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Evaluation of Secondary Infections in COVID-19 Patients Hospitalized in Intensive Care Unit: Retrospective Observational Study

Yoğun Bakımda Ünitesinde Yatan COVID-19 Tanılı Hastalardaki Sekonder Enfeksiyonların Değerlendirilmesi: Retrospektif Gözlemsel Çalışma

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ABSTRACT Objective: Patients infected with severe acute respiratory syndrome-coronavirus-2 may progress with severe clinical symptoms and patients may be hospitalized in intensive care for a long time. In patients with long-term intensive care hospitalization, secondary infections develop as a result of the pathophysiology of the disease and the treatments used. The aim of this study is to investigate the incidence of secondary infections in patients with coronavirus disease-2019 (COVID-19) and to identify common pathogen groups. **Material and Methods:** Four hundred and sixty one patients with a diagnosis of COVID-19 who were followed up in the intensive care unit at Afyonkarahisar Health Sciences University Faculty of Medicine Hospital between 20 March 2020 and 31 May 2021 were included in the study. Demographic data, co-morbidities, clinical features, laboratory data and culture growth data of the patients were recorded retrospectively. **Results:** Nosocomial secondary infections were detected in 132 (28.6%) of 461 patients. *Acinetobacter baumannii* 39/53 (73.5%) growth was observed in the majority of the lower respiratory tract sample cultures. There was 28/49 (57.1%) *Staphylococcus aureus* growth in blood cultures, and 21/42 (50%) *candida spp*. growth in urine cultures. **Conclusion:** In this study, we found that the incidence of infection secondary to COVID-19 pneumonia was high. In addition, it was determined that the secondary infection rate was high in patients with PaO_2/FiO_2<200.

Keywords: *Acinetobacter baumannii*; bacterial infections; COVID-19; nosocomial infections; secondary infections

ÖZET Amaç: Şiddetli akut solunum sendromu-koronavirüs-2 ile enfekte olan hastalar ciddi klinik semptomlarla seyredebilir ve uzun süre yoğun bakımda kalabilir. Uzun süreli yoğun bakımda kalışlarla birlikte hastalığın patofizyolojisi ve kullanılan tedaviler sonucunda sekonder enfeksiyonlar gelişmektedir. Bu çalışmanın amacı, koronavirüs hastalığı-2019 [coronavirus disease-2019 (COVID-19)] olan hastalarda ikincil enfeksiyonların insidansını araştırmak ve yaygın patojen gruplarını tanımlamaktır. **Gereç ve Yöntemler:** Afyonkarahisar Sağlık Bilimler Üniversitesi Tıp Fakültesi Hastanesinde 20 Mart 2020-31 Mayıs 2021 tarihleri arasında COVID-19 yoğun bakım ünitesinde takip edilen 461 COVID-19 tanılı hasta çalışmaya dâhil edildi. Retrospektif olarak hastaların demografik verileri, komorbiditeleri, klinik özellikleri, laboratuvar verileri ve kültür üreme verileri kaydedildi. **Bulgular:** Toplam 461 hastanın 132'sinde (%28,6) de nozokomiyal sekonder enfeksiyon tespit edildi. Alt solunum yolu örnek kültürünün çoğunluğunda *Acinetobacter baumannii* 39/53 (%73,5) üremesi olurken, kan kültürlerinde 28/49 (%57,1) *Staphylococcus aureus* üremesi, idrar kültüründe ise 21/42 (%50) *candida spp*. üremesi oldu. **Sonuç:** Bu çalışmada, COVID-19 pnömonisine sekonder gelişen enfeksiyon gelişme insidansının yüksek olduğunu bulduk. PaO_2/FiO_2<200 olan hastalarda sekonder enfeksiyonların yüksek olduğunu tespit ettik.

Anahtar Kelimeler: *Acinetobacter baumannii*; bakteriyel enfeksiyonlar; COVID-19; nozokomiyal enfeksiyon; sekonder enfeksiyonlar

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Coronavirus disease-2019 (COVID-19) is a worldwide pandemic caused by severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2). It has been reported that secondary bacterial and fungal infections significantly increase morbidity and mortality, especially in critically ill COVID-19 patients followed in intensive care units.[1,2]

Rapid and accurate identification of bacterial or fungal infections occurring during the follow-up of COVID-19 patients is an important step in the success of treatment.[3-5]

In critically ill patients followed up with the diagnosis of COVID-19, the frequency of secondary infections and the primary responsible pathogens are not clearly known. In this study, secondary infections detected in patients followed in the intensive care unit with the diagnosis of COVID-19 are analyzed.

MATERIAL AND METHODS

Patients who were followed up with the diagnosis of COVID-19 in the intensive care unit of Afyonkarahisar Health Sciences University Hospital between 20 March 2020 and 31 May 2021 were included in our study. This retrospective research project was ethically approved by the Ethics Committee of Afyonkarahisar Health Sciences University (dated: October 1, 2021, decision no: 482). The study was conducted following the Declaration of Helsinki, and patients gave their written consent.

Patients with radiologically and clinically severe COVID-19 pneumonia, who were defined as probable cases according to the "Republic of Türkiye Ministry of Health, COVID-19 Diagnosis, Treatment and Follow-up Guideline" but for whom SARS-CoV-2 positivity could not be detected by real-time-polymerase chain reaction (RT-PCR) in swab sampling, and patients with severe pneumonia who were found to be positive for SARS-CoV-2 by RT-PCR in nasopharyngeal or lower respiratory tract samples (deep trachealaspirate) were accepted. Patients with at least one of the following criteria were considered as patients with severe pneumonia.[6]

a. Tachypnea ≥30 breaths/minute, SpO_2 level <90% in room air, PaO_2/FiO_2<300 in the patient with oxygen support

b. Presence of specific radiological findings (bilateral lobular, peripherally located, diffuse patchy ground-glass opacities) for COVID-19 on lung tomography

c. Mechanical ventilation requirement

d. Signs of acute organ dysfunction; SOFA Score>2 (sepsis-related organ failure assessment score)

In patients who met the criteria for severe COVID 19 pneumonia, a diagnosis of nosocomial infection was made at least 48 hours after admission to the intensive care unit. Blood, urine and respiratory secretion cultures were obtained. Nosocomial infection criteria of the Centers for Disease Control and Prevention were used in the diagnosis.[7] Cultures taken from patients with infection in any of the blood circulation system, urinary system or lower respiratory tract were evaluated.

Demographic findings, co-morbidities, clinical and laboratory characteristics of all patients included in the study were reviewed retrospectively. The patients were divided into 2 groups as those with and without growth in the cultures. Demographic, clinical features and laboratory values of these two groups were evaluated.

STATISTICAL ANALYSIS

Data obtained in the study were analyzed statistically using SPSS vn. 26.0 software (IBM Corpn, Armonk, NY, USA). Descriptive statistics were stated as mean±standard deviation and median (minimum-maximum) values. Conformity of the data to normal distribution was assessed with the Shapiro-Wilk test. In the comparison of categorical data, the chi-square test was applied, and in the comparisons of two groups, the Students t-test, or the Mann-Whitney U test. A value of $p<0.05$ was accepted as statistically significant.

RESULTS

The study included 461 patients hospitalized in the intensive care unit with the diagnosis of COVID-19

pneumonia. Nosocomial infections were detected in 132 of these patients. 178 (38.6%) of 461 patients needed mechanical ventilator support. Microorganism growth was detected in the cultures of 62 (81.1%) of the patients on mechanical ventilator support. When the patients with and without microorganism growth in cultures were compared; there was no statistically significant difference in terms of age, gender, comorbidity. Procalcitonin, C-reactive protein, lymphocyte and ferritin levels were compared between the two groups and no statistically significant difference was observed.

The PaO_2/Fio_2 ratio of the patients at the time of hospitalization was found to be statistically significantly lower in the group with microorganism growth (p=0.018). Demographic characteristics and laboratory findings of patients with nosocomial infections are shown in Table 1.

A total of 327 microbiological samples were taken from 132 patients with nosocomial infections included in the study. One hundred thirteen were blood cultures (24.5%), 117 were urine cultures (25.3%), and 97 were trachealaspirate cultures (21%). A microorganism associated with nosocomial infection was grown in 144 (44%) of 327 culture samples taken. Of these 144 microorganisms, 49 were in blood culture, 42 in urine culture, 53 in deep tracheal aspirate culture.

Among the 461 patients included in the study, 23/461 (4.8%) had blood circulation infection only, 22/461 (4.7%) had only urinary tract infection and 30/461 (6.5%) had only lower respiratory tract infection. *Acinetobacter baumannii* 39/53 (73.5%) was grown in the majority of the lower respiratory tract sample cultures. There were 28/49 (57.01%) *Staphylococcus aureus* and *A. baumannii* 11/49 (22.44%)

TABLE 1: Characteristics of the patients admitted to ICU with COVID-19.

	Overall (n=461)	Secondary infection (growth in the culture) (n=107)	Secondary infection (without growth in the culture) (n=25)	p value
Age (years)	67.7±12.27	69.21±10.83	66.68±12.39	0.307
Male sex	308 (66.8%)	72 (79.1%)	19 (20.9%)	0.545
Hypertension	216 (46.9%)	55 (80.9%)	13 (19.1%)	0.991
Diabetes mellitus	148 (32.1%)	32 (74.4%)	11 (25.6%)	0.267
Coronary heart disease	113 (24.5%)	31 (86.1%)	5 (13.9%)	0.512
Chronic obstructive pulmonary disease	99 (21.5%)	26 (83.9%)	5 (16.1%)	0.840
Chronic kidney disease	38 (3.8%)	10 (83.3%)	2 (16.7%)	0.592
Malignancies	57 (12.4%)	14 (87.5%)	2 (12.5%)	0.374
Mechanical ventilator	178 (38.6%)	62 (81.1%)	18 (18.9%)	0.286
PaO_2/FiO_2 (median)	116 (58-320)	114 (58-250)	123 (80-250)	0.018
Lactates, (mg/dL) (median)	8 (4-120)	16 (7-120)	18 (4-48)	0.502
White blood cells, per 10^3/uL	9.00 (28.550-140)	6.60 (0.84-18.10)	7.60 (0.74-25.60)	0.463
Lymphocytes, per 10^3/uL	680 (0.74-3100)	660 (0.84-1810)	760 (0.74-2560)	0.461
Haemoglobin, g/dL	12.6 (19.6-6.4)	12.4 (6.40-17.60)	12.90 (7.70-15.70)	0.952
Platelets, per 10^3/uL	209.0 (883000-6000)	216.0 (26.0-883.00)	192.00 (96-421)	0.212
C-reactive protein, (mg/dL)	11 (51.4-0.20)	11.3 (0.60-43.97)	11.54 (0.60-34.15)	0.991
Procalcitonin, (ng/mL)	0.21 (100-0)	1.1 (0.04-41.50)	0.34 (0.03-14.12)	0.255
D-dimer, (µg/mL)	1.09 (0.04-87.1)	1.1 (0.04-41.50)	1.00 (0.12-39.00)	0.730
Ferritin, (ng/mL)	682 (6.1-9604)	717.90 (52-2019)	623 (144.80-2000)	0.880
Lactate dehydrogenase, (U/L)	451 (17-1910)	471 (89-1781)	547 (206-1303)	0.631
Creatine kinase, (IU/L)	98 (12-10846)	107 (14-9345)	135 (54-2200)	0.124
Alanine aminotransferase, (U/L)	25 (3-489)	24 (8-131)	25 (11-222)	0.425
Aspartate aminotransferase, (U/L)	40 (11-945)	40 (14-361)	43 (12-468)	0.612
Cytokine adsorption therapy	41 (8.8%)	18 (16.8%)	2 (8%)	0.218

ICU: Intensive care unit.

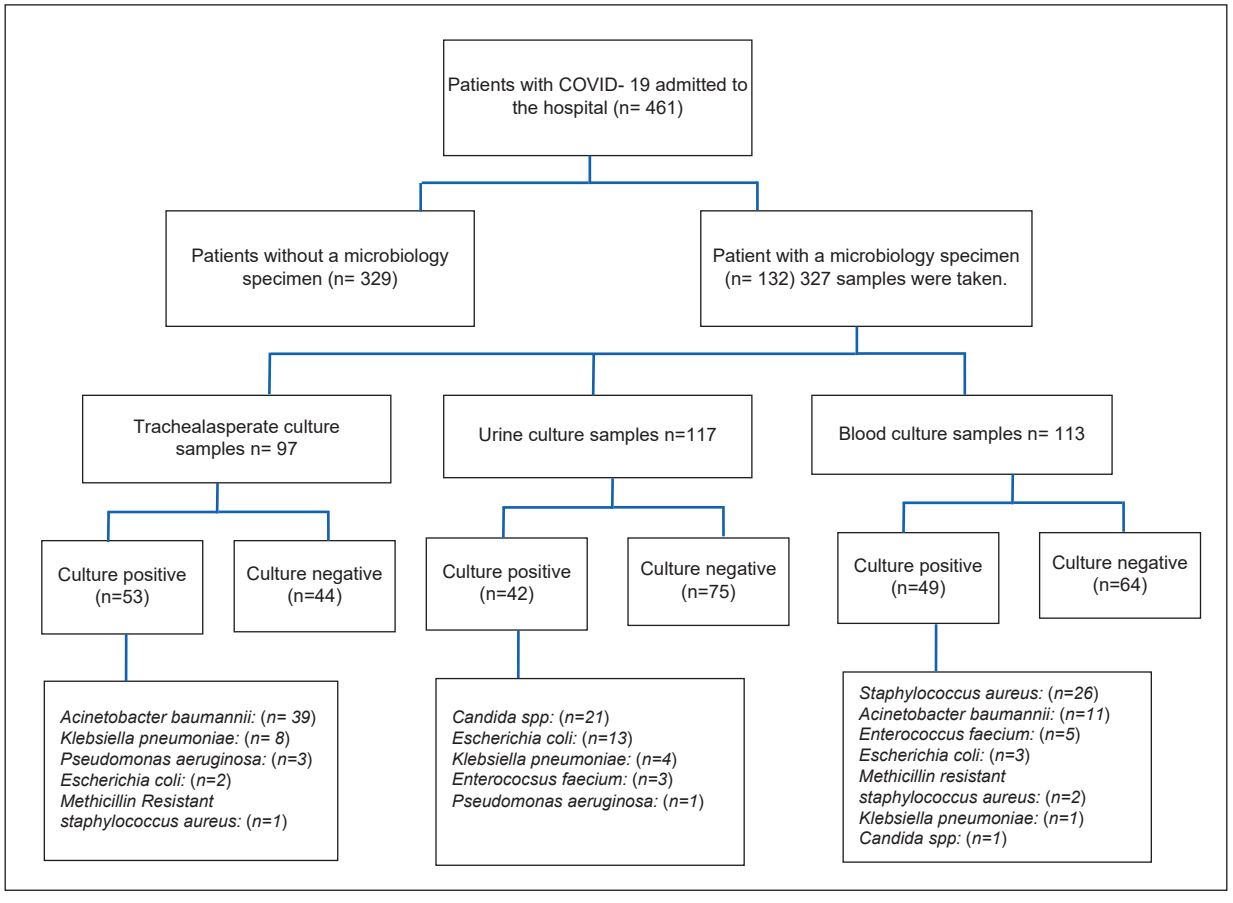

FIGURE 1: Distribution of the microbiological culture samples.

growths in blood cultures, 21/42 (50%) *candida spp.* 13/42 (30.95%) *Escherichia coli* growths in urine cultures. Culture data are shown in Figure 1.

DISCUSSION

In this study, we described the nosocomial secondary infections detected in patients with severe COVID-19 pneumonia followed in the intensive care unit, and the demographic data, laboratory data and microbiological growth of these patients. Secondary infections ranging from 5% to 30% were reported in two different studies in COVID-19 patients.[8-13] In the results of our study, our secondary infection rate was 28.6%, which is compatible with the literature.

It has been stated that viral infections may weaken the host immunity and increase the development of secondary bacterial infections.[14] Respiratory viral infections such as influenza predispose the body to secondary infections, and as a result, may increase the severity of the disease and mortality.[14,15]

The irregular increase in inflammatory cytokines in severe COVID-19 infection causes deterioration of the immune system, suggesting that this situation increases the susceptibility to secondary bacterial infections.[16]

In some studies, it has been reported that bacteria such as *Streptococcus pyogenes*, *Neisseria meningitidis*, *Moraxella catarrhalis*, *Streptococcus pneumoniae, Haemophilus influenzae* and *S. aureus* may accompany influenza infection.[17,18]

In studies on COVID-19 patients; positive culture rates in respiratory tract culture samples taken from hospitalized COVID-19 patients have been reported to vary between 2.0% and 17.2%.[4,5,10] In our

study, the respiratory tract culture positivity rate of COVID-19 patients hospitalized in the intensive care unit was 21%. Sharifipour et al. reported that *A. baumannii* (90%) is the most common microorganism in respiratory tract secondary infections in COVID-19 patients hospitalized in intensive care units.[4] In our study, the most common microorganism in deep tracheal aspirate culture in patients with COVID-19 was *A. baumannii* (73%).

There are studies reporting that the incidence of secondary bacterial bloodstream infections in critically ill COVID-19 patients is between 3.4% and 50%.[19,20] Giacobbe et al. reported that the most common microorganisms detected in secondary blood-circulatory tract infections in patients with COVID-19 were *S. aureus* with 43.6% and *Enterococcus spp*. with 10.3%.[19] Buetti et al. reported that 37% of *S. aureus* and 18% of *Enterococcus spp*. were seen in secondary blood-circulatory infections.[20] In our study, secondary blood-circulatory tract infection was 4.8%. The most common secondary blood-circulatory tract infections were *S. aureus* (57.1%) and *Enterococcus spp*. (10.2%).

Denny et al. in their study, which they compared with the period before the covid pandemic, they reported that the rates of *coagulase negative staphylococci ve S. aureus* increased significantly in catheter-related and non-catheter related bloodstream infections ($p<0.01$). They associated the reason for this increase with possible contamination associated with the increased use of personal protective equipment and inappropriate antibiotic use.[21] We believe that the intensive care unit had to work beyond its capacity during the pandemic period, leading to an increase in blood-circulatory tract infections due to *S. aureus* due to the decrease in compliance with aseptic techniques in the management of intravascular devices.

Díaz Pollán et al. reported that 3.81% of secondary infections in COVID-19 patients were urinary tract infections, and the most isolated microorganisms were 28.4% *E. coli* and 26.3% *Enterococcus faecalis*.[22] In our study, urinary tract infections were found in 4.7% of the patients we followed up in the intensive care unit. Most of our patients had urinary catheters and 50% of the growths in the urine culture were *candida spp.* and 30% were *E. coli*.

In studies, it has been reported that severe acute respiratory distress syndrome develops in COVID-19 patients hospitalized in the intensive care unit due to widespread damage to alveolar surfactant release and deterioration in its structure, and therefore the need for mechanical ventilation increases. It has been stated that the susceptibility to bacterial and fungal infections increases in the case of prolonged stay on mechanical ventilator support.[1,23]

In another study which evaluated secondary infection in COVID-19 patients, the rate of secondary infection was reported to be higher in patients with a PaO_2/FiO_2 ratio <200. It was also stated in the same study that a low lymphocyte count increased the rates of secondary infections.[24] Patients in the current study with severe hypoxia (PaO_2/FiO_2 ratio <200) were determined with a higher rate of secondary infections, but no correlation was determined between low lymphocyte count and secondary infection.

There are some limitations of our study. First of all, our study is a retrospective and single-center study. Second, the study might also suffer from selection bias since the decision to obtain bacterial cultures was done by the treating clinician and most probably was affected by the severity of the disease. Our third limitation was that the different treatments applied to the patients included in the study were not taken into account. Our fourth limitation is that the intubation times of the patients were not specified.

CONCLUSION

In this study, we found that the incidence of infection secondary to COVID-19 pneumonia was high. In these patients, the rate of development of secondary pneumonia was the highest, followed by blood-circulatory infection and catheter-related urinary tract infections. We found that the rate of development of secondary infection is high in patients with severe hypoxia (PaO_2/FiO_2<200).

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and /or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Semiha Orhan, Neşe Demirtürk;* ***Design:*** *Alper Sarı;* ***Control/Supervision:*** *Semiha Orhan, Neşe Demirtürk;* ***Data Collection and/or Processing:*** *Semiha Orhan, Alper Sarı;* ***Analysis and/or Interpretation:*** *Kemal Yetiş Gülsoy, Semiha Orhan, Neşe Demirtürk;* ***Literature Review:*** *Semiha Orhan, Alper Sarı, Kemal Yetiş Gülsoy;* ***Writing the Article:*** *Semiha Orhan, Kemal Yetiş Gülsoy, Neşe Demirtürk;* ***Critical Review:*** *Neşe Demirtürk, Semiha Orhan;* ***References and Fundings:*** *Semiha Orhan;* ***Materials:*** *Semiha Orhan.*

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