.235
Albumin (g/l)	30 (15-44)	29.5 (13-40)	30 (13-44)	0.145
Lactate (mmol/L)	1.8 (0.4-13)	1.7 (0.8-13.3)	1.8 (0.4-13.3)	0.809
Interleukin-6 (pg/mL)	41.8 (2.2-79130)	52.7 (2-2145)	43 (2-79130)	0.398
Hemoglobin (g/dl)	11.8 (3.4-17)	11.7 (6.1-16.3)	11.7 (3.4-17)	0.870
Hematocrit (%)	35.4 (9.9-52)	36.1 (11.2-47.2)	35.4 (9.9-52)	0.805
Glucose (mg/dl)	132 (42-1000)	146 (53-637)	134.5 (42-1000)	0.129
ALT (U/L)	30 (5-3283)	34 (5-219)	30.5 (5-3283)	0.093
AST (U/L)	34 (9-4202)	39.5 (13-158)	36 (9-4202)	0.134
BUN (mg/dl)	51 (9-384)	53.5 (14-280)	51 (9-384)	0.527
Creatinine (mg/dl)	1.2 (0.3-15.8)	1.2 (0.3-10.3)	1.2 (0.3-15.8)	0.695
LDH (U/L)	647 (16-9114)	710.5 (205-1673)	659 (16-9114)	0.200
Troponin (ng/mL)	26.3 (0.1-50000)	21 (1.4-26452)	24.1 (0.1-50000)	0.860
BNP (pg/mL)	154.9 (10-11473)	140.7 (10-14736)	151 (10-14736)	0.915
D-Dimer (ng/mL)	1240 (10-32300)	1390 (50-21000)	1280 (10-32300)	0.773
Fibrinogen (mg/dl)	591 (40-1840)	620 (106-1077)	596.5 (40-1840)	0.723
Ferritin ng/mL	633 (12-34363)	576 (21.5-5485)	621 (12-34363)	0.591
Fever ≥ 38 °C	167 (44.5)	40 (41.7)	207 (43.9)	0.614
Respiratory Rate	26 (10-48)	28 (15-45)	26 (10-48)	0.077
PaO_2/ FiO_2 ratio	**117 (43-464)**	**97.5 (42-275)**	**112 (42-464)**	**0.004**
Length of intensive care unit, day	**6 (1-32)**	**14 (1-77)**	**7 (1-77)**	**< 0.001**
Hospitalization, day	**11 (1-62)**	**18 (2-120)**	**12 (1-120)**	**< 0.001**
Invasive mechanical ventilation	**167 (44.5)**	**81 (84.4)**	**248 (52.7)**	**< 0.001**
Invasive mechanical ventilation, day	**5 (0-22)**	**12 (1-52)**	**6 (0-52)**	**< 0.001**
Tidal volume	450 (300-750)	440 (287-650)	450 (287-750)	0.114
PEEP	10 (5-24)	10 (5-15)	10 (5-24)	0.172
Plateau pressure	**26 (13-40)**	**28 (15-45)**	**28 (13-45)**	**0.038**
$PaCO_2$	38 (17-108)	38.5 (23-86)	38 (17-108)	0.889
pH	7.4 (6.8-7.6)	7.4 (7-7.6)	7.4 (6.8-7.6)	0.759
Antibiotic treatment				0.314
No	27 (7.2)	3 (3.1)	30 (6.4)	
Narrow spectrum	156 (41.6)	44 (45.8)	200 (42.5)	
Broad spectrum	192 (51.2)	49 (51)	241 (51.2)	
Sepsis	**65 (17.3)**	**29 (30.2)**	**94 (20)**	**0.008**
Septic shock	53 (14.1)	22 (22.9)	75 (15.9)	0.052
Renal replacement therapy	**33 (8.8)**	**18 (18.8)**	**51 (10.8)**	**0.009**
ECMO	1 (0.3)	2 (2.1)	3 (0.6)	0.107
Prone positioning	**88 (23.5)**	**49 (51)**	**137 (29.1)**	**< 0.001**
Initial Oxygenotherapy				**< 0.001**
Conventional oxygenotherapy*	**172 (45.9)**	**20 (20.8)**	**192 (40.8)**	
High flow	**101 (26.9)**	**35 (36.5)**	**136 (28.9)**	
High flow+Non-invasive mechanical ventilation	**20 (5.3)**	**13 (13.5)**	**33 (7)**	
Invasive mechanical ventilation	**82 (21.9)**	**28 (29.2)**	**110 (23.4)**	
Last status				**< 0.001**
Alive	197 (52.5)	24 (25)	221 (46.9)	
Exitus	178 (47.5)	72 (75)	250 (53.1)	

APACHE II: Acute Physiology And Chronic Health Evaluation II; SOFA: Sequential Organ Failure Assessment; CRP: C-reactive protein; ALT: alanine aminotransferase; AST: aspartate aminotransferase; BUN: Blood urea nitrogen; LDH :Lactate dehydrogenase; BNP: B-type natriuretic peptide; PEEP: Positive End-Expiratory Pressure; ECMO: Extracorporeal Membrane Oxygenation; ICU: Intensive Care Unit; *Conventional oxygenotherapy: It is a method that provides oxygenation with nasal cannula and mask; which reaches flow rates up to 15 lt / min.

Use of invasive mechanical ventilation ($p < 0.001$), plateau pressure (P_{plat}) ($p = 0.038$), sepsis, renal replacement therapy and prone position were significantly higher in the infected group. Treatment with a corticosteroid, dose of corticosteroid (100 mg/d, at least 3 days), and dose of Interleukin 6 (IL-6) inhibitor were higher in the cohort of patients diagnosed with secondary bacterial pneumonia.

Respective C-reactive protein (CRP), procalcitonin (PCT) levels, CRP/albumin ratio, neutrophil-lymphocyte ratio were significantly higher and lymphocyte levels, and PaO_2 / fraction of inspired oxygen (FiO_2) (P/F) ratio was lower among the patients with secondary bacterial pneumonia (Table 1).

On univariate analysis, numerous factors were found to be associated with secondary bacterial pneumonia (Table 2). On multivariate analysis, we analyzed the factors associated with secondary bacterial pneumonia in COVID-19 patients. Corticosteroid treatment (OR 6.250, 95% CI 1.383-28.571, $p = 0.017$), corticosteroid dosage (OR 8.862, CI 2.299-70.258, $p = 0.006$), duration of mechanical ventilation (OR 1.199, CI 1.088-1.322, $p < 0.001$) were found to be significantly associated with secondary bacterial pneumonia in COVID-19 patients (Table 2).

Risk factors for mortality were analyzed among patients with secondary bacterial pneumonia. The level of lactate dehydrogenase (LDH) (OR 1.003, CI 1.001-1.005, $p = 0.015$), length of hospital stay (OR 0.844, CI 0.781-0.913, $p < 0.001$), dialysis (OR 8.266, CI 1.032-66.218, $p = 0.047$) and prone position (OR 3.957 CI 0.997-15.698, $p = 0.050$) were found to be associated with mortality (Table 3).

A total of 96 sputum cultures were positive.

The 43 foremost pathogens were *A. baumannii* (44.8%), *K. pneumoniae* (39.6%), *P. aeruginosa* (4.2%), *E. coli* (3.1%), *MRSA (*3.1%), *S. pneumoniae* (3.1%), and 1 *MSSA* (1%).

Discussion

Our study suggests that patients with COVID-19 could have high incidences of secondary bacterial pneumonia. *A. baumannii* were the most isolated agents. Our study is consistent with previous studies reporting a 27% incidence of respiratory bacterial infections among COVID-19 patients [8]. In a meta-analysis the researchers identified secondary bacterial infection in 14.3% of COVID-19 patients during hospitalization [9]. In our study, the results are lower than the one previously reported with an incidence of respiratory bacterial infection (43%) among the patients on invasive mechanical ventilation [10]. Our cohort not only includes the patients under invasive mechanical ventilation, but it also included the patients under non-invasive mechanical ventilation as conventional or high-flow oxygen therapy which may partially explain

Table 2. Evaluation of risk factors affecting the development of secondary bacterial pneumonia.

Characteristics	Univariate Analysis		Multivariate Analysis	
	OR (CI 95%)	*p*-value	OR (CI 95%)	*p* value
Age, years	0.992 (0.978-1.006)	0.253		
Applied Treatments				
Corticosteroid usage	**2.119 (1.299-3.456)**	**< 0.001**	**6.250 (1.383-28.571)**	**0.017**
Corticosteroid dosage				
No	Reference	1.000	Reference	1.000
Yes (Low+High)	**2.491 (1.556-3.988)**	**< 0.001**	**8.862 (2.299-70.258)**	**0.006**
Interleukin-6 Inhibitors usage	**1.675 (1.002-2.803)**	**0.049**	0.721 (0.296-1.754)	0.471
Colchicine usage	1.151 (0.719-1.844)	0.558		
Comorbidities	1.354 (0.660-2.776)	0.409		
Lung disease	1.522 (0.941-2.462)	0.087		
CRP	**1.003 (1.001-1.006)**	**0.016**	1.000 (0.978-1.012)	0.533
Lymphocyte	0.877 (0.650-1.183)	0.389		
LDH	1.000 (1.000-1.000)	0.569		
PaO_2/ FiO_2 ratio	**0.994 (0.991-0.998)**	**0.003**	1.000 (0.992-1.005)	0.593
Length of intensive care unit, day	**1.165 (1.124-1.208)**	**< 0.001**	1.062 (0.958-1.178)	0.254
Hospitalization, day	**1.071 (1.048-1.095)**	**< 0.001**	0.985 (0.917-1.058)	0.684
Invasive mechanical ventilation	**6.726 (3.738-12.101)**	**< 0.001**	0.719 (0.095-5.459)	0.750
Invasive mechanical ventilation, day	**1.221 (1.150-1.297)**	**< 0.001**	**1.199 (1.088-1.322)**	**< 0.001**
Sepsis	**2.064 (1.238-3.442)**	**0.005**	1.844 (0.740-4.595)	0.189
Renal replacement therapy	**2.392 (1.280-4.467)**	**0.006**	0.748 (0.305-1.832)	0.525
Prone positioning	**3.400 (2.134-5.419)**	**< 0.001**	1.898 (0.456-4.080)	0.123
Baseline ICU Oxygenotherapy				
Conventional oxygenotherapy*	Reference	1.000	Reference	1.000
High flow	**2.980 (1.633-5.440)**	**< 0.001**	1.364 (0.456-4.080)	0.579
High flow+Non-invasive mechanical ventilation	**5.590 (2.418-12.921)**	**< 0.001**	1.626 (0.384-6.893)	0.509
Invasive mechanical ventilation	**2.937 (1.562-5.521)**	**< 0.001**	1.321 (0.446-3.906)	0.615

CRP: C-Reactive Protein; LDH: Lactate dehydrogenase; *Conventional oxygenotherapy: It is a method that provides oxygenation with nasal cannula and mask; which reaches flow rates up to 15 lt / min.

these differences. Inexperienced and unpredictable pressure on the healthcare system during the pandemic may have resulted in reduced adherence to infection control and prevention guidelines, which may have contributed to the high rate of infection.

The risk factors associated with the acquisition of secondary bacterial pneumonia were, treatment with corticosteroids, administration of the cumulative dose of corticosteroids, and longer invasive mechanical ventilation day. Routine administration of corticosteroids was not part of the COVID-19 treatment protocol during the early period of the pandemic and was administrated according to the clinical condition. Later, current guidelines advise the administration of corticosteroids to COVID-19 patients [11]. Corticosteroids are known as suppressors of the immune system [12]. The risk of secondary bacterial infection increases linearly with the dose and duration of corticosteroid therapy [13]. Therefore, patients receiving corticosteroids, and administering of a cumulative dose of corticosteroids are more likely to develop a bacterial infection due to immunosuppression. Patients with longer invasive mechanical ventilation had higher risk of secondary bacterial pneumonia. Aspiration of oropharyngeal secretions and leakage of secretions around the cuff leads to infection. Pneumonia occurring 48 hours after intubation is referred as VAP which is responsible for 27% of all critically ill patients. The risk rises with the duration of ventilation. The incidence of VAP increases by 1% per day with invasive mechanical ventilation [14]. Strategies should be implemented to reduce VAP. Implementation of VAP bundle care decreases the incidence of VAP in ICU [15]. Daily assessment of the preparation for extubation, which is included in this package of measures, will prevent VAP.

Critically ill COVID-19 patients, especially under mechanical ventilation, often require prolonged ICU and hospital stays that result in healthcare-associated infections. In our study, the mean incidence of secondary bacterial pneumonia was recorded on the 9th day of the ICU admission. Fernando *et al* reported the peak incidence of infection between 8- and 14-days following ICU admission [8]. In our cohort of patients, the duration of ICU stay did affect neither secondary bacterial pneumonia rate nor mortality.

In our study, renal replacement therapy and sepsis were significantly higher among secondary bacterial infected patients. Higher levels of CRP and PCT (> 0.5 ng/mL), and lower lymphocyte count are associated

Table 3. Evaluation of risk factors for mortality of patients with secondary bacterial pneumonia.

Characteristics	Univariate Analysis		Multivariate Analysis	
	OR (CI 95%)	***p* value**	**OR (CI 95%)**	***p* value**
Age; years	**1.024 (1.011-1.036)**	**< 0.001**	1.024 (0.987-1.063)	0.198
Applied Treatments				
Corticosteroid usage	1.253 (0.867-1.811)	0.229	3.437 (0.461-25.620)	0.228
Corticosteroid dosage				
No	Reference	1.000	Reference	1.000
Yes (Low + High)	**0.649 (0.451-0.934)**	**0.020**	0.234 (0.028-1.943)	0.179
Interleukin -6 Inhibitors usage	0.901 (0.577-1.406)	0.646		
Colchicine usage	**0.673 (0.457-0.989)**	**0.044**	0.503 (0.126-2.014)	0.332
Isolated Microorganism				
None	Reference	1.000	Reference	1.000
Klebsiella	**2.128 (1.057-4.287)**	**0.034**	1.012 (0.168-6.097)	0.990
Acinetobacter	**8.411 (3.239-21.840)**	**< 0.001**	2.386 (0.446-12.765)	0.309
Others	1.660 (0.579-4.757)	0.345	1.004 (0.078-12.820)	0.998
Comorbidities	**2.410 (1.372-4.232)**	**0.002**	2.278 (0.401-12.987)	0.353
Lung disease	**1.152 (1.001-2.282)**	**0.049**	2.659 (0.732-9.660)	0.137
CRP	1.002 (1.000-1.004)	0.096		
Lymphocyte	0.946 (0.846-1.058)	0.332		
LDH	**1.000 (1.000-1.001)**	**0.020**	**1.003 (1.001-1.005)**	**0.015**
PaO_2/ FiO_2 ratio	**0.993 (0.990-0.996)**	**< 0.001**	1.002 (0.993-1.011)	0.661
Length of ICU; day	1.019 (0.996-1.042)	0.104		
Hospitalization; day	**0.959 (0.941-0.978)**	**< 0.001**	**0.844 (0.781-0.913)**	**< 0.001**
Invasive Mechanical ventilation	**40.303 (23.782-68.301)**	**< 0.001**	0.897 (0.426-1.235)	0.650
Invasive Mechanical ventilation; day	**0.925 (0.891-0.959)**	**< 0.001**	1.037 (0.950-1.132)	0.420
Sepsis	**2.472 (1.521-4.020)**	**< 0.001**	1.805 (0.533-6.112)	0.343
Renal replacement therapy	**7.866 (3.285-18.832)**	**< 0.001**	**8.266 (1.032-66.218)**	**0.047**
Prone position	**2.383 (1.569-3.620)**	**< 0.001**	**3.957 (0.997-15.698)**	**0.050**
Initial Oxygenotherapy in ICU				
Conventional oxygenotherapy*	Reference	1.000	Reference	1.000
High flow	**2.185 (1.392-3.429)**	**< 0.001**	2.468 (0.352-17.309)	0.363
High flow + Non-invasive mechanical ventilation	**4.600 (2.065-10.245)**	**< 0.001**	1.861 (0.103-33.482)	0.674
Invasive mechanical ventilation	**10.222 (5.680-18.395)**	**< 0.001**	2.100 (0.508-8.695)	0.305

CRP: C-Reactive Protein; LDH: Lactate dehydrogenase; ICU: Intensive Care Unit; *Conventional oxygenotherapy: It is a method that provides oxygenation with nasal cannula and mask; which reaches flow rates up to 15 lt / min.

with poor outcomes [16]. Higher levels of PCT and CRP may be due to secondary bacterial infection or associated with the severity of COVID-19 [17]. Therefore, bacterial infection should also be investigated in COVID-19 patients with high PCT and CRP levels. The incidence of bacterial infection was found to be higher in fatal cases of patients with COVID-19 [9]. We found that the mortality rate was higher among patients with secondary bacterial pneumonia as expected.

In our study administration of higher doses of corticosteroid and IL6 inhibitors was higher in the infected group. We think that this situation is due to the immunosuppressive effects of these drugs.

Prone position ventilation was significantly higher among patients with secondary bacterial pneumonia. Prone position ventilation improves oxygenation in patients with severe ARDS [18]. An enormous number of patients with COVID-19 have benefitted from prone position ventilation [19]. Whereas the drainage of respiratory secretions generally observed in the prone position would be expected to reduce VAP. In a prospective multicentre randomized controlled trial, researchers found that, severe ARDS patients prone to positioning did not reduce the incidence of VAP [20].

Common pathogens include aerobic Gram-negative bacilli, such as *A. baumannii, K. pneumoniae, P. aeruginosa, E. coli,* and Gram-positive cocci such as *Staphylococcus aureus* and *S. pneumoniae.* A recently published multicenter study in Turkey reported that the rate of *P. aeruginosa* in hospital-acquired pneumonia is increasing [21].

Among patients with COVID-19, the overall proportion of the usage of antibiotics was similar between patients with secondary bacterial pneumonia and patients without secondary bacterial pneumonia. There is insufficient evidence to support the usage of antibiotics in patients with COVID-19.

In our study, a high level of LDH, duration of the hospital stay, prone position ventilation, and renal replacement therapy was a significant predictor of mortality among patients infected with secondary bacterial pneumonia. The prolonged duration of hospitalization is known to be a predictor for mortality [22].

Our study has several limitations: the retrospective nature of the study, and the lack of data on the severity of the clinical condition of patients receiving corticosteroids. However, our study has several strengths. This study consisted of a large population of patients with COVID-19 in the ICU and comorbidities, age, and gender that affect the outcome of the patients with COVID-19 were similar in both groups.

Conclusions

In conclusion, secondary bacterial pneumonia could be a significant, contributing factor to disease severity among critically ill COVID-19 patients. Administration of corticosteroids and high-dose corticosteroids were associated with an increased risk of secondary bacterial infection. Longer invasive mechanical ventilation day is a risk factor for secondary bacterial pneumonia among COVID-19 patients. A longer duration of hospital stay is associated with mortality in these patients. Based on our findings, we suggest that infection prevention guidelines should be improved, and regular microbiological surveillance and strict infection control measures should be implemented to reduce the development of secondary bacterial pneumonia. Implications of antimicrobial stewardship should be optimised.

Authors' Contributions

İnşa Gül Ekiz İşcanlı and Bengü Şaylan and Mehtap Aydın conceived and designed the study, wrote the protocol, and directed the study. İnşa Gül Ekiz İşcanlı and Mehtap Aydın interpreted the statistics and data. İnşa Gül Ekiz İşcanlı writing the original draft, review and editing İnşa Gül Ekiz İşcanlı responded to the comments of the reviewers. All authors contributed to the revisions. All authors were involved in data collection, data analysis and interpretation and reviewed and approved the final version.

Availability of data and materials

Data is available from the corresponding author, upon reasonable request.

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