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ORIGINAL RESEARCH / *ÖZGÜN ARAŞTIRMA*

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The Effect of Secondary Infections on Mortality in Patients with COVID-19 Associated Severe ARDS

COVİD-19 ile İlişkili Şiddetli ARDS Hastalarında Sekonder Enfeksiyonların Mortalite Üzerine Etkisi

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ABSTRACT *Objective:* In the beginning of the coronavirus disease-2019 (COVID-19) pandemic, secondary bacterial, fungal and viral infections have been reported in the intensive care unit (ICU), but there is limited experience with infections in critically ill patients over time. The aim this study was to evaluate the characteristics of secondary infections related to ICU and their effects on mortality in COVID-19 patients.
Materials and Methods: Our study was planned as a retrospective single-center case-control study involving 145 patients with severe severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) pneumonia hospitalized in the ICU between March and June 2020. The epidemiological, clinical and microbiological characteristics and results of ICU-related infections were evaluated.
Results: The mean age of the patients was 61.2 years and mean body mass index was 28 kg/m^2. At least one comorbidity was found in 140 patients (96.6%). Seventy seven of (53.1%) the patients diagnosed with COVID-19 included in the study died. In addition to SARS-CoV-2, the isolation of different pathogens was observed in 62 (42.75%) patients' samples. In the group with secondary infections, a significant increase in lymphocyte and lactate levels was observed between the time of admission and time of sampling culture (p<0.001). There was statistical significance in lymphocyte (p<0.026) and lactate (p<0.020) levels between the groups with and without infection. There was a significant increase in C-reactive protein, ferritin, procalcitonin levels and Acute Physiology and Chronic Health Evaluation-II scores in the group with secondary infection compared to the group without secondary infection (p<0.041, p<0.009 p<0.001, and p=0.028, respectively). In the group without secondary infection, the D-dimer levels patients were significantly lower (p<0.014).
Conclusion: In conclusion, bacterial and fungal secondary infections are a common complication in patients with COVID-19 admitted to the ICU. It usually occurs as a severe form of infection accompanying comorbidity and is associated with high mortality and prolonged ICU stay.
Keywords: COVID-19, intensive care unit, co-infection, mortality

ÖZ *Amaç:* Koronavirüs hastalığı-2019 (COVİD-19) pandemisinin ilk dönemlerinde yoğun bakım ünitesinde (YBÜ) takip edilen hastalarda bakteriyel, fungal ve viral kaynaklı daha az sekonder enfeksiyonlar olduğu bildirilmiştir. COVİD-19'lu kritik hastalarda bakteriyel enfeksiyon deneyimi sınırlıdır. Bu çalışmanın amacı, COVİD-19 hastalarında YBÜ kaynaklı sekonder enfeksiyonların özelliklerini ve mortalite üzerine olan etkilerini değerlendirmektir.
Gereç ve Yöntem: Çalışmamız, Mart ve Haziran 2020 tarihleri arasında YBÜ'de yatan ve şiddetli akut solunum yolu yetersizliği sendromu (SARS-CoV-2) pnömonisi olan 145 hastayı içeren tek merkezli retrospektif bir olgu-kontrol çalışması olarak planlandı. YBÜ kaynaklı enfeksiyonların epidemiyolojik, klinik ve mikrobiyolojik özellikleri ve sonuçları değerlendirildi.
Bulgular: Hastaların ortalama yaşı 61,2 yıl ve vücut kitle indeksleri 28 kg/m^2 olarak saptandı. Yüz kırk (%96,6) hastada en az bir komorbidite olduğu belirlendi. Çalışmadaki tüm COVİD-19 tanılı hastalardan 77'sinde (%53,1) ölüm gerçekleşti. Altmış iki (%42,75) hastada SARS-CoV-2'ye ek olarak farklı patojen üremesi saptandı. Kültürde ek mikroorganizma üreyen grupta ilk ölçülen lenfosit ve laktat düzeyleri ile kültür alındıktan sonra yapılan ölçümler arasında anlamlı bir artış belirlendi (p<0,001). Üreme olan ve olmayan gruplar arasında ölçülen lenfosit (p<0,026) ve laktat (p<0,020) düzeylerinde de istatistiksel anlamlılık görüldü. Üreme olan grupta üreme olmayan gruba göre C-reaktif protein, ferritin, prokalsitonin düzeylerinde ve de Akut Fizyoloji ve Kronik Sağlık Değerlendirmesi-II skorlarında anlamlı bir artış olduğu görüldü (sırasıyla; p<0,041, p<0,009, p<0,001 ve p=0,028). Üreme olmayan grupta ise hayatta kalan hastalar ile ölen hastaların D-dimer düzeyleri önemli ölçüde düşük saptandı (p<0,014).

Sonuç: Sonuç olarak bakteriyel ve fungal sekonder enfeksiyonlar, YBÜ'ye yatan COVİD-19'lu hastalarda yaygın bir komplikasyondur. Genellikle şiddetli bir enfeksiyon şekli olarak ortaya çıkar ve eşlik eden komorbidite ile birlikte yüksek mortalite ve uzamış YBÜ yatış süresi ile ilişkilidir.
Anahtar Kelimeler: COVİD-19, yoğun bakım ünitesi, ko-enfeksiyon, mortalite

Introduction

Coronavirus disease-2019 (COVID-19) pandemic is spread over the world starting from Wuhan in December 2019 (1). The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), an enveloped RNA betacoronavirus, is responsible for the infection. Fever, cough and respiratory failure are known as its most common symptoms (2). Advanced age and the presence of chronic diseases have been associated with a worse prognosis and higher mortality in patients diagnosed with COVID-19 (3). In addition to the disease, different levels of bacterial or fungal co-infection have been observed in other respiratory viruses such as influenza, Middle East respiratory syndrome, and SARS-CoV-1; it is thought that this situation may result in more serious problems in infectious diseases (4). Infections are among the most important causes of mortality, especially in patients followed up in the intensive care unit (ICU). Comorbidities, age of the patients and invasive procedures applied in ICUs cause an increase in development of infection in these patients. After the acute inflammatory reaction and pulmonary tissue damage caused by viral infections, a repair phase occurs in the lung tissue. Therefore, bacterial co-infection may develop following viral infection and this may cause an increase in mortality rate (5). Recognition of the SARS-CoV-2 infection is important to ensure implementation of appropriate infection control procedures and administration of appropriate antiviral therapy (6-8).

In this study it is aimed to determine the secondary infection rate, distribution of causative agents of these infections, selection of antibiotics for treatment and resistance patterns of microorganisms in patients with acute respiratory distress syndrome (ARDS) secondary to SARS-CoV-2 viral pneumonia who followed-up in ICU and analyze the effects of secondary infection on mortality and morbidity retrospectively.

Materials and Methods

Our study was initiated by obtaining the approval of the clinical local ethical committee of University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital dated 08/06/2020, numbered 2020-12-29. Patients aged 18 years and older who applied to the emergency department of our hospital, whose polymerase chain reaction positivity was detected in the nasopharyngeal swab and who were followed up in the ICU for at least 72 hours were included in the study (between March 16, 2020 and June 1, 2020). The data of the patients were obtained by scanning of files in the electronic system and archive of the infection control committee. Infections in patients are classified according to the definition of healthcare-associated infections. Patients who had infection within the first 48 hours of admission to ICU or patients transferred from another clinic and had hospital infection at the time of acceptance to ICU were excluded from the study. The data of patients was recorded during the follow-up in the ICU or in other departments to where they were transferred. The data were recorded via case follow-up forms by observing the patients until the date of discharge or death.

Statistical Analysis

SPSS 27.0 (IBM Corporation, Armonk, New York, United States) and PAST 3 (Hammer, Ø., Harper, D.A.T., Ryan, P.D. 2001. Paleontological statistics) programs were used in the analysis of variables. The suitability of univariate data to normal distribution was evaluated using the Shapiro-Wilk francia test, while variance homogeneity was evaluated with the Levene test. Mardia (Dornik and Hansen omnibus) test was used for normal distribution of multivariate data, while Box-M test was used for variance homogeneity. Independent samples t-test was used together with Bootstrap results, while Mann-Whitney U test was used together with Monte Carlo results in comparing the two indepent groups in term of quantitative data. Wilcoxon signed-ranks test was used with Monte Carlo results to compare dependent quantitative variables and duplicate measurements. Comparison of categorical variables was tested with Pearson chi-square and Fisher Exact Monte Carlo simulation techniques, and the column proportions were compared with each other and expressed according to the Benjamini-Hochberg corrected p-value results. Quantitative variables were expressed as mean (standard deviation) and median (percentile 25/ percentile 75) in the tables, while categorical variables were shown as n (%). Variables were analyzed at a 95% confidence level, and a p-value of less than 0.05 was considered significant.

Results

A total of 145 patients diagnosed with COVID-19 pneumonia [55 (37.9%) female and 90 (62.1%) male] were included in the study. The mean age of the patients was 61.18±16 years, and the mean body mass index (BMI) level was 28.04±5.8 kg/m^2. At least one comorbidity was found in 140 (96.6%) patients. The most common comorbidities are hypertension (HT) (34.3%) and diabetes mellitus (DM) (26.4%), and 15.7% of the patients had HT + DM diagnosis together. Different pathogens were isolated in 62 patients in addition to SARS-CoV-2. Secondary infections that developed on the basis of all SARS-CoV-2-related pneumonia were hospital-acquired infections (The earliest occurrence of secondary infections was detected at the 48th hour of intensive care admission.). Thirteen patients had positive endotracheal aspirate (ETA) cultures ventilator associated pneumonia, 56 patients had positive blood cultures, 13 patients had positive urine cultures, 16 patients had positive ETA–and blood cultures (simultaneously), 8 patients had positive blood, urine and ETA cultures (simultaneously), 2 patients had positive ETA and urine cultures (simultaneously), and 2 patients had positive blood and urine cultures (simultaneously) (Table 1).

There was no difference between the patients with or without secondary infection in terms of age, gender, BMI, presence of comorbidity, duration of mechanical ventilation and length of stay (Table 2). Tocilizumab was administered to 44 of 62 patients whose causative agent could be isolated [the mean procalcitonin (PCT) value of the patients using tocilizumab was 4.2±1.2 ng/mL and ferritin ≥700 mg/dL].

The first Acute Physiology and Chronic Health Evaluation-II (APACHE-II) and Sequential Organ Failure Assesment (SOFA) scores, C-reactive protein, white blood count (WBC), neutrophil, PCT, lactate, lactate dehydrogenase and D-dimer levels were found to be similar in patients with or without infection. However, the lymphocyte level of the patients with secondary infection was found to be lower (0.35 vs. 0.53, p=0.026). It was determined that the patients with secondary infection had higher APACHE-II scores and higher PCT levels at the time of sampling for culture (p<0.001 and p=0.028, respectively).

Seventy seven (53.1%) of the patients hospitalized with the diagnosis of COVID-19 pneumonia in the ICU did not survive. All of the patients who died had at least one comorbidity (p<0.021). No difference was found between patients who died or survived in terms of age, gender, BMI,

Table 1. Demographic characteristics, pathogens and focus

	Mean (SD)	Median (min/max)
Age	61.18 (16.00)	61 (18/100)
BMI	28.04 (5.80)	27.34 (16.65/50.78)
	n	**%**
Gender		
Female	55	37.9%
Male	90	62.1%
Mortality		
Alive	68	46.9%
Exitus	77	53.1%
Secondary infection		
No	83	57.2%
Yes	62	42.8%
Pathogens		
Acinetobacter	4	6.5%
Candida	20	32.3%
Klebsiella	9	14.5%
Enterococcus	11	17.7%
Pseudomonas	6	9.7%
E. coli	8	12.9%
Enterobacter	4	6.5%
Isolation of pathogens		
No	35	24.1%
Yes	110	75.9%
Focus of infection		
ETA	13	11.8%
Blood	56	50.9%
Urine	13	11.8%
ETA and blood (simultaneously)	16	14.5%
ETA and urine (simultaneously)	2	1.8%
Blood and urine (simultaneously)	2	1.8%
Blood, urine and ETA (simultaneously)	8	7.3%
Comorbidity		
No	5	3.4%
Yes	140	96.6%
Comorbidity		
HT	48	34.3%
DM	37	26.4%
HT + DM	22	15.7%

Table 1. Continued		
	Mean (SD)	Median (min/max)
Coronary artery disease	4	2.9%
COPD	13	9.3%
Cerebral ischemia/ hemorrhage	1	0.7%
Cancer	9	6.4%
Other	6	4.3%

COPD: Chronic obstructive pulmonary disease, DM: diabetes mellitus, ETA: endotracheal aspirate, HT: hypertansion SD: standard deviation, min: minimum, max: maximum, BMI: body mass index

sources of infection, APACHE-II and SOFA scores (p>0.005) (Table 3). Comparison of the changes in the data of the patients in terms of the presence of secondary infection is shown at Table 4.

Discussion

In this study, it was determined that 140 patients had comorbidity which had a significant effect on hospital mortality, 62 patients had secondary infection and 77 patients died among the 145 patients diagnosed with COVID-19 pneumonia in the ICU of our center.

In a study conducted in the first months of the epidemic in the Lombardy region of Italy, hospital mortality was defined as 48.8% and 53.4% in patients hospitalized in the ICU. In the same study, it was emphasized that COVID-19 mortality increased due to increased length of stay in the ICU and the need for long-term respiratory support (7). In a study conducted in Spain, it was reported that 33% of the COVID-19 patients' in ICUs died due to hospital-acquired infections (8). Yang et al. (9) stated in their study that the mortality rate increased to 81% in their patients who were under mechanical ventilation support.

Ferrando et al. (10) reported that patients with common comorbidities such as HT, obesity, and diabetes had higher APACHE-II and SOFA score and mortality rate was higher in these patients. In another similar study, it was indicated that the overall mortality rate in the ICU was 31% as a result of conditions other than COVID-19- related ARDS (11). It was analyzed whether a secondary infection developed or not with the cultures taken after the increase in PCT levels from the patients hospitalized in the ICU in our study and observed that there was secondary infection in 62 of 145 patients. It was found that APACHE-II and SOFA scores which were evaluated at the time of sampling for culture in the group with secondary infection were found to be significantly higher. In both groups, it was observed that there was a proportional increase between the APACHE-II score and the length of stay in the ICU. Also, all patients who died had at least one comorbidity.

Table 2. Differences in ICU data of patients in the presence and absence of secondary infection			
	Patients without seondary infection (n=83)	Patients with secondary infection (n=62)	p
Age mean (SD)	59.96 (15.59)	62.81 (16.51)	0.293[t]
BMI median (Q1/Q3)	24.69 (27.68/30.12)	24.22 (26.12/29.41)	0.566[u]
Gender, n (%)			
Female	31 (37.3)	24 (38.7)	0.999[c]
Male	52 (62.7)	38 (61.3)	
Mortality, n (%)			
Alive	40 (48.2)	28 (45.2)	0.739[c]
Exitus	43 (51.8)	34 (54.8)	
Comorbidity, n (%)			
No	2 (2.4)	3 (4.8)	0.651[f]
Yes	81 (97.6)	59 (95.2)	
Length of stay (hours), median (Q1/Q3)	89 (171/360)	99 (222/451)	0.382[u]
Ventilator dependent (hours), median (Q1/Q3)	59 (111/308)	60 (174/345)	0.313[u]

[t]Independent samples t-test (Bootstrap), [u]Mann-Whitney U test (Monte Carlo), [c]Pearson chi-square test (Monte Carlo), [f]Fisher Exact test (Monte Carlo), SD: standard deviation, Q1: percentile 25, Q3: percentile 75, BMI: body mass index, ICU: intensive care unit

Table 3. Evaluation of patients with and without secondary infections			
	Patients without secondary infection (n=83)	**Patients with secondary infection (n=62)**	**p[u]**
APACHE-II, median (Q1/Q3)			
First	15 (22/28)	18 (23/29)	0.300
Sampling time	23 (25/29)	26 (31/34)	<0.001
Difference (first-sampling time)	-2 (5/13)	0 (7/13)	0.260
p (for within group comparison)[w]	<0.001	<0.001	
SOFA, median (Q1/Q3)			
First	6 (10/12)	6 (10/12)	0.960
Sampling time	7 (8/12)	8 (12/14)	0.012
Difference (first-sampling time)	-4 (0/5)	-3 (2/5)	0.154
p (for within group comparison)[w]	0.945	0.058	
CRP, median (Q1/Q3)			
First	155 (206/290)	163 (195/286)	0.960
Sampling time	159.42 (208.3/275)	160 (180.5/290)	0.516
Difference (first-sampling time)	-18.58 (0/20)	-26 (0/14)	0.886
p (for within group comparison)[w]	0.655	0.820	
Procalcitonin, median (Q1/Q3)			
First	0.23 (0.76/2.24)	0.25 (0.735/6.7)	0.372
Sampling time	0.12 (0.62/2.08)	0.33 (1.1/4.95)	0.028
Difference (first-sampling time)	-0.19 (0/0)	-0.07 (0/0.29)	0.226
p (for within group comparison)[w]	0.330	0.893	
WBC, median (Q1/Q3)			
First	7.67 (11.3/15.51)	7.97 (10.265/16.57)	0.934
Sampling time	7.97 (10.73/14.16)	8.1 (13.725/16.98)	0.078
Difference (first-sampling time)	-0.84 (0/0.61)	-0.57 (0/4.79)	0.269
p (for within group comparison)[w]	0.953	0.078	
Neu, median (Q1/Q3)			
First	6.31 (9.63/12.81)	6.71 (9.31/14.89)	0.653
Sampling time	6.64 (8.39/12.08)	7.16 (11.755/15.61)	0.114
Difference (first-sampling time)	-0.079 (0/1.07)	-1 (0/4.37)	0.455
p (for within group comparison)[w]	0.538	0.126	
Lym, median (Q1/Q3)			
First	0.53 (0.75/1.23)	0.35 (0.56/1.04)	0.026
Sampling time	0.57 (0.78/1.34)	0.57 (0.955/1.36)	0.378
Difference (first-sampling time)	0 (0/0.2)	0 (0.015/0.67)	0.013
p (for within group comparison)[w]	0.441	<0.001	
Lactate, median (Q1/Q3)			
First	1 (1.4/1.8)	0.9 (1.4/1.9)	0.480
Sampling time	1 (1.5/2.4)	1.3 (1.7/2.6)	0.069
Difference (first-sampling time)	0 (0/0.5)	0 (0.3/0.8)	0.020
p (for within group comparison)[w]	0.269	<0.001	

Table 3. Continued			
	Patients without secondary infection (n=83)	**Patients with secondary infection (n=62)**	**p[u]**
LDH, median (Q1/Q3)			
First	364 (531/701)	298 (457.5/670)	0.225
Sampling time	294 (494/701)	298 (407.5/576)	0.152
Difference (first-sampling time)	-112 (0/0)	-80 (0/41)	0.509
p (for within group comparison)[w]	0.265	0.577	
Ferritin, median (Q1/Q3)			
First	468 (891.6/1492.7)	606.1 (932.6/1587)	0.475
Sampling time	327.5 (763.8/2789)	146.6 (643.15/2557)	0.624
Difference (first-sampling time)	-374.1 (0/381.9)	-669.2 (-4.3/125)	0.227
p (for within group comparison)[w]	0.471	0.570	
D-dimer, median (Q1/Q3)			
First	0.66 (1.78/3.5)	0.85 (1.755/3.95)	0.507
Sampling time	0.84 (1.94/3.65)	0.93 (2.355/4.56)	0.301
Difference (first-sampling time)	0 (0/0.93)	0 (0/0.53)	0.680
p (for within group comparison)[w]	0.105	0.108	

[u]Mann-Whitney U test (Monte Carlo), [w]Wilcoxon signed-ranks test (Monte Carlo), Q1: percentile 25, Q3: percentile 75, *for within group comparison, APACHE-II: Acute Physiology and Chronic Health Evaluation-II, SOFA: Sequential Organ Failure Assesment, CRP: C-reactive protein, WBC: white blood count, LDH: lactate dehydrogenase

In another study, in terms of secondary infection rates, it was reported that the relationship between COVID-19 and other respiratory tract pathogens was higher than reported in previous publications (12). It was stated that 28% of the patients in ICUs in France had secondary infection after admission and the etiological agent of infections were *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Enterobacteriaceae* (13).

There is insufficient study on the prevalence of bacterial or viral secondary infections in patients admitted to the ICU because of ARDS related COVID-19 (14). Secondary infections were reported in 41% of the patients admitted to the ICU in North America (15,16).

Bacterial and fungal secondary infection is common in patients with viral pneumonia, and the rate of secondary infections among patients infected with respiratory viruses is between 11% and 35% (17). In our study; Candida, *Enterococcus*, *Klebsiella*, *Escherichia coli*, *Pseudomonas*, *Acinetobacter* and *Enterobacter* species were isolated in respectively 32.3%, 17.7%, 14.5%, 12.9%, 9.7%, 6.5%, 6.5% of hospitalized patients in the ICU with secondary infection. The results of our study are in accordance with the literature information reporting the bacterial or fungal secondary infection rate of patients infected with COVID-19.

It is known that the development of bacterial and fungal secondary infections with COVID-19 could increase the severity of the disease and mortality (18). Secondary infection caused by bacteria or fungi has a great impact on the progression and prognosis of the disease, especially in critically ill patients. It causes increase in the need for intensive care supply and multiple antibiotic treatment, and most importantly, an increase in mortality (19). In a study regarding secondary infection in SARS-CoV-2 patients, it was indicated that the group with secondary infection had more severe lung lesions histopathologically, and significantly increased proinflammatory cytokines expression (20). The level of pro-inflammatory cytokines associated with severe lung injury increases significantly in COVID-19 patients, and it has been found that there is a 2.5-fold increase in mortality in patients diagnosed with COVID-19 due to the development of secondary infection (21). Regarding laboratory markers of COVID-19 patients were admitted to the ICU, the highest PCT level and platelet count have been associated with mortality. High levels of interleukin 6 were observed in deceased patients. Similarly, ferritin levels were detected to be lower than expected in previously reported hemophagocytic lenfohistiocytosis subtypes (11).

It was determined that in the group without secondary infection, there were higher differences between

Table 4. Comparison of the changes in the data of the patients in terms of the presence of secondary infection in the ICU and mortality

	Patients without infection		Patients with infection		Patients without infection	Patients with infection	Alive	Ex
	Alive	Ex	Alive	Ex	p (alive-ex)	p (alive-ex)	p Isolation (yes-no)	p Isolation (yes-no)
	(n=40)	(n=43)	(n=28)	(n=34)				
Age, mean (SD)	57.28 (16.27)	62.47 (14.67)	63.04 (16.72)	62.62 (16.59)	0.124[t]	0.927[t]	0.163[t]	0.966[t]
BMI, median (Q1/Q3)	24.88 (26.79/31.76)	24.65 (27.76/29.41)	24.65 (26.21/29.39)	24.22 (25.55/31.25)	0.990[u]	0.978[u]	0.630[u]	0.899[u]
Gender, n (%)								
Female	15 (37.5)	16 (37.2)	10 (35.7)	14 (41.2)	0.999[c]	0.975[c]	0.999[c]	0.815[c]
Male	25 (62.5)	27 (62.8)	18 (64.3)	20 (58.8)	-	-	-	-
Comorbidity, n (%)								
No	2 (5)	0 (0)	3 (10.7)	0 (0)	0.229[f]	0.087[f]	0.333[f]	-
Yes	38 (95)	43 (100)	25 (89.3)	34 (100)	-	-	-	-
Length of stay (hours), median (Q1/Q3)	95 (239/369)	82 (130/360)	132 (252/483.5)	95 (176.5/291)	0.269[u]	0.199[u]	0.493[u]	0.657[u]
Mechanical ventilation (hours), median (Q1/Q3)	59.5 (112/281.5)	58 (111/326)	55 (167.5/346.5)	60 (174.5/292)	0.914[u]	0.759[u]	0.637[u]	0.341[u]
Difference (sampling time-first)								
APACHE-II, median (Q1/Q3)	-1 (7/14)	-3 (3/10)	-1 (9/13)	1 (6/12)	0.016[u]	0.552[u]	0.995[u]	0.092[u]
SOFA, median (Q1/Q3)	-2 (1.50/6)	-7 (-3/3)	-3.50 (2/8.50)	-3 (2/4)	0.002[u]	0.249[u]	0.841[u]	0.051[u]
CRP, median (Q1/Q3)	-18.85 (0/50.50)	-18.58 (0/3)	-62.32 (-0.39/1.51)	-15 (0.31/49)	0.477[u]	0.041[u]	0.129[u]	0.214[u]
PCT, median (Q1/Q3)	-0.16 (0/0.02)	-0.19 (0/0)	-0.19 (0/0.26)	0 (0/0.29)	0.707[u]	0.634[u]	0.714[u]	0.180[u]
WBC, median (Q1/Q3)	-0.94 (0/0.36)	-0.50 (0/1.34)	-1.89 (0/5.30)	0 (0/4.79)	0.725[u]	0.494[u]	0.701[u]	0.296[u]
Neu, median (Q1/Q3)	-0.95 (0/0.87)	-0.50 (0/1.55)	-2.59 (0/4.36)	0 (0/4.37)	0.546[u]	0.267[u]	0.908[u]	0.318[u]
Lym, median (Q1/Q3)	0 (0/0.28)	-0.21 (0/0.12)	0 (0.06/0.81)	0 (0/0.53)	0.570[u]	0.540[u]	0.071[u]	0.101[u]
Lactate, median (Q1/Q3)	-0.15 (0/0.60)	0 (0/0.40)	0 (0.40/0.95)	0 (0.15/0.80)	0.716[u]	0.488[u]	0.073[u]	0.187[u]
LDH, median (Q1/Q3)	-113.50 (0/2)	-90 (0/0)	-97.50 (0/27)	-74 (0/67)	0.598[u]	0.505[u]	0.839[u]	0.299[u]
Ferritin, median (Q1/Q3)	-427.99 (0/348.2)	-321.80 (0/506.7)	-796.1 (-446.30/-4.3)	-206.40 (0/1704)	0.567[u]	0.009[u]	0.063[u]	0.815[u]
D-dimer, median (Q1/Q3)	0 (0/1.80)	-0.10 (0/0.08)	-0.02 (0/0.60)	0 (0/0.53)	0.014[u]	0.693[u]	0.294[u]	0.097[u]

[t]Independent samples t-test (Bootstrap), [u]Mann-Whitney U test (monte Carlo), [c]Pearson chi-square test (Monte Carlo), [f]Fisher Exact test (Monte Carlo), SD: standard deviation, Q1: percentile 25, Q3: percentile 75, BMI: body mass index, APACHE-II: Acute Physiology and Chronic Health Evaluation-II, SOFA: Sequential Organ Failure Assesment, CRP: C-reactive protein, PCT: procalcitonin, WBC: white blood count, LDH: lactate dehydrogenase

APACHE-II and SOFA scores measured at the time of admission and sampling for culture. Likewise, there was a significant increase in the levels of ferritin in surviving and deceased patients in the group with secondary infection. According to this finding, it suggests that secondary infections were developed after COVID-19 infections play an important role in the clinical outcomes of patients. In the group without secondary infections, the d-dimer levels of the surviving and deceased patients decreased significantly. We believe that secondary infection in COVID-19 patients may cause an increase in the severity of the disease with systemic inflammation and delay the recovery time.

Conclusion

As a result, secondary infection with different bacteria or fungi on the background of SARS-COV-2 is a serious problem in the COVID-19 pandemic. However, there are few reports of SARS-CoV-2 coexistence with bacterial, fungal, viral infections. The clinical data of secondary infection associated with SARS-CoV-2 play an important role in guiding evidence-based treatment of COVID-19. Critically ill patients who had secondary infections caused by viruses, bacteria, and fungi have a significantly higher rate of mortality and longer length of stay in the ICU than patients without secondary infection. For this reason, it is necessary to reveal the comorbidities of patients with COVID-19, especially in the ICU, as well as the development of secondary infections in the early period. Taking such an approach to COVID-19 patients provides an important insight to the clinician in terms of definitive treatment, accurate prevention and treatment of infectious complications, and helps to effectively reduce the mortality rate of patients infected with the coronavirus.

The study was pallned retrospective.

Ethics

Ethics Committee Approval: University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital Training and Research Hospital garnered on 08/06/2020 under number 2020-12-29.

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: Z.Ç., Y.T.Ş., Design: Y.T.Ş., E.G., Data Collection and Process: Z.Ç., Y.T.Ş., Analysis or Interpretation: Y.T.Ş., E.G., Z.Y., Literature Search: Z.Ç., Y.T.Ş., Writing: Z.Ç., Y.T.Ş

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References

1. World Health Organization (WHO). Coronavirus disease 2019 Situation Report 51 11th March 2020. World Heal Organ. 2020;2019(March):2633.
2. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. N Engl J Med 2020;382:727-33.
3. Zheng Z, Peng F, Xu B, Zhao J, Liu H, Peng J, et al. Risk factors of critical & mortal COVID-19 cases: A systematic literature review and meta-analysis. J Infect 2020;81:e16-25.
4. Lansbury L, Lim B, Baskaran V, Lim WS. Co-infections in people with COVID-19: a systematic review and meta-analysis. J Infect 2020;81:266-75.
5. Paget C, Trottein F. Mechanisms of Bacterial Superinfection Post-influenza: A Role for Unconventional T Cells. Front Immunol 2019;10:336.
6. Lai CC, Wang CY, Hsueh PR. Co-infections among patients with COVID-19: The need for combination therapy with non-anti-SARS-CoV-2 agents? J Microbiol Immunol Infect 2020;53:505-12.
7. Avan Mutlu T, Bozok T. Identification of Bacterial Agents Isolated from Lower Respiratory Samples of COVID-19 Patients and Investigation of their Antibacterial Resistance Patterns. Turk Mikrobiyol Cemiy Derg 2022;52:48-55.
8. Bardi T, Pintado V, Gomez-Rojo M, Escudero-Sanchez R, Azzam Lopez A, Diez-Remesal Y, et al. Nosocomial infections associated to COVID-19 in the intensive care unit: clinical characteristics and outcome. Eur J Clin Microbiol Infect Dis 2021;40:495-502.
9. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med 2020;8:475-81.
10. Ferrando C, Mellado-Artigas R, Gea A, Arruti E, Aldecoa C, Bordell A, et al. Patient characteristics, clinical course and factors associated to ICU mortality in critically ill patients infected with SARS-CoV-2 in Spain: A prospective, cohort, multicentre study. Rev Esp Anestesiol Reanim (Engl Ed) 2020;67:425-37.
11. Bellani G, Laffey JG, Pham T, Fan E, Brochard L, Esteban A, et al. Epidemiology, Patterns of Care, and Mortality for Patients With Acute Respiratory Distress Syndrome in Intensive Care Units in 50 Countries. JAMA 2016;315:788-800.
12. Kim D, Quinn J, Pinsky B, Shah NH, Brown I. Rates of Co-infection Between SARS-CoV-2 and Other Respiratory Pathogens. JAMA 2020;323:2085-6.
13. Contou D, Claudinon A, Pajot O, Micaëlo M, Longuet Flandre P, Dubert M, et al. Bacterial and viral co-infections in patients with severe SARS-CoV-2 pneumonia admitted to a French ICU. Ann Intensive Care 2020;10:119.
14. Cox MJ, Loman N, Bogaert D, O'Grady J. Co-infections: potentially lethal and unexplored in COVID-19. Lancet Microbe 2020;1:e11.
15. Tayşi MR, Yıldırım F. COVID-19 hastalarında ko-enfeksiyonlar ve sekonder enfeksiyonlar: sıklığı ve yönetimi. In: Ekicibaşı ME, editor. COVID-19 ve Sağlık Araştırmaları 1. İstanbul, Efe Akademi Yayınları; 2021. p. 86-95.
16. Lehmann CJ, Pho MT, Pitrak D, Ridgway JP, Pettit NN. Community-acquired Coinfection in Coronavirus Disease 2019: A Retrospective Observational Experience. Clin Infect Dis 2021;72:1450-2.
17. Klein EY, Monteforte B, Gupta A, Jiang W, May L, Hsieh YH, et al. The frequency of influenza and bacterial coinfection: a systematic review and meta-analysis. Influenza Other Respir Viruses 2016;10:394-403.
18. Garazzino S, Montagnani C, Donà D, Meini A, Felici E, Vergine G, et al. Multicentre Italian study of SARS-CoV-2 infection in children and adolescents, preliminary data as at 10 April 2020. Euro Surveill 2020;25:2000600.
19. Lim YK, Kweon OJ, Kim HR, Kim TH, Lee MK. Impact of bacterial and viral coinfection in community-acquired pneumonia in adults. Diagn Microbiol Infect Dis 2019;94:50-4.
20. Brockmeier SL, Loving CL, Nicholson TL, Palmer MV. Coinfection of pigs with porcine respiratory coronavirus and Bordetella bronchiseptica. Vet Microbiol 2008;128:36-47.
21. Martins-Filho PR, Tavares CSS, Santos VS. Factors associated with mortality in patients with COVID-19. A quantitative evidence synthesis of clinical and laboratory data. Eur J Intern Med 2020;76:97-9.