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The Relationship between Secondary Infections Causing Septic Shock and Procalcitonin, CRP, and Leukocyte Values and COVID-19 Vaccination in SARS-CoV-2-Related Intensive Care Patients

SARS-CoV-2 İlişkili Yoğun Bakım Hastalarında Septik Şoka Neden Olan Sekonder Enfeksiyonların Prokalsitonin, CRP, Lökosit ve COVİD-19 Aşılanma ile İlişkisi

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ABSTRACT

AIM: Secondary infections in patients with severe and critical COVID-19 have been seen to entail a higher mortality rate. However, COVID-19-related mortality declined with the development of vaccines. The purpose of this study was to examine the relationship between septic shock development associated with secondary infection and COVID-19 vaccination in patients with COVID-19 and to evaluate the agents of secondary infection and their distribution patterns. This research also evaluated the correlation between pre- and post-empiric antimicrobial therapy CRP, leukocyte, and procalcitonin values and clinical worsening.

MATERIAL AND METHOD: This retrospective, cross-sectional, single-center study was conducted with patients aged over 18, diagnosed with COVID-19 (confirmed by nasopharyngeal swab RT-PCR), and developing septic shock in association with secondary infection during their ICU stays.

RESULTS: The patients' median age was 69 years (23-95), and 54.60% were men. The 28-day mortality rate was 80.4% (n=225), and the median length of stay in the ICU was 18 days (3-106). Additional disease was present in 77.1% (n=216) of patients. Secondary infection developed in 76.10% (n=213) of the patients. The exitus rate was significantly higher among men (p=0.006). The exitus rate among the unvaccinated individuals, 85.1% (n=143), was significantly higher than in the vaccinated group (p=0.014). Mean pre- and post-empiric antimicrobial therapy procalcitonin and leukocyte values were significantly higher in the exitus cases than in the survivors (p<0.05). The total incidence of secondary infections, 83.3% (n=140), was significantly higher in the unvaccinated patient group than in the vaccinated patients (p<0.01).

CONCLUSION: The secondary infection rate were significantly high in the unvaccinated patient group admitted to the COVID-19 ICU. This represents a risk in terms of mortality. Although procalcitonin and leukocyte values indicated pre- and post-empiric antimicrobial therapy mortality, CRP was unable to do so.

Keywords: SARS-CoV-2, secondary infection, COVID19 vaccine, procalcitonin, leukocyte

ÖZET

AMAÇ: Şiddetli ve kritik COVID-19 hastalarda sekonder enfeksiyonların daha yüksek bir mortalite oranına yol açtığı görülmüştür. Bununla birlikte, aşıların geliştirilmesiyle COVID-19 ilişkili mortalite oranı azalmıştır. Bu çalışmada COVID-19 tanılı yoğun bakım hastalarında, sekonder enfeksiyona bağlı septik şok gelişimi ile COVID-19 aşılama arasında nasıl bir ilişki olduğunun araştırılması ve sekonder enfeksiyon etkenleri ve dağılım oranlarının değerlendirilmesi amaçlandı. Aynı zamanda bu hasta grubunda uygulanan ampirik antimikrobiyal tedavi öncesi ve sonrası CRP, prokalsitonin ve lökosit değerlerinin klinik kötüleşme ile korelasyonu değerlendirildi.

GEREÇ VE YÖNTEM: Çalışma COVID-19 enfeksiyon tanısı alan (nazofarengeal sürüntü örneği RT-PCR ile doğrulanan), yoğun bakım yatışı sırasında sekonder enfeksiyona bağlı septik şok gelişen, 18 yaş üstü hastalarda retrospektif, kesitsel ve tek merkezli olarak yapıldı.

BULGULAR: Hastaların medyan yaşı 69 (23-95) olup %54,6'sının erkek olduğu görülmüştür. 28 günlük mortalite oranı %80,4 (n=225) olarak bulunmuştur. Hastaların yoğun bakım medyan yatış süresi 18 (3-106) gün olarak hesaplandı. Hastaların %77,1'inde (n=216) ek hastalık mevcuttu. Hastaların %76,1'inde (n=213) sekonder enfeksiyon gelişmişti. Erkekler arasında mortalite oranı anlamlı derecede yüksek bulundu (p=0,006). Aşılanmamış hasta grubunda mortalite oranı (n=143, %85,1) aşılanmış gruba göre anlamlı derecede yüksek saptanmıştır (p=0,014). Ölen hasta grubunda ampirik antimikrobiyal tedavi öncesi ve sonrası ortalama prokalsitonin ve lökosit değerleri, sağ kalanlara göre anlamlı derecede yüksekti (p<0,05). Aşılanmamış hasta grubunda toplam sekonder enfeksiyon görülme oranı %83,3 (n=140) olup, aşı yapılan hasta grubuna göre anlamlı derecede yüksekti (p<0,01).

SONUÇ: COVID-19 yoğun bakım ünitesine kabul edilen aşılanmamış hasta grubunda sekonder enfeksiyon oranı önemli ölçüde yüksektir. Bu durum mortalite açısından bir risk teşkil etmektedir. Prokalsitonin ve lökosit değerleri ampirik antimikrobiyal tedavi öncesi ve sonrası mortaliteyi göstermesine rağmen CRP gösterememiştir.

Anahtar kelimeler: SARS-CoV-2, sekonder enfeksiyon, COVID-19 aşı, prokalsitonin, lökosit

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INTRODUCTION

Secondary infections added to COVID-19 infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) exacerbate the clinical condition and increase mortality (1,2). Secondary infections in patients with severe and critical COVID-19 have been seen to entail a higher mortality rate (2).
Several inflammatory markers have been shown to rise in COVID-19, a disease characterized by inflammatory damage in pulmonary endothelial tissues in particular. Monitoring these markers serves as a guide to the disease course (3). Research has predicted that among these markers, elevated C-reactive protein (CRP), leukocyte, and procalcitonin values may be associated with mortality in patients with COVID-19, and that mortality may be associated with hyperinflammation (4,5).
Immunization via vaccination significantly lowers COVID-19 disease-related mortality rates, thus significantly preventing transmission and a severe clinical course (6,7).
Although studies have investigated secondary infections developing in association with COVID-19, to the best of our knowledge none has addressed the type of relationship that exists between COVID-19 vaccination and secondary infection (8-11).
The purpose of this study was to examine the relationship between septic shock development associated with secondary infection and COVID-19 vaccination in patients with COVID-19 and to evaluate the agents of secondary infection and their distribution patterns.
This research also evaluated the correlation between pre- and post-empiric antimicrobial therapy CRP, leukocyte, and procalcitonin values and clinical worsening.

MATERIAL AND METHOD

Following receipt of the requisite permission from the Turkish Ministry of Health, approval for this study was granted by the Marmara University Medical Faculty clinical research ethical committee (decision no. 09.2021.16). The research involved patients hospitalized, intubated, and receiving mechanical ventilation in the Marmara University Pendik Education and Research Hospital tertiary COVID-19 intensive care unit (ICU) between 15.01.2022 and 15.07.2022. This retrospective, cross-sectional, single-center study was conducted with patients aged over 18, diagnosed with COVID-19 (confirmed by nasopharyngeal swab reverse transcriptase polymerase chain reaction (RT-PCR)), and developing septic shock in association with secondary infection during their ICU stays. Septic shock was diagnosed based on the criteria published by Singer et al. These criteria were lactate levels greater than 2 mmol/L without hypovolemia and vasopressor being required to keep mean arterial blood pressure above 65 mm/Hg.12 The culture results (peripheral blood, central venous catheter bloodstream, urine, endotracheal aspirate, pleural fluid, wound site (abscess or decubitus), and central venous catheter tip) from clinical specimens from patients admitted to the hospital for 48 hour or longer, and developing septic shock while being followed-up in the COVID-19 tertiary ICU and started on antimicrobial therapy were evaluated retrospectively. If the same microorganısm grew in blood and another culture (aspirate, urine, wound, or blood fluid), this was regarded as two distinct growths. The correlation between pre- and post-empiric antimicrobial therapy CRP, leukocyte, and procalcitonin values and clinical worsening, and the secondary infection agents and their distributions in SARS-CoV-2 patients were also investigated. The type of relationship existing between COVID-19 vaccination and the development of secondary infection was also examined.
Patients' demographic data, comorbidity status, 28-day mortality, and clinical and laboratory data (CRP, leukocyte, and procalcitonin values, RT-PCR, and culture results) on admission to the ICU were retrieved from the hospital's data management system. RT-PCR negative patients, those with unknown vaccination status, patients aged under 18 or hospitalized for less than 48 hours, patients with hematological disorders, nonintubated patients and pregnant women were excluded.
The study was performed in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. Due to the study's retrospective design, the voluntary informed consent form was waived. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist was used during the writing of the article (13).

Three hundred ninety-one patients were evaluated, of whom 111 were excluded for failing to meet the inclusion criteria. Two hundred eighty patients were thus finally enrolled in the study

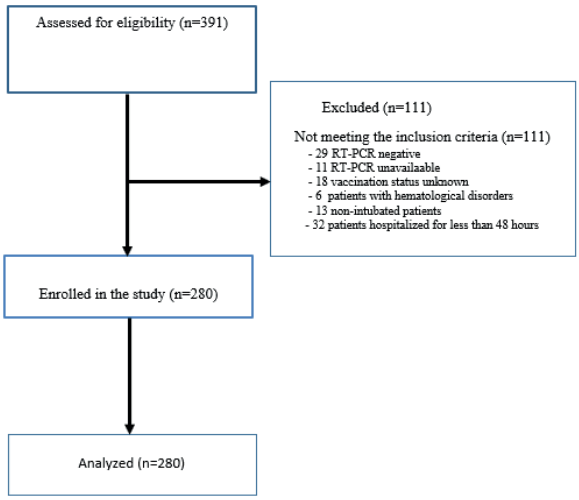

Figure 1. Study flow chart

Statistical analysis

The study data were analyzed using Statistical Package for the Social Sciences (SPSS) version 27 software. Quantitative variables were presented using descriptive methods such as mean, standard deviation, median, minimum and maximum values, and qualitative variables as frequency and percentage values. Normality of distribution was evaluated using the Shapiro Wilk test and box plot graphs. Student's t-test was applied to compare normally distributed quantitative data between the two groups. Non-normally distributed variables were compared between two groups using the Mann Whitney-U test, while Wilcoxon's Signed Rank test as applied for intragroup evaluations. Quantitative data were compared using the chi-square test, Yates Continuity Correction, Fisher's Exact test, and the Fisher Freeman Halton test. The results were evaluated at a 95% confidence interval, p values <0.05 being regarded as significant.

RESULTS

The demographic and clinical characteristics of the 280 ICU patients are shown in

Table 1. The Patients' Demographic and Clinical Characteristics

Gender; *n(%)*	Male	153 (54.6)
	Female	127 (45.4)
Age, years	*Mean±SD*	67.16±15.21
	Median (Min-Max)	69 (23-95)
Mortality; *n(%)*	Survived	55 (19.6)
	Exitus	225 (80.4)
Length of ICU stay, days	Mean±SD	22.71±18.51
	Median (Min-Max)	18 (3-106)
Vaccinated; *n(%)*	Yes	112 (40.0)
	No	168 (60.0)
Name of vaccine; *n(%)*	Inactive Covid-19 vaccine	87 (77.7)
	mRNA Covid-19 vaccine	14 (12.5)
	mRNA Covid-19 vaccine + Inactive Covid-19 vaccine	11 (9.8)
Number of doses; *n(%)*	1	33 (29.5)
	2	46 (41.1)
	≥ 3	33 (29.5)
Presence of additional disease; *n(%)*	Yes	216 (77.1)
	No	64 (22.9)
•Name of additional disease; *n(%)*	HT	131 (46.8)
	DM	88 (31.4)
	CAD – CHF	13 (4.6)
	Dementia	78 (27.9)

• More than one additional disease observed

Quantitative data were defined as mean and standard deviation (SD); qualitative data were defined as number (n) and percentage (%)

The patients' median age was 69 years (range 23-95), and 54.60% were men. The 28-day mortality rate was 80.4% (n=225), and the median length of stay in the ICU was 18 days (range 3-106).
Forty percent (n=112) of the patients had been vaccinated, of whom 77.7% (n=87) received inactive COVID-19 vaccine, 12.5% (n=14) mRNA COVID-19 vaccine, and 9.8% (n=11) inactive COVID-19 vaccine + mRNA COVID-19 vaccine. In addition, 29.5% (n=33) of patients had received one dose, 41.1% (n=46) two doses, and 29.5% (n=33) three or more doses.
Additional disease was present in 77.1% (n=216) of patients, hypertension in 46.8% (n=131) of those with additional diseases, diabetes mellitus (DM) in 31.4%, coronary artery disease (CAD) + congestive heart failure (CHF) in 4.6% (n=13), and dementia in 27.9% (n=78).
Secondary infection developed in 76.10% (n=213) of the patients. More specifically, 48.90% (n=137) of the secondary infections derived from peripheral blood, 23.60% (n=66) from central venous catheter (CVC) blood, 44.60% (n=125) from urine, 42.10% (n=118) from endotracheal aspirate, 3.60% (n=10) from the central venous catheter tip, 2.10% (n=6) from pleural fluid, and 5.00 (n=14) from the wound site

Table 2. Distributions of Secondary Infections

		n (%)
Presence of Secondary Infection	Yes	213 (76.10)
	No	67 (23.90)
Peripheral Circulation Infection	No	143 (51.10)
	Yes	137 (48.90)
	Coagulase-negative staphylococcus-MSSA	24 (17.5)
	Non-albicans candida spp	20 (14.6)
	Enterococcus spp	17 (12.4)
	Acinetobacter baumannii	29 (21.2)
	Stenotrophomonas	17 (12.4)
	Other Gram-positive	18 (13.1)
	Other Gram-negative	12 (8.8)
Central Venous Catheter Bloodstream Infection	No	214 (76.40)
	Yes	66 (23.60)
	Acinetobacter baumannii	17 (25.8)
	Non-albicans candida spp	14 (21.2)
	Stenotrophomonas	10 (15.2)
	Other Gram-positive	17 (25.8)
	Other Gram-negative	8 (12.1)
Urinary Tract Infection	No	155 (55.40)
	Yes	125 (44.60)
	E. coli	23 (18.4)
	Candida albicans	20 (16.0)
	Non-albicans Candida spp	32 (25.6)
	Klebsiella pneumoniae	8 (6.4)
	Enterococcus spp.	18 (14.4)
	Other Gram-negative	20 (16.0)
	Other Gram-positive	4 (3.2)
Respiratory Tract Infection	No	162 (57.90)
	Yes	118 (42.10)
	Acinetobacter baumannii	60 (50.8)
	MRSA	9 (7.6)
	Candida albicans	8 (6.8)
	Serratia marcescens	3 (2.5)
	Moraxella catarrhalis	2 (1.7)
	Stenotrophomonas maltophilia	8 (6.8)
	Pseudomonas aeruginosa	8 (6.8)
	Enterococcus faecium	3 (2.5)
	Corynebacterium striatum	3 (2.5)
	Streptococcus pneumoniae	3 (2.5)
	Klebsiella pneumoniae	8 (6.8)
	E. coli	3 (2.5)
Central Venous Catheter Tip Infection	No	270 (96.40)
	Yes	10 (3.60)
	Acinetobacter baumannii	6 (60.0)
	Candida parapsilosis	1 (10.0)
	Coagulase-negative staphylococcus	3 (3.6)
Pleural Fluid Infection	No	274 (97.90)
	Yes	6 (2.10)
	MSSA	3 (50.0)
	Klebsiella pneumoniae	1 (16.7)
	Methicillin-resistant Staphylococcus epidermidis	2 (33.3)
Wound Site Infection	No	266 (95.00)
	Yes	14 (5.00)
	Pseudomonas aeruginosa	4 (28.6)
	Candida albicans	6 (42.9)
	E. coli	1 (7.1)
	Enterococcus faecium	3 (21.4)

Data were described as count (n) and percentage (%)

Examination of contamination classes from peripheral blood revealed that 17.5% (n=24) were coagulase negative staphylococci (CNS) – methicillin resistant Staphylococcus aureus (MSSA), 14.6% (n=20) non-albicans Candida spp., 12.4% (n=17) Enterococcus spp., 21.25 (n=29) Acinetobacter baumannii, 12.4% (n=17) Stenotrophomonas maltophilia, 13.1% (n=18) other Gram positive pathogens, and 8.8% other Gram negative pathogens.
In terms of contamination classes from central venous catheter blood, 25.8% (n=17) were A. baumannii, 21.2% (n=14) non-albicans Candida spp., 15.2% (n=10) S. maltophilia, 25.8% (n=17) other Gram positive pathogens, and 12.1% (n=8) other Gram negative pathogens.
Examination of contamination classes from the urinary tract showed that 18.4% (n=23) E. coli, 16% (n=20) C. albicans, 25.6% (n=32) non-albicans Candida spp., 6.4% (n=8) K. pneumoniae, 14.4% (n=18) Enterococcus spp., 16% (n=20) other Gram negative pathogens, and 3.2% (n=4) other Gram positive pathogens.
In terms of contamination classes from endotracheal aspirate,

50.8% (n=60) were A. baumannii, 7.6% (n=9) MRSA, 6.8% (n=8) C. albicans, 2.5% (n=3) Serratia marcescens, 1.7% (n=2) Moraxella catarrhalis, 6.8% (n=8) S. maltophilia, 6.8% (n=8) P. aeruginosa, 2.5% (n=3) Corynebacterium striatum, 2.5% (n=3) S. pneumoniae, 2.5% (n=3) Enterococcus faecium, 6.8% (n=8) K. pneumoniae, and 2.5% (n=3) E. coli.

Examination of classes of contamination from the central venous catheter tip revealed 60% (n=6) A. baumannii, 10% (n=1) Candida parapsilosis, and 3.6% (n=3) CNS.

Examination of classes of contamination from pleural fluid revealed 50% (n=3) MSSA, 16.7% (n=1) K. pneumoniae, and 3.3% (n=2) methicillin-resistant Staphylococcus epidermidis (MRSE).

In terms of contamination classes from the wound site, 28.6% were (n=4) P. aeruginosa, 42.9% (n=6) C. albicans, 7.1% (n=1) E. coli, and 21.4% (n=3) E. faecium.

A comparison of descriptive characteristics according to mortality is shown in

Table 2. A Comparison of Descriptive Characteristics According to Mortality

		Mortality		p
		Surviving (n=55)	Exitus (n=225)	
Gender	Male	21 (13.7)	132 (86.3)	[a]0.006**
	Female	34 (26.8)	93 (73.2)	
Age	Mean±SD	63.62±17.14	68.03±14.62	[b]0.054
	Median (Min-Max)	62 (23-95)	70 (29-91)	
Length of ICU stay, days	Mean±SD	31.04±24.46	20.68±16.17	[b]0.004**
	Median (Min-Max)	27 (5-106)	18 (3-92)	
Vaccination	Yes	30 (26.8)	82 (73.2)	[a]0.014*
	No	25 (14.9)	143 (85.1)	
Additional disease	Yes	42 (19.4)	174 (80.6)	[a]0.878
	No	13 (20.3)	51 (79.7)	
Total Secondary Infection	Yes	41 (74,5)	172 (76,4)	[a]0,787
	No	14 (25,5)	53 (23,6)	
Peripheral Venous Catheter Bloodstream Infection		20 (36,4)	117 (52,0)	[a]0,038*
Central Venous Catheter Bloodstream Infection		15 (27,3)	51 (22,7)	[a]0,471
Urinary Tract Infection		27 (49,1)	98 (43,6)	[a]0,459
Respiratory Tract Infection		20 (36,4)	98 (43,6)	[a]0,333
Central Venous Catheter Tip Infection		3 (5,5)	7 (3,1)	[a]0,401
Pleural Fluid Infection		0	6 (2,7)	[a]0,221
Wound Site Infection		7 (12,7)	7 (3,1)	[a]0,001**

[a]Pearson's Chi-Square

[Illegible] Test

[b]Mann Whitney-U Test

**p<0.01 *p<0.05

The exitus rate was significantly higher among men (p=0.006). No statistically significant association was observed between age and mortality (p>0.05). The median length of ICU stay among the exitus patients was 18 (3-92) days, significantly lower than that in the surviving patients (p=0.004). The exitus rate among the unvaccinated individuals, 85.1% (n=143), was significantly higher than in the vaccinated group (p=0.014). No significant association was determined between mortality status and the presence of additional disease (p>0.05). No significant difference was detected between secondary infection rates in terms of mortality (p>0.05). Peripheral secondary infection rates differed significantly in terms of mortality (p<0.05); infection rates were significantly higher in peripheral specimens from exitus patients. No statistically significant difference was determined between the rates of secondary infection sites such as catheter, urinary tract infection, DTA, catheter tip, and pleural infections according to mortality (p>0.05). However, wound site infection rates differed significantly in terms of mortality (p<0.01), being significantly lower in the exitus patients.

A comparison of laboratory parameters according to mortality is shown in

Table 5. The Distribution of Secondary Infections According to Vaccination Status

		Unvaccinated	Vaccinated	P
		n (%)	n (%)	
Total Secondary Infection	No	28 (16.7)	39 (34.8)	0.001**
	Yes	140 (83.3)	73 (65.2)	
Peripheral Bloodstream Infection	No	73 (43.5)	70 (62.5)	0.002**
	Yes	95 (56.5)	42 (37.5)	
Central Venous Catheter Bloodstream Infection	No	123 (73.2)	91 (81.3)	0.121
	Yes	45 (26.8)	21 (18.8)	
Urinary Tract Infection	No	81 (48.2)	74 (66.1)	0.003**
	Yes	87 (51.8)	38 (33.9)	
Respiratory Tract Infection	No	91 (54.2)	71 (63.4)	0.126
	Yes	77 (45.8)	41 (36.6)	
Central Venous Catheter Tip Infection	No	159 (94.6)	111 (99.1)	0.055
	Yes	9 (5.4)	1 (0.9)	
Pleural Fluid Infection	No	162 (96.4)	112 (100)	0.084
	Yes	6 (3.6)	0 (0)	
Wound Site Infection	No	157 (93.5)	109 (97.3)	0.146
	Yes	11 (6.5)	3 (2.7)	

[a]Pearson's Chi-Square test **p<0.01

Data were described as count (n) and percentage (%)

Table 4. A Comparison of Laboratory Parameters According to Mortality

		Mortality		Total	p
		Surviving (n=55)	Exitus (n=225)		
Pre- empiric therapy procalcitonin µg/L	Mean±SD	1.62±1.94	7.04±27.17	5.97±24.46	[b]0.010*
	Median (Min-Max)	0.36 (0.06-5.84)	1.04 (0.04-352)	0.89 (0.04-352)	
Post-empiric therapy procalcitonin µg/L	Mean±SD	4.17±11.73	11.19±38.52	9.81±35.02	[b]0.001**
	Median (Min-Max)	0.78 (0.05-52.06)	1.51 (0.06-521.2)	1.21 (0.05-521.2)	
	p	[b]0.289	[b]0.001**		
Δ procalcitonin	Mean±SD	2.54±10.91	4.16±44.38		
Pre- empiric therapy leukocyte x10³/µL	Mean±SD	13.24±7.70	17.69±10.69	16.82±10.31	[b]0.005**
	Median (Min-Max)	12.90 (0.14-33.90)	15.30 (4.40-60.40)	15.20 (0.14-60.40)	
Post-empiric therapy leukocyte x10³/µL	Mean±SD	12.88±7.35	18.02±10.32	17.01 (10.01)	[b]0.001**
	Median (Min-Max)	12.40 (2.20-30.10)	15.70 (3.50-49.80)	14.9 (2.2-49.8)	
	p	[b]0.451	[b]0.436		
Δ leukocyte	Mean±SD	-0.56±5.21	0.52±8.08		
Pre-empiric therapy CRP mg/L	Mean±SD	141.62±97.29	150.84±111.97	149.03±109.14	[b]0.709
	Median (Min-Max)	100.29 (19.40-387.60)	119.48 (4.38-488.76)	113.80 (4.38-488.76)	
Post-empiric therapy CRP mg/L	Mean±SD	132.74±97.87	156.00±118.27	151.44±114.76)	[b]0.224
	Median (Min-Max)	85 (37.20-369.10)	128.20 (4-532)	124 (4-532)	
	p	[b]0.044*	[b]0.810		
Δ CRP	Mean±SD	-8.88±87.98	5.16±97.07		

[b]Mann Whitney-U test

[a]Wilcoxon Signed Ranks test

**p<0.01 *p<0.05

Mean pre- (p=0.010) and post-empiric antimicrobial therapy (p=0,001) procalcitonin values were significantly higher in the exitus cases than in the survivors. No significant difference was determined between pre- and post- post-empiric antimicrobial therapy procalcitonin values in the surviving cases (p>0.05). A statistically significant 4.16±44.38 unit increase was detected in post-post-empiric antimicrobial therapy procalcitonin values compared to before treatment in the exitus cases (p=0.001).

Pre- (p=0.005) and post-empiric antimicrobial therapy (p=0.001) leukocyte values were significantly higher in the exitus cases

compared to the survivors. No significant difference in pre- and post-treatment leukocyte values among the surviving cases (p>0.05). However a significant difference in leukocyte values was detected between pre- and post-empiric antimicrobial therapy in the exitus cases (p>0.05).
No significant difference was observed in pre- (p=0.709) and post-empiric antimicrobial therapy (p=0,224) CRP values according to mortality. A statistically significant decrease (mean -8.88±67.98 unit) in CRP values compared to pre-empiric antimicrobial therapy was determined in the surviving cases (p=0.044). No statistically significant difference in CRP measurements was observed post-treatment compared to pre-treatment in the exitus group (p>0.05).
The distribution of secondary infections according to vaccination status is shown in The total incidence of secondary infections was significantly higher in the unvaccinated patient group than in the vaccinated patients (p<0.01). The incidence of infection in specimens taken from peripheral blood and urine was also significantly higher in the unvaccinated group (p<0.01).
No statistically significant differences according to vaccination status were observed in secondary infection rates in pleural fluid, wound site, respiratory tract, central venous catheter tip, or central venous catheter blood specimens (p>0.05), although all were higher in the unvaccinated group.

DISCUSSION

The results of this study are important in terms of showing whether or not a relationship exists between COVID-19-related secondary infection in ICU patients and COVID-19 vaccination. It is also valuable in terms of showing the nature of the relationship between pre- and post-treatment CRP, procalcitonin and leukocyte values in patients who developed septic shock as a result of secondary infection and received empirical antimicrobial therapy.
The total secondary infection rate was significantly higher in the unvaccinated patient group compared to the vaccinated patients (p<0.01). Infection rates were significantly higher in specimens collected from peripheral blood and urine in the unvaccinated group (p<0.01).
The exitus rate in the unvaccinated patient group, 85.1%, was also significantly elevated (p=0.014). Mean leukocyte and procalcitonin values in the exitus patient group were significantly high both before and after empiric antimicrobial therapy (p<0.05).
Pulmonary epithelial cell damage resulting from COVID-19 produces a suitable environment for micro-organs to proliferate and settle (14,15). Secondary bacterial infection developing as a result of this is a potential risk factor for severity and complications (15).
In cases of COVID-19, bacteria can cause secondary infection with various virulence factors, such as outer membrane proteins, secretion systems, surface adhesions, glycoconjugate, and iron absorption activities (16).
Patients with severe SARS-CoV-2 infection exhibit higher bacterial and fungal secondary infection rates (12). SARS-CoV-2 particularly infects type 2 pneumocytes in the lungs in the early period and can lead to pneumonia capable of progressing to acute respiratory distress syndrome and creates a disposition to secondary bacterial infection by impairing the pulmonary immune response. SARS-CoV-2 infection induces an inflammatory response in the gastrointestinal tract, thus permitting pathogenic bacteria to enter the bloodstream from the intestinal lumen (17).
Viral infections create a predisposition to secondary bacterial infections using several strategies, which include the provision of a more suitable site for adhesion, modifying the immune response, and invasive infection through cell and tissue damage (18). The SARS-CoV-2 pandemic has been linked to secondary bacterial infections, and thus to poor prognosis and mortality (10,18,19).
The median age of the patients in this study was 69 years (23-95), and 54.60% were men. The exitus rate in men, 86.3%, was significantly higher than that among women (p=0.006). Additional disease was present in 77.1% (n=216) of patients. The most common additional disease, was HT in 46.8% (n=131). The mean length of stay in the ICU was 22.71 days. These results were consistent with those of other studies of COVID-19 patients developing secondary infection (20,21).
Secondary infection developed in 76.10% of our patients. This was higher than the secondary infection development rates in patients with COVID-19, ranging between 6.8% and 58.89%, reported in other studies (2,11,17,20-23). This may be ascribed to the presence of severe and critical cases in the ICU and to the likelihood of hospital-scquired (2).
A previous study of hospitalized COVID-19 patients reported mortality in 49.0% of those with secondary bacterial infection (11). While another study reported mortality in 37.2% of those developing secondary infection (20). The 28-day mortality rate in the present study was higher, at 80.4%. This high mortality rate may be explained by the entire study group consisting of patients with secondary infection and septic shock in intensive care.
Analysis showed that 48.90% of secondary infections were observed in peripheral blood, 23.60% in central venous catheter blood, 44.60% in urine, 42.10% in endotracheal aspirate, 3.60% in the central venous catheter tip, 2.10% in pleural fluid, and 5.00% in the wound site. The blood, urine, and endothelial aspirate pathogen growth rates in the current research were similar to those of other studies (2,20). The isolation of secondary infections mostly in blood and urine samples in COVID-19 patients with lung damage was attributed to the use of invasive methods such as urinary catheters, central venous catheters and peripheral venous catheters, which are frequently used in ICU patients.
Examination of peripheral bloodstream infections revealed that the three most common microorganism agents were A. baumannii at 21.2% (n=29), CNS-MSSA at 17.5% (n=24), and non-albicans Candida spp at 14.6% (n=20) non-albicans Candida spp. In terms of central venous catheter bloodstream infections, the three most common microorganisms were A. baumannii at 25.8% (n=17), other Gram positive bacteria at 25.8% (n=17), and non-albicans Candid spp at 21.2% (n=14). These findings included pathogens similar to those in Zhang et al., with primary Gram negative and Gram positive bacteria followed by fungal growths (2).
The four most commonly identified microorganisms in urinary tract infections non-albicans spp at 25.6% (n=32), E. coli at 18.4% (n=23), C. albicans at 16% (n=20), and other Gram negative microorganisms at 16% (n=20). These findings included pathogens similar to those in Zhang et al., with primary Gram negative growth followed by fungi and Gram positive growth (2).
The six most commonly identified microorganisms in respiratory tract infections were A. baumannii in 50.8% (n=60), S. aureus (MRSA) in 7.6% (n=9), C. albicans in 6.8% (n=8), S. maltophilia in 6.8% (n=8), P. aeruginosa in 68% (n=8), and K. pneumoniae in 6.8% (n=8). The most frequently detected pathogens in respiratory tract infections were thus Gram negative bacteria, followed by Gram positive bacteria and fungi. This pathogen distribution was consistent with previous research (2,15,19).
The most common pathogens agent in central venous catheter tip infections was A. baumannii in 60% (n=6), while MSSA was the most common in pleural fluid at 50% (n=3) and C. albicans in wound site infections at 42.9% (n=6). Previous studies have not specifically reported these infection rates (119. The present study is thus more instructive in this area. Due to the low numbers in these groups, subgroup analysis in the form of vaccinated and non-vaccinated could not be performed.
Forty percent (n=112) of the patients had been vaccinated. More specifically, 77.7% (n=87) had received inactive COVID-19 vaccine 12.5% (n=14) mRNA COVID-19 vaccine, and 9.8% (n=11) inactive COVID-19 vaccine + mRNA COVID-19 vaccine. The exitus rate among the non-vaccinated patient group was significantly high at 85.1% (p=0,014). This finding was compatible with the previous literature (6).
Mean procalcitonin levels pre- and post-empiric antimicrobial therapy were significantly higher in the exitus group (p<0.05). The mean 4.16±44.38 rise in procalcitonin levels after empiric antimicrobial therapy compared to pre-treatment was statistically significant in terms of mortality in the exitus patient group (p=0.001). Other studies have also shown that procalcitonin can predict mortality (24,25).
Mean leukocyte values before (p=0.005) and after (p=0.001) antimicrobial therapy were significantly elevated in the exitus patient group (p<0.05). These findings were compatible with the previous literature (26).
No significant difference was observed in CRP values before and after empiric antimicrobial therapy in the exitus patient group (p>0.05).
The total secondary infection rate and the infection rates in specimens from peripheral blood and urine were significantly elevated in the unvaccinated group (p<0.01).
No statistically significant difference was observed in the incidences of central venous catheter blood, endothelial aspirate, central

venous catheter tip, pleural fluid, or wound site infection depending on vaccination status (p>0.05), although the elevation in all these parameters in the unvaccinated group was noteworthy.
There are a number of limitations to this study. One is that viral infections were not included as agents of secondary infection. Other limitations include the study's single-center nature and relatively small sample size. However, it is important in showing the relationship between secondary infections and vaccination and inflammatory markers.
One particular strength of this study is that it distinguished between community- and hospital-acquired COVID-19 patients by selecting cases within 48 hours of hospitalization. Another strength is that all the cases involved intensive care and septic shock patients.

CONCLUSION

The total secondary infection rate and the infection rates in specimens from peripheral blood and urine were significantly high in the unvaccinated patient group admitted to the COVID-19 ICU. This represents a risk in terms of mortality. Although procalcitonin and leukocyte values indicated pre- and post-empiric antimicrobial therapy mortality, CRP was unable to do so. Further studies with large patient numbers and in which vaccinations have been completed are now needed.

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