Original Article

HEALTH SCIENCES
MEDICINE

DOI: 10.32322/jhsm.1136479
J Health Sci Med 2022; 5(5): 1252-1258

The effect of immunosuppressive therapy on the development of ventilator-associated pneumonia in patients with COVID-19

Kadir Canoğlu, Ömer Ayten

Health Sciences University, Sultan 2. Abdülhamid Han Training and Research Hospital, Department of Pulmonology, İstanbul, Turkey

Cite this article as: Canoğlu K, Ayten Ö. The effect of immunosuppressive therapy on the development of ventilator-associated pneumonia in patients with COVID-19. J Health Sci Med 2022; 5(5): 1252-1258.

ABSTRACT

Aim: It remains unclear whether immunosuppressive treatments such as corticosteroids and IL-6 receptor blockers have an effect on the development of ventilator-associated pneumonia (VAP). The aim of this study was to investigate the effect of immunosuppressive therapy on the development of VAP in critically ill patients with COVID-19.

Material and Method: Two hundred thirty five patients with critically ill patients with COVID-19, who were treated in the intensive care unit (ICU) and received mechanical ventilator support, were evaluated retrospectively. VAP development, secondary infections, microorganisms isolated, and resistance patterns were compared between the groups that received and did not receive immunosuppressive therapy, and also the groups that did not receive immunosuppressive therapy, received only corticosteroid, received only tocilizumab, and received corticosteroid plus tocilizumab were compared in the subgroup analysis.

Results: In the immunosuppressive treatment group, VAP development (40.2% vs. 21.2%; p=0.001), secondary infection development (48.4% vs. 29.2%; p=0.003), at least one drug resistant bacteria growth (46.7% vs. 27.4%; p=0.001), extensively-drug resistant (XDR) microorganism growth (89.8% vs. 72.7%; p=0.033) were higher than the group that did not receive immunosuppressive treatment. VAP (53.3%; p=0.004), secondary infection (73.3%; p=0.0002), the growth of bacteria resistant to at least one drug (70%; p=0.0003) were highest in the corticosteroid plus tocilizumab group in the subgroup analysis. In addition, XDR (95.5% vs. 72.7%; p=0.032) and pan-drug resistant (PDR) microorganism growth (31.8% vs. 9.1% p=0.032) were higher in the corticosteroid plus tocilizumab group than the no immunosuppressive therapy group. There was no difference between the groups in terms of mortality (p>0.05).

Conclusion: Immunosuppressive therapy has been found to potentially enhance the risk of VAP and secondary infections in critically ill patients with COVID-19 pneumonia as well as the growth of bacteria resistant to at least one drug, the length of stay in hospital and ICUs. In addition, it has been evaluated that there may be an increase in the growth of XDR and PDR microorganisms when corticosteroid and tocilizumab are used together. Although there was no difference in mortality, using immunosuppressive therapy may require careful use of targeted antibiotics and longer-term antimicrobial therapy.

Keywords: Corticosteroids, COVID-19, IL-6 receptor, ventilator-associated pneumonia

INTRODUCTION

Globally, 525 million people have been affected by the coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2, and approximately 6.3 million people have died since the pandemic began in December 2019 (1). COVID-19 patients may have asymptomatic or mild symptoms, but they may require invasive mechanical ventilation in the intensive care unit (ICU) due to respiratory failure and acute respiratory distress syndrome (ARDS). Approximately 80% of severe COVID-19 patients require oxygen support, and 30-40% require mechanical ventilation support. This increases the likelihood of nosocomial infection, particularly ventilator-associated pneumonia (VAP) (2-4). VAP is defined as pneumonia that develops 48 hours after being connected to a mechanical ventilator in ICU patients with hospital-acquired pneumonia (HAP). According to international guidelines, the incidence of HAP ranges from 5 to 20 per thousand. It is most common in immunocompromised, surgically treated, and elderly patients (5).

Corresponding Author: Kadir Canoğlu, kadircano@gmail.com
Received: 27.06.2022 **Accepted:** 11.07.2022

The World Health Organization (WHO) recommends corticosteroids and interleukin-6 (IL-6) receptor blockers for severe or critically ill COVID-19 patients (6). However, the use of these drugs raises concerns of secondary infection adverse effects. Secondary bacterial infection has been reported at varying rates in the literature when IL-6 receptor blockers are used. In the REMAP-CAP study, the rate of secondary bacterial infection in the tocilizumab arm was 0.3% (1/353) (7). In the COVACTA study, serious infection development in the tocilizumab arm was 21% (62/294) (8). Studies on the development of VAP in COVID-19 patients in the literature have mainly focused on microorganisms detected (9, 10). It is unclear whether treatments such as corticosteroids and IL-6 receptor blockers influence the development of VAP.

The aim of this study was to investigate the effect of immunosuppressive therapy on the development of VAP in critically ill patients with COVID-19. Furthermore, it was determined whether there were differences in growing microorganisms and resistance patterns between the groups.

MATERIAL AND METHOD

This study was approved by the Ethics Committee of İstanbul Ümraniye Training and Research Hospital (Date: 26.05.2022, Decision No: 167). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

This retrospective study included 235 COVID-19 patients over the age of 18 who were treated at İstanbul Sultan 2. Abdülhamid Han Training and Research Hospital between April 2020 and November 2021 and had a positive reverse transcriptase-polymerase chain reaction (PCR). All patients were followed up and treated in the ICU, and all required invasive mechanical ventilation. Patients under the age of 18 who did not enter the ICU and did not receive invasive mechanical ventilation were excluded from the study.

International guidelines recommend obtaining a quantitative culture for the diagnosis of VAP, because various diseases may mimic lung infection on radiological imaging (5, 11). In this study, VAP was diagnosed with clinical and radiological abnormalities, as well as microbiological growth, at least 48 hours after the patient was placed on mechanical ventilation support. As a conclusion, the presence of all of the following was used to determine VAP diagnostic criteria; a) recently detected radiological infiltration and; b) clinically at least one of them (fever >38°C, leukopenia or leukocytosis, increased sputum production or purulence, impaired gas exchange); and c) microorganism growth in quantitative endotracheal aspirate or blood culture (9,12). The patients with a PaO_2/FiO_2 ratio ≤300 and/or requiring mechanical ventilation or high flow oxygen support were given ≥40mg/day corticosteroid therapy for at least 10 days. Tocilizumab was given to patients with a PaO_2/FiO_2 ratio ≤300 and/or requiring mechanical ventilation or high flow oxygen support, persistent fever, persistent C-reactive protein (CRP) and IL-6 elevation, cytokine storm findings such as increased ferritin and D-dimer, lymphopenia, thrombocytopenia, and negative procalcitonin at a dose of 800 mg/day once or 400 mg/day for two consecutive days.

Age, gender, immunosuppressive therapy used (no immunosuppressive therapy, only corticosteroid, only tocilizumab, corticosteroid and tocilizumab together), Acute Physiology and Chronic Health Evaluation II (APACHE II) and Sequential Organ Failure Evaluation Score (SOFA) scores, comorbidities, infection parameters such as leukocyte, neutrophil, lymphocyte, CRP and procalcitonin, and length of stay in ICU, the entire length of hospital stay, the development of VAP, the detection of microorganisms and antibiotic resistance were all recorded. The patients were divided into two groups: those who were given immunosuppressive therapy and those who were not. Furthermore, a comparison was made as a subgroup analysis between four groups: those who did not receive immunosuppressive therapy, those who received only steroids, those who received only tocilizumab, and those who utilized both immunosuppressive agents. *Klebsiella pneumonia*, *Pseudomonas Aeruginosa*, *Acinetobacter Baumanii*, *Staphylococcus Aureus*, and *Streptococcus Pneumonia* were among the microorganisms observed in patients. Multi-drug resistant (MDR) microorganisms were defined as having resistance to at least one drug in at least three antimicrobial categories. Extensively-drug resistant (XDR), a subgroup of MDR, was defined as having resistance to at least one drug in all categories but no resistance in two or fewer categories (susceptibility in one or two antimicrobial categories). Pan-drug resistance (PDR) as a subgroup of MDR and XDR, was defined as having resistance to all agents in all antimicrobial categories (13).

Frequency distributions, percentage, mean, standard deviation, median, minimum and maximum were used as descriptive analyses in the analysis of data in the study. Normality of the data was ensured by Kolmogorov-Smirnov test. ANOVA (Post Hoc. Bonferroni), t test, chi-square test, Fisher's Exact test, Kruskal Wallis H test, Mann Whitney U Test were applied. IBM SPSS ver 20 and Microsoft Excel computer programs were used for data analysis.

RESULTS

This study comprised 235 critically ill patients with COVID-19 who were followed in the ICU and on mechanical ventilation. Eighty-four (35.7%) of the patients were female, whereas 151 (64.3%) were male. The mean age of the patients was 70.67±14.01 years. Sixty (25.5%) of the patients died, and 175 (74.5%) survived. One hundred and twenty-two (51.9%) patients were given immunosuppressive therapy. One hundred and six (45.1%) of the patients received corticosteroids and 46 (19.6%) received tocilizumab. Thirty (12.7%) of patients received corticosteroid and tocilizumab both, whereas 76 (32.3%) received corticosteroid only and 16 (4.3%) received tocilizumab only. The APACHE II score was 60.61±25.4 and the SOFA score was 6.23±3.32. Two hundred fourteen (91.1%) of the patients had comorbid disease, which included pulmonary disease in 70 (29.8%), coronary artery disease in 66 (28.1%), diabetes mellitus in 89 (37.9%), heart failure in 51 (21.7%), renal failure in 41 (17.4%), malignancy in 35 (14.9%), neurological disease in 62 (26.4%) and arrhythmia in 28 (11.9%) patients.

Seventy-three (31.1%) patients had VAP diagnosed in accordance with the protocol, while 162 (68.9%) patients did not have VAP diagnosed. The total length of hospital stay was 14.36±12.83 days, and the length of stay in the ICU was 11.1±9.68 days. Seventy-three (31.1%) patients with VAP had a total of 92 microorganisms present in their blood and tracheal aspirate cultures. Because of the different microorganism growths in a patient, they were evaluated separately. The majority of microorganisms were *Acinetobacter Baumanii*, which was found in 44 (47.8%) of 92 growths. *Klebsiella pneumonia* was found in 35 (38.0%) of the isolates, *Pseudomonas Aeruginosa* in 8 (8.7%), *Staphylococcus Aureus* in 4 (4.3%) and *Streptococcus Pneumonia* in 1 (1.0%). In addition, MDR was found in 88 (95.7%) of the 92 growths, XDR in 77 (83.7%) and PDR in 15 (16.3%) (**Table 1**).

The difference in study variables between the groups of patients who received immunosuppressive therapy (corticosteroid only, tocilizumab only, corticosteroid plus tocilizumab) and those who did not was investigated in this study. The no-immunosuppressive therapy group had a higher SOFA score (7.57±3.37 vs. 5±2.75; p =0.001) and mean age (73.12±12.74 vs. 68.39±14.78 years; p=0.01).

Gender, APACHE II score, and comorbid disease presence did not vary between groups (p>0.05). The heart failure (30.1% vs. 13.9%; p=0.001) and arrhythmia (16.8% vs. 7.4%; p=0.03) were higher in the no-immunosuppressive treatment group. CRP (97.17±82.29 vs. 42.94±60.88; p=0.001), length of stay in the ICU (13.66±10.27 vs. 8.34±8.18 days; p=0.001), and overall hospital stay (17.86±14.34 vs. 10.58±9.7 days; p=0.001) were all greater in the immunosuppressive therapy group than in the no-immunosuppressive treatment group. Mortality rates in both groups were similar (22.1% (n=25) vs. 28.7% (n=35); p=0.25). VAP (40.2% (n=49) vs. 21.2% (n=24); p=0.001) and secondary infection (48.4% (n=59) vs. 29.2% (n=33); p=0.003) were more common in the immunosuppressive treatment group than in the no-immunosuppressive treatment group. In addition, the growth of bacteria resistant to at least one drug was higher in the group receiving immunosuppressive therapy compared to the other group (46.7% (n=57) vs. 27.4% (n=31); p=0.001). When the number of growing microbiological microorganisms was examined between the groups, the number of *Klebsiella pneumonia* (33.3% vs. 40.7%; p=0.486), *Pseudomonas Aeruginosa* (15.2% vs. 5.1%; p=0.100), *Acinetobacter Baumanii* (45.5% vs. 49.2%; p=0.733), *Staphylococcus Aureus* (3% vs. 5.1%; p=0.643) and *Streptococcus Pneumonia* (3% vs. 0%; p=0.179) were similar. While there was no difference in MDR (93.9% vs. 96.6%; p=0.547) or PDR (9.1 vs 20.3%; p=0.161), the number of XDR microorganisms growing was higher in the immunosuppressive therapy group than in the no-immunosuppressive therapy group (89.8% (n=53) vs. 72.7% (n=24); p=0.033) (**Table 1**).

The groups that received no immunosuppressive therapy, corticosteroid only, tocilizumab only, and corticosteroid plus tocilizumab therapy were compared in the subgroup analysis. The highest mean age was 73.12±12.74 in the no-immunosuppressive treatment group, followed by 71.12±15.26 in the corticosteroid only group (p=0.002). The tocilizumab only group had the least APACHE II score (p=0.049), while the corticosteroid plus tocilizumab group had the least SOFA score (p=0.0001). The corticosteroid plus tocilizumab group had the longest overall hospital stay and ICU stay (p=0.0001). VAP was highest in the corticosteroid plus tocilizumab group (n=16, 53.3%), followed by the corticosteroid only group (n=28, 36.8%) and the tocilizumab only group (n=5, 31.3%) (p=0.004).

Secondary infections were most common in the corticosteroid plus tocilizumab group (n=22, 73.3%), followed by tocilizumab only (n=7, 43.8%) and corticosteroid only (n=30, 39.5%) (p=0.0002). Similarly, resistant bacteria were most prevalent in the corticosteroid plus tocilizumab group (n=21, 70.0%), followed by only tocilizumab (n=7, 43.8%) and only corticosteroid (n=29, 38.2%) (p=0.0003). There was no difference in mortality between the groups (p=0.55). Furthermore, there was no difference in subgroup analyses between the groups for growing microorganisms and MDR, XDR and PDR (p>0.05). However, XDR (95.5% (n=21) vs. 72.7% (n=24); p=0.032) and PDR (31.8% (n=7) vs. 9.1% (n=3); p=0.032) were higher in the corticosteroid plus tocilizumab group than the no-immunosuppressive therapy group (**Table 2**).

Table 1. Baseline characteristics of the patients and identified microorganisms

Variables	Overall (n= 235)	No immunosuppressive therapy (n=113)	Immunosuppressive therapy (n=122)	p
Age[a] (years)	70.67±14.01	73.12±12.74	68.39±14.78	0.01*
Female[b]	84 (35.7)	41 (36.3)	43 (35.2)	0.87
APACHE II score[a]	60.61±25.4	59.69±27.75	61.46±23.08	0.60
SOFA score[a]	6.23±3.32	7.57±3.37	5±2.75	0.001*
Comorbidities[b]	214 (91.1)	105 (92.9)	109 (98.3)	0.34
Pulmonary disease[b]	70 (29.8)	33 (29.2)	37 (30.3)	0.85
CAD[b]	66 (28.1)	37 (32.7)	29 (23.8)	0.13
DM[b]	89 (37.9)	46 (40.7)	43 (35.2)	0.39
Hearth failure[b]	51 (21.7)	34 (30.1)	17 (13.9)	0.001*
Kidney disease[b]	41 (17.4)	21 (18.6)	20 (16.4)	0.66
Malignancy[b]	35 (14.9)	18 (15.9)	17 (13.9)	0.67
HT[b]	132 (56.2)	63 (55.8)	69 (56.6)	0.90
Neurological disease[b]	62 (26.4)	35 (31.0)	27 (22.1)	0.12
Arrhythmia[b]	28 (11.9)	19 (16.8)	9 (7.4)	0.03*
CRP[a] (mg/L)	72.09±77.88	42.94±60.88	97.17±82.29	0.001*
Procalcitonin[a] (ng/mL)	4.57±11.47	4.93±11.67	4.27±11.33	0.67
Lymphocyte[a] (10^3/mm^3)	1.15±3.08	1.06±1.25	1.23±4.05	0.68
Neutrophil[a] (10^3/mm^3)	10.28±6.62	10.96±7.61	9.71±5.59	0.16
Ferritin[a] (ng/mL)	1416.67±2327.88	1475.92±3047.16	1369.67±1548.69	0.76
Fever[b] (°C)	128 (54.5)	58 (51.3)	70 (57.4)	0.35
Total LOS[a] (days)	14.36±12.83	10.58±9.7	17.86±14.34	0.001*
ICU LOS[a] (days)	11.1±9.68	8.34±8.18	13.66±10.27	0.001*
VAP[b]	73 (31.1)	24 (21.2)	49 (40.2)	0.001*
Death[b]	60 (25.5)	25 (22.1)	35 (28.7)	0.25
Secondary infection[b]	92 (39.1)	33 (29.2)	59 (48.4)	0.003*
Resistant bacteria[b]	88 (37.4)	31 (27.4)	57 (46.7)	0.001*
Causative microbiology	**Overall MO isolated (n=92)**	**No Immunosuppressive therapy. MO isolated (n=33)**	**Immunosuppressive therapy. MO isolated (n=59)**	**p**
Klebsiella pneumonia[b]	35 (38.0)	11 (33.3)	24 (40.7)	0.486
Pseudomonas aeruginosa[b]	8 (8.7)	5 (15.2)	3 (5.1)	0.100
Acinetobacter baumanii[b]	44 (47.8)	15 (45.5)	29 (49.2)	0.733
Staphylococcus aureus[b]	4 (4.3)	1 (3.0)	3 (5.1)	0.643
Streptococcus pneumonia[b]	1 (1.0)	1 (3.0)	0 (0)	0.179
MDR[b]	88 (95.7)	31 (93.9)	57 (96.6)	0.547
XDR[b]	77 (83.7)	24 (72.7)	53 (89.8)	0.033*
PDR[b]	15 (16.3)	3 (9.1)	12 (20.3)	0.161

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Evaluation Score; CAD, coronary artery disease; DM, diabetes mellitus; HT, hypertension; CRP, C-reactive protein; LOS, length of stay; VAP, ventilator-associated pneumonia; MO, microorganisms; MDR, multi-drug resistant; XDR, extensively drug resistant; PDR, pun-drug resistant. [a]Values are mean±SDs. [b]Values are n (%). *Statistical significance.

DISCUSSION

According to the study's findings, the development of VAP, secondary infection, bacterial growth resistant to at least one drug, length of hospital stay and ICU stay, and XDR microorganism growth were higher in the group using immunosuppressive therapy compared to not using it. There was no difference in mortality between the groups. Furthermore, the development of XDR and PDR was higher in the corticosteroid plus tocilizumab group than in the no-immunosuppressive therapy group in the subgroup analysis.

Hyperinflammatory syndrome is a disease that progresses with a severe cytokine storm and is most commonly caused by viral infections. It is characterized by fever, elevated ferritin, an increase in proinflammatory cytokines such as IL-6, and cytopenia, and can result in manifestations such as ARDS in the lung (14). In cytokine storm, the IL-6 receptor antagonists (tocilizumab, sarilumab) or IL-6 antagonists (siltuximab) cause rapid improvement in lung and hemodynamic parameters (15). In the RECOVERY study, the corticosteroid therapy reduced 28-day mortality in patients requiring oxygen support or invasive mechanical ventilation (16). In the CHIC study, mortality was 65% lower and the requirement for invasive mechanical ventilation was 71% lower in the treatment arm, which included high-dose methylprednisolone and tocilizumab were added if needed, compared to the control group, which did not receive immunosuppressive therapy (17). In our study,

although the SOFA score in the no-immunosuppressive therapy group was higher, there was no difference in mortality between the groups that received and did not receive immunosuppressive therapy.

In the meta-analysis conducted by Ippolito et al. (18), the risk of VAP was 3.24-fold higher in patients with COVID-19 than in individuals without COVID-19. In the COVID-19 group, however, there was no difference in mortality between patients with and without VAP (18). There was no difference in the use of tocilizumab and corticosteroids between groups with and without VAP in the study of Martinez-Martinez et al. (19). According to Roumier et al. (20), VAP development was lower in the tocilizumab arm compared to the control group (8% vs. 26%). There was no difference in VAP development between the dexamethasone group and the non-dexamethasone group (63% vs. 57%) in the study of Gragueb-Chatti et al. (21). Unlike previous studies, VAP development was higher in the immunosuppressive therapy group than in the no-immunosuppressive therapy group in the current study (40.2% vs. 21.2%). The corticosteroid plus tocilizumab group had the highest risk of VAP in the subgroup analysis (53.3%).

Table 2. Baseline characteristics of patients and identified microorganisms based on immunosuppressive therapy group

Variables	No immunosuppressive therapy (n=113)	Only corticosteroid (n=76)	Only tocilizumab (n=16)	Corticosteroid plus tocilizumab (n=30)	p
Age[a] (years)	73.12±12.74	71.12±15.26	64.88±14.32	63.37±12.24	0.002*
Female[b]	41 (36.3)	32 (42.1)	4 (25.0)	7 (23.33)	0.24
APACHE II score[a]	59.69±27.75	65.36±22.8	46.59±22	59.5±21.5	0.049*
SOFA score[a]	7.57±3.37	5.61±2.9	4.88±2.42	3.53±1.87	0.0001*
Comorbidities[b]	105 (92.9)	70 (92.1)	12 (75.0)	27 (90.0)	0.13
Pulmonary disease[b]	33 (29.2)	21 (27.6)	5 (31.3)	11 (36.7)	0.83
CAD[b]	37 (32.7)	19 (25.0)	3 (18.8)	7 (23.3)	0.46
DM[b]	46 (40.7)	25 (32.9)	4 (25.0)	14 (46.7)	0.35
Hearth failure[b]	34 (30.1)	14 (18.4)	2 (12.5)	1 (3.3)	0.008*
Kidney disease[b]	21 (18.6)	16 (21.1)	1 (6.3)	3 (10.0)	0.34
Malignancy[b]	18 (15.9)	16 (21.1)	0 (0)	1 (3.3)	0.04*
HT[b]	50 (44.3)	31 (40.8)	8 (50.0)	14 (46.7)	0.89
Neurological disease[b]	35 (31.0)	24 (31.6)	1 (6.3)	2 (6.7)	0.009*
Arrhythmia[b]	19 (16.8)	8 (10.5)	1 (6.3)	0 (0)	0.064
CRP[a] (mg/L)	42.94±60.88	109.03±85.95	51.91±69.26	91.29±71.65	0.0001*
Procalcitonin[a] (ng/mL)	4.93±11.67	6.42±13.92	1.44±2.95	0.39±0.43	0.064
Lymphocyte[a] (10^3/mm^3)	1.06±1.25	1.53±5.13	0.71±0.28	0.75±0.45	0.564
Neutrophil[a] (10^3/mm^3)	10.96±7.61	9.75±5.69	9.12±4.86	9.91±5.86	0.54
Ferritin[a] (ng/mL)	1475.92±3047.16	1457.22±1780.64	1289.31±1147.69	1193.66±1047.46	0.939
Fever[b], (°C)	58 (51.3)	42 (55.3)	12 (75.0)	16 (53.3)	0.36
Total hospital LOS[a] (days)	10.58±9.7	15.17±9.21	20.75±15.65	23.13±21.44	0.0001*
ICU LOS[a] (days)	8.34±8.18	11.43±7.43	14.25±9.36	19±14.47	0.0001*
VAP[b]	24 (21.2)	28 (36.8)	5 (31.3)	16 (53.3)	0.004*
Death[b]	25 (22.1)	21 (27.6)	6 (37.5)	8 (26.7)	0.55
Secondary infection[b]	33 (29.2)	30 (39.5)	7 (43.8)	22 (73.3)	0.0002*
Resistant bacteria[b]	31 (27.4)	29 (38.2)	7 (43.8)	21 (70.0)	0.0003*
Causative microbiology	**No immunosuppressive therapy. MO isolated (n=33)**	**Only corticosteroid. MO isolated (n=30)**	**Only tocilizumab. MO isolated (n=7)**	**Corticosteroid plus tocilizumab. MO isolated (n=22)**	**p**
Klebsiella pneumonia[b]	11 (33.3)	9 (30.0)	2 (28.6)	13 (59.1)	0.137
Pseudomonas aeruginosa[b]	5 (15.2)	3 (10.0)	0 (0)	0 (0)	0.207
Acinetobacter baumanii[b]	15 (45.5)	15 (50.0)	5 (71.4)	9 (40.9)	0.549
Staphylococcus aureus[b]	1 (3.0)	2 (6.7)	0 (0)	1 (4.5)	0.555
Streptococcus pneumonia[b]	1 (3.0)	0 (0)	0 (0)	0 (0)	0.613
MDR[b]	31 (93.9)	29 (96.7)	7 (100.0)	21 (95.5)	0.890
XDR[b]	24 (72.7)	25 (83.3)	7 (100.0)	21 (95.5)	0.089[1]
PDR[b]	3 (9.1)	4 (13.3)	1 (14.3)	7 (31.8)	0.148[1]

Abbreviations:APACHE II, Acute Physiology and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Evaluation Score; CAD, coronary artery disease; DM, diabetes mellitus; HT, hypertension; CRP, C-reactive protein; LOS, length of stay; VAP, ventilator-associated pneumonia; MO, microorganisms; MDR, multi-drug resistant; XDR, extensively drug resistant; PDR, pun-drug resistant. [a]Values are mean±SDs. [b]Values are n (%). *Statistical significance. [1]XDR and PDR were higher in corticosteroid plus tocilizumab group than no immunosuppressive therapy group (p=0.032)

There was no difference in mortality between the tocilizumab and placebo groups in the randomized controlled study of Stone et al. (22). However, the development of serious infections was lower in the tocilizumab arm compared to placebo (8.1% vs. 17.1%) (22). On the contrary, superinfection was found more frequently in the tocilizumab arm compared to the control group (54% vs. 26%) in the study by Somers et al. (15). In the CoDEX study, there was no difference in secondary infection between dexamethasone and standard treatment groups (21.9% vs. 29.1%) (23). In the study by Naik et al. (24), secondary infection was roughly 5.5-fold greater in the high-dose dexamethasone group than in the tocilizumab group. In current study, secondary infection was more common in the group that got immunosuppressive therapy than in the group that did not (48.4% vs. 29.2%). In the subgroup analysis, it was highest in the corticosteroid plus tocilizumab group (73.3%), followed by tocilizumab only (43.8%) and corticosteroid only (39.5%).

According to the pre-pandemic statistics, *Acinetobacter Baumanii* was responsible for roughly 47% of VAP development in the ICU (25). Giacebbo et al. (26) reported 77 culture positivities (45%) in 171 VAP and COVID-19 patients. *Pseudomonas Aeruginosa* (35%) was found to be the most often isolated microorganism among the growing microorganisms (26). In their study evaluating MDR growth, Baiou et al. (27) discovered Stenotrophomonas maltophilia (24.5%) and *Klebsiella pneumonia* (23.5%) most commonly. Karatas et al. (28) identified *Acinetobacter Baumanii* as the most prevalent respiratory infection pathogen among COVID-19 patients, and concluded that the prevalence of MDR *Acinetobacter Baumanii* increased during the pandemic compared to the pre-pandemic period. In our study, microbiological culture positive was observed in 92 (39.1%) of the patients, with *Acinetobacter Baumanii* (47.8%) being the most common pathogen found. This was followed by *Klebsiella pneumonia* in 38% of the patients and *Pseudomonas Aeruginosa* in 8.7%. There was no relationship between immunosuppressive therapy and microorganisms.

When MDR infections trigger the development of VAP in the ICU, mortality might reach up to 60% (29). Bentivegna et al. (30) evaluated MDR infections from 2017 to 2020 and found a decrease in MDR infections during the pandemic era compared to the pre-pandemic times. This was assumed to be due to hand washing and the usage of personal protective equipment. During the pandemic, however, MDR infections were higher in COVID-19 clinics than in non-COVID clinics (29% vs 19%) (30). Baiou et al. (27) investigated the link between the development of MDR infection and immunosuppressive therapy and found that corticosteroid and tocilizumab treatments were not associated with the development of MDR. In current study, there was no difference in MDR and PDR between groups that got and did not receive immunosuppressive therapy, however the development of XDR was higher in the group that received immunosuppressive therapy compared to those who did not (89.8% vs. 72.7%). In the subgroup analysis, the development of XDR and PDR was higher in the corticosteroid plus tocilizumab group than in those who did not receive immunosuppressive therapy.

The limitations of the study were that it was single-center and retrospective. Furthermore, no microorganisms other than respiratory bacterial pathogens were evaluated in this study.

CONCLUSIONS

Immunosuppressive therapy may increase the development of VAP, the risk of secondary infection, the growth of bacteria resistant to at least one drug, and the length of stay in hospital and ICUs in patients with critically ill COVID-19 pneumonia. Furthermore, when corticosteroid and tocilizumab were used together, it was determined that the proliferation of XDR and PDR microorganisms may be increased. Although there was no difference in mortality between groups, it was determined that when immunosuppressive therapy was used, targeted antibiotics and longer-term antimicrobial therapy might be required.

ETHICAL DECLARATIONS

Ethics Committee Approval: This study was approved by the Ethics Committee of İstanbul Ümraniye Training and Research Hospital (Date: 26.05.2022, Decision No: 167).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contribution: All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

REFERENCES

1. World Health Organization. WHO coronavirus (COVID-19) dashboard. Available from: https://covid19.who.int/ cited on 28 May 2022.
2. Russo A, Olivadese V, Trecarichi EM, Torti C. Bacterial ventilator-associated pneumonia in COVID-19 patients: data from the second and third waves of the pandemic. J Clin Med 2022; 11: 2279.

3. Gustine JN, Jones D. Immunopathology of hyperinflammation in COVID-19. Am J Pathol 2021; 191: 4-17.
4. Sahin Ozdemirel T, Akkurt ES, Ertan O, Gokler ME, Akıncı Ozyurek B. Complications with moderate-to-severe COVID-19 during hospital admissions in patients with pneumonia. J Health Sci Med 2021; 4: 766-71.
5. Torres A, Niederman MS, Chastre J, et al. International ERS/ESICM/ESCMID/ALAT guidelines for the management of hospital-acquired pneumonia and ventilator-associated pneumonia: guidelines for the management of hospital-acquired pneumonia (HAP)/ventilator-associated pneumonia (VAP) of the European Respiratory Society (ERS), European Society of Intensive Care Medicine (ESICM), European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and Asociación Latinoamericana del Tórax (ALAT). Eur Respir J 2017; 50: 1700582.
6. World Health Organization. Therapeutics and COVID-19: living guideline. Available from: https://www.who.int/publications/i/item/WHO-2019-nCoV-therapeutics-2022.3. cited on 28 May 2022.
7. REMAP-CAP Investigators, Gordon AC, Mouncey PR, et al. Interleukin-6 receptor antagonists in critically ill patients with COVID-19. N Engl J Med 2021; 384: 1491-502.
8. Rosas IO, Bräu N, Waters M, et al. Tocilizumab in hospitalized patients with severe COVID-19 pneumonia. N Engl J Med 2021; 384: 1503-16.
9. Maes M, Higginson E, Pereira-Dias J, et al. Ventilator-associated pneumonia in critically ill patients with COVID-19. Crit Care 2021; 25: 25.
10. Meawed TE, Ahmed SM, Mowafy SMS, Samir GM, Anis RH. Bacterial and fungal ventilator associated pneumonia in critically ill COVID-19 patients during the second wave. J Infect Public Health 2021; 14: 1375-80.
11. Kalil AC, Metersky ML, Klompas M, et al. Executive summary: management of adults with hospital-acquired and ventilator-associated pneumonia: 2016 clinical practice guidelines by the Infectious Diseases Society of America and the American Thoracic Society. Clin Infect Dis 2016; 63: 575-82.
12. Pawlik J, Tomaszek L, Mazurek H, Mędrzycka-Dąbrowska W. Risk factors and protective factors against ventilator-associated pneumonia- a single-center mixed prospective and retrospective cohort study. J Pers Med 2022; 12: 597.
13. Basak S, Singh P, Rajurkar M. Multidrug resistant and extensively drug resistant bacteria: a study. J Pathog 2016; 2016: 4065603.
14. Mehta P, McAuley DF, Brown M, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet 2020; 395: 1033-4.
15. Somers EC, Eschenauer GA, Troost JP, et al. Tocilizumab for treatment of mechanically ventilated patients with COVID-19. Clin Infect Dis 2021; 73: e445-54.
16. RECOVERY Collaborative Group, Horby P, Lim WS, et al. Dexamethasone in hospitalized patients with COVID-19. N Engl J Med 2021; 384: 693-704.
17. Ramiro S, Mostard RLM, Magro-Checa C, et al. Historically controlled comparison of glucocorticoids with or without tocilizumab versus supportive care only in patients with COVID-19-associated cytokine storm syndrome: results of the CHIC study. Ann Rheum Dis 2020; 79: 1143-51.
18. Ippolito M, Misseri G, Catalisano G, et al. Ventilator-associated pneumonia in patients with COVID-19: a systematic review and meta-analysis. Antibiotics (Basel) 2021; 10: 545.
19. Martínez-Martínez M, Plata-Menchaca EP, Nuvials FX, Roca O, Ferrer R. Risk factors and outcomes of ventilator-associated pneumonia in COVID-19 patients: a propensity score matched analysis. Crit Care 2021; 25: 235.
20. Roumier M, Paule R, Vallée A, et al. Tocilizumab for severe worsening COVID-19 pneumonia: a propensity score analysis. J Clin Immunol 2021; 41: 303-14.
21. Gragueb-Chatti I, Lopez A, Hamidi D, et al. Impact of dexamethasone on the incidence of ventilator-associated pneumonia and blood stream infections in COVID-19 patients requiring invasive mechanical ventilation: a multicenter retrospective study. Ann Intensive Care 2021; 11: 87.
22. Stone JH, Frigault MJ, Serling-Boyd NJ, et al. Efficacy of tocilizumab in patients hospitalized with COVID-19. N Engl J Med 2020; 383: 2333-44.
23. Tomazini BM, Maia IS, Cavalcanti AB, et al. Effect of dexamethasone on days alive and ventilator-free in patients with moderate or severe acute respiratory distress syndrome and COVID-19: the CoDEX randomized clinical trial. JAMA 2020; 324: 1307-16.
24. Naik NB, Puri GD, Kajal K, et al. High-dose dexamethasone versus tocilizumab in moderate to severe COVID-19 pneumonia: a randomized controlled trial. Cureus 2021; 13: e20353.
25. Lima WG, Brito JCM, da Cruz Nizer WS. Ventilator-associated pneumonia (VAP) caused by carbapenem-resistant Acinetobacter baumannii in patients with COVID-19: two problems, one solution? Med Hypotheses 2020; 144: 110139.
26. Giacobbe DR, Battaglini D, Enrile EM, et al. Incidence and prognosis of ventilator-associated pneumonia in critically ill patients with COVID-19: a multicenter study. J Clin Med 2021; 10: 555.
27. Baiou A, Elbuzidi AA, Bakdach D, et al. Clinical characteristics and risk factors for the isolation of multi-drug-resistant gram-negative bacteria from critically ill patients with COVID-19. J Hosp Infect 2021; 110: 165-71.
28. Karatas M, Yasar-Duman M, Tunger A, Cilli F, Aydemir S, Ozenci V. Secondary bacterial infections and antimicrobial resistance in COVID-19: comparative evaluation of pre-pandemic and pandemic-era, a retrospective single center study. Ann Clin Microbiol Antimicrob 2021; 20: 51.
29. Póvoa HCC, Chianca GC, Iorio NLPP. COVID-19: an alert to ventilator-associated bacterial pneumonia. Infect Dis Ther 2020; 9: 417-20.
30. Bentivegna E, Luciani M, Arcari L, Santino I, Simmaco M, Martelletti P. Reduction of multidrug-resistant (MDR) bacterial infections during the COVID-19 pandemic: a retrospective study. Int J Environ Res Public Health 2021; 18: 1003.