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Could SARS-CoV-2 Sepsis Be a Different Phenotype of Sepsis? COVID-19 Pneumosepsis with Its Similarities and Differences

COVİD-19 Sepsisi Farklı Bir Sepsis Fenotipi Olabilir mi? Benzerlikleri ve Farklılıkları ile COVİD-19 Pnömosepsisi

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ABSTRACT *Objective:* By comparing viral sepsis caused by SARS CoV-2 with pneumosepsis caused by other pathogens, we aimed to compare the pathogen– host relationship, organ damage affecting the clinic, and similar and different features of the two types of sepsis.
Materials and Methods: A total of 414 patients diagnosed with critical COVID-19 between 2019 and 2021 and 303 pneumosepsis cases that met the diagnostic criteria for sepsis-3 between 2016 and 2019 admitted to the Anesthesiology and Reanimation Intensive Care Unit (ICU) were retrospectively screened. The patient's demographic data, mortality rates, length of stay in the intensive care unit, development of secondary organ dysfunction, presentation values of laboratory and mechanical ventilation, and changes within the 1-week follow-up were compared.
Results: The SOFA scores were significantly higher in the COVID-19 sepsis group at presentation (8.2±2.9 vs.7.2±3.7; p<0.0001) and during follow-up (8.9 ± 4.9 vs. 7.8 ± 3.7; p=0.002). The mean age of the patients was 65.4 ± 17.2 years in the non-COVID-19 sepsis group and 57.9 ± 17.1 years in the COVID-19 sepsis group (p<0.0001). The number of days on mechanical ventilation was significantly higher in the COVID-19 sepsis group (p=0.018). Mortality was detected in 299 patients (41.7%) in total, with no significant difference being observed between the two groups (p=0.592).
Conclusion: Despite the patient population having a lower mean age and fewer comorbidities, organ dysfunction was higher in COVID-19 sepsis patients during admission to the ICU and follow-up. While the pathogen causing sepsis can be brought under control with rapid diagnosis and appropriate antimicrobial treatment, organ damage cannot be controlled with appropriate antiviral treatment in COVID-19 sepsis. In COVID-19 sepsis, secondary organ damage may be more evident as a result of damage and immunomicrothrombosis, which causes high mortality and morbidity, the mechanism of which has not yet been fully elucidated.
Keywords: COVID-19 sepsis, SOFA score, pneumosepsis, organ damage

ÖZ *Amaç:* SARS CoV-2 etkenli viral sepsisi diğer patojenlere bağlı gelişen pnömosepsis ile karşılaştırarak; patojen-konak ilişkisi, kliniği etkileyen organ hasarı, iki sepsis türünün benzer ve farklı özelliklerinin karşılaştırılması amaçlandı.
Gereç ve Yöntem: 2019-2021 yılları arasında kritik COVID-19 tanısı alan toplam 414 hasta ve 2016-2019 yılları arasında Anesteziyoloji ve Reanimasyon Yoğun Bakım Ünitesi'ne başvuran ve sepsis-3 tanı kriterlerini karşılayan 303 pnömopsis vakası retrospektif olarak tarandı. Hastaların demografik verileri, mortalite oranları, yoğun bakımda kalış süreleri, sekonder organ disfonksiyonu gelişimi, laboratuvar ve mekanik ventilasyon başvuru değerleri ve bir haftalık takipteki değişimleri karşılaştırıldı.
Bulgular: SOFA skorları COVID-19 sepsis grubunda başvuruda (8,2±2,9'a karşı 7,2±3,7; p<0,0001) ve takipte (8,9 ± 4,9'a karşı 7,8 ± 3,7; p=0,002) anlamlı olarak yüksekti. Hastaların ortalama yaşı COVID-19 olmayan sepsis grubunda 65,4 ± 17,2, COVID-19 sepsis grubunda 57,9 ± 17,1 idi (p<0,0001). Mekanik ventilatörde geçirilen gün sayısı COVID-19 sepsis grubunda anlamlı olarak yüksekti (p=0,018). Toplam 299 hastada (%41,7) mortalite saptandı ve iki grup arasında anlamlı fark görülmedi (p=0,592).
Sonuç: Yaş ortalaması daha düşük ve komorbiditeleri daha az olan hasta popülasyonuna rağmen, Covid-19 sepsis hastalarında yoğun bakıma yatış ve takiplerinde organ disfonksiyonunun daha fazla olduğu görüldü. Hızlı tanı ve uygun antimikrobiyal tedavi ile sepsise neden olan patojen kontrol altına alınabilirken, Covid-19 sepsisinde uygun antiviral tedavi ile organ hasarı kontrol altına alınamamaktadır. Covid-19 sepsisinde mekanizması henüz tam olarak aydınlatılamayan yüksek mortalite ve morbiditeye neden olan hasar ve immünomikrotromboz sonucunda sekonder organ hasarı daha belirgin olabilmektedir.
Anahtar Kelimeler: COVID-19 sepsis, SOFA skor, pnömosepsis, organ hasarı

Introduction

Sepsis, one of the leading causes of infection-related mortality, is defined as a life-threatening organ dysfunction associated with an irregular host response due to infection (1). Sepsis agents are heterogeneous and can often develop due to bacterial, fungal, and viral pathogens (2). The most common infections in the intensive care unit (ICU) are those originating from the lungs (60%), abdomen (18%), and bloodstream (15%) (2). However, it has also recently been emphasized that respiratory viruses are often overlooked in sepsis and septic shock.

The coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) rapidly spread across the world, causing the death of millions of people, with 490 million cases and 6 million deaths being reported over two years (3, 4). Many clinicians consider severe COVID-19 as a viral sepsis caused by SARS-CoV-2 and use bacterial sepsis as a prototype to better understand its pathogenesis (5, 6). Although many studies have been conducted on sepsis, a heterogeneous syndrome, there is only limited research comparing COVID-19 sepsis and pneumosepsis due to other pathogens (non-COVID-19 sepsis) (7). In this study, we retrospectively investigated clinical changes in the host caused by COVID-19-related sepsis and other non-COVID-19 pneumosepsis agents with a primary focus on infection in the lungs, evaluated the data recorded during the intensive care follow-up, and compared the similarities and differences between these two groups.

Materials and Methods

Study Design and Patient Population

After receiving approval from the local ethics committee (2021/489), the patients followed up in the ICU of Bakirkoy Dr. Sadi Konuk Training and Research Hospital between April 2019 and May 2021 with a COVID-19 and sepsis diagnosis and those that met the diagnostic criteria for sepsis-3 between October 2016 and January 2019 were retrospectively screened.

According to the diagnosis guidelines of the Turkish Ministry of Health COVID-19 Scientific Committee, patients who were found to be positive for COVID-19 in the real-time polymerase chain react test and met the criteria of the World Health Organization (WHO) were considered to have COVID-19. The diagnosis of sepsis was using the sepsis-3 electronic early warning system [an increase of 2 or more points in the sequential organ failure assessment (SOFA) score] and the presence of clinical suspicion of infection.

Patients with a diagnosis of non-COVID-19 pneumosepsis followed up in ICU and met the diagnostic criteria for sepsis-3 and those admitted to ICU due to severe COVID-19 according to the WHO guidelines were included in the study. Patients who had an ICU follow-up of fewer than 24 hours, cases in which acute physiology and chronic health evaluation APACHE II and SOFA scores were not calculated, pregnant women, patients with missing data, those with an autoimmune disease or history of immunomodulatory treatment, those with secondary infections during the follow-up, postoperative patients, and those younger than 18 years were excluded.

The patients' demographic and laboratory parameters were obtained at the time of admission to the ICU, and the mean laboratory and hemodynamic parameters were instantly recorded during the seven-day follow-up period. The acceptance values of prognostic scores, such as APACHE II and SOFA, as well as changes in the seventh-day SOFA scores, were evaluated. For the calculation of the SOFA score, respiratory, hepatic, hematological, neurological, renal, and cardiovascular system evaluations were made. Each organ system score was evaluated separately, and organ dysfunctions were separately compared between the two sepsis groups. The SOFA parameters were obtained using structured query language queries. In addition, mortality rates, length of ICU stay, number of days without mechanical ventilation, and continuous venovenous hemodiafiltration requirement were compared between the two groups. The follow-up period was determined as seven days in both groups. The data of the patients were recorded using the electronic clinical decision support system (ImdSoftMetavision/QlinICU).

Due to the pandemic condition, verbal informed consent was obtained from the relatives of the patients included in the study. This study was not financially supported.

Statistical Analysis

The Shapiro-Wilk test was used to evaluate the normality of the distribution of numerical data. The independent-sample t-test was conducted to compare normally distributed numerical data, and the Mann-Whitney U test was for comparisons between two groups in terms of data that did not have a normal distribution. The Pearson chi-square or Fisher exact test was used to examining the difference between categorical data. The descriptive statistics of the data were expressed as mean ± standard deviation for normally distributed numerical variables, median (interquartile range) for non-normally distributed numerical variables, and frequency (percentage) for categorical variables. All statistical analyses were performed and reported using IBM SPSS Statistics v. 22.0 software at α=0.05 significance and 95% confidence levels.

Results

After applying the inclusion and exclusion criteria, 717 patients were included in the study. There were 303 (42.3%) patients in the non-COVID-19 sepsis group (Group 1) and 414 (57.5%) patients in the COVID-19 sepsis group (Group 2). The mean age was 65.4 ± 17.2 years in Group 1 and 57.9 ± 17.1 years in Group 2, indicating a significant difference between the two groups (p<0.0001). Body mass index was significantly lower in Group 1 (p=0.005). The demographic data of the groups are shown in Table 1. Comorbidities were detected in 273 (90%) patients in Group 1 and 301 (72.7%) patients in Group 2, and there was a significant difference was detected between the two groups (p<0.0001). Table 2 presents the comorbidities of the groups.

When the admission hemogram parameters were examined, the white blood cell (WBC) count was significantly higher in Group 1 (p<0.0001), and the hemoglobin and hematocrit levels were significantly higher in Group 2 (p<0.0001 and p=0.001, respectively). There was also a significant difference between the two groups in terms of the neutrophil count (p<0.0001).

The admission biochemistry sodium values were found to be significantly higher in Group 1 (p=0.008). Group 2 had significantly higher glucose, lactate dehydrogenase, albumin, triglyceride, and C-reactive protein (CRP) values (p<0.0001, p=0.006, p=0.013, p=0.003, and p=0.001, respectively). In Group 1, significantly higher creatine kinase and procalcitonin levels were detected (p=0.049 and p<0.0001, respectively). The international normalized ratio (INR) was significantly higher in Group 1, and the fibrinogen value was significantly

Table 1. Demographic data

Parameters (mean ± SD)	Total n=717	Non-COVID-19 sepsis n = 303 (42.3%)	COVID-19 sepsis n = 414 (57.5%)	p
Age (year)	**61.1 ± 17.5**	65.4 ± 17.2	57.9 ± 17.1	**<0.0001**
Gender, n (%)				
Female	300 (41.8)	135 (44.6)	165 (39.4)	
Male	417 (58.2)	168 (55.4)	249 (60.1)	0.221
BMI (kg/m^2)	27.5 ± 6.2	26.7 ± 6.9	28 ± 5.6	**0.005**

SD: standard deviation; BMI: body mass index

Table 2. Comorbidities

Parameters n (%)	Total n = 717	Non-COVID-19 sepsis n = 303 (42.3)	COVID-19 sepsis n = 414 (57.5)	p
Comorbidity	574 (80)	273 (90)	301 (72.7)	**<0.0001**
Hypertension	319 (44.4)	138 (45.5)	181 (43.7)	0.594
Diabetes mellitus	217 (30.2)	77 (25.4)	140 (33.8)	**0.021**
COPD	130 (18.1)	70 (23.1)	60 (14.4)	**0.003**
CRF	111 (15.4)	58 (19.1)	53 (12.8)	**0.021**
Hepatitis	26 (3.6)	9 (2.9)	17 (4.1)	0.545
CAD	200 (27.8)	103 (33.9)	97 (23.4)	**0.002**
CVE	84 (11.7)	61 (20.1)	23 (5.5)	**<0.0001**
Dementia	38 (5.2)	30 (9.9)	8 (1.9)	**<0.0001**
Malignancy	118 (16.4)	68 (22.4)	50 (12)	**<0.0001**
Other	93 (12.9)	45 (14.8)	48 (11.5)	**0.215**

COPD: chronic obstructive pulmonary disease, CRF: chronic renal failure, CAD: coronary artery disease, CVE: cerebrovascular event higher in Group 2 (p=0.002 and p<0.0001, respectively). The admission values of the laboratory parameters and comparisons between the two groups are shown in Table 3.

The admission data on the mechanical ventilation parameters are given in Table 4.

According to the comparison of the first week averages of the hemodynamic parameters, Group 1 had a significantly higher mean heart rate and significantly lower systolic, diastolic, and mean blood pressure values. The amounts of all vasopressor and inotropic agents, such as adrenaline, noradrenaline, dopamine, and dobutamine used during the first-week follow-up were found to be significantly higher in Group 1 (p<0.0001, p<0.0001, p<0.0001, and p=0.047, respectively). No significant difference was observed between the two groups in relation to the APACHE II admission and mortality values. Continuous renal replacement therapy (CRRT) requirement was significantly higher in Group 2 (p<0.0001). There was no significant difference between the two groups in terms of the length of ICU stay. When the duration of mechanical ventilation was compared, the median value was 6.6 (11.8) days in Group 1 and 8.3 (10.3) days in Group 2, with a significantly higher value being observed in the latter (p= 0.018). There was no significant difference in the mortality rates of the two groups. Mortality was detected in a total of 299 patients (41.7%) (Table 5).

In parallel to the admission parameters, the comparison of the first-week averages of the hemogram parameters also revealed that the WBC and neutrophil values were significantly higher in Group 1 (p<0.0001 for both), and the mean hemoglobin and hematocrit values were significantly higher in Group 2 (p<0.0001 and p=0.001, respectively). The mean platelet level was significantly higher in Group 2, and the neutrophil/lymphocyte ratio was significantly higher in Group 1 (p=0.002 and p=0.008, respectively), despite no significant difference at the time of ICU admission. Similar to the evaluation at admission, the mean lymphocyte count was significantly higher in Group 1 (p=0.008).

As in the evaluation of laboratory parameters at ICU admission, the mean glucose value over the seven-day

Table 3. Comparison of the ICU admission parameters between the groups

Parameters (mean ± SD)	Total n=717	Non-COVID-19 sepsis n = 303 (42.3%)	COVID-19 sepsis n = 414 (57.5%)	p
Hemogram				
WBC (10^3/uL)	16.4 ± 8.1	19.3 ± 6.5	15.5 ± 8.3	**<0.0001**
Hemoglobin (g/dL)	10.9 ± 2.2	10.2 ± 1.9	11.1 ± 2.2	**<0.0001***
Hematocrit (%)	34.1 ± 6.9	32.2 ± 6.2	34.8 ± 7	**0.001**
Platelet+ (10^3/uL)	226.5 (137.7)	213.5 (145)	228.5 (141.6)	0.234*
Lymphocyte+ (10^3/uL)	0.8 (0.7)	0.9 (0.8)	0.8 (0.7)	**0.002***
Neutrophil (10^3/uL)	14.5 ± 7.5	16.9 ± 6.1	13.7 ± 7.8	**<0.0001**
Neutrophil/lymphocyte+	15.3 (15)	16.8 (18)	14.7 (15)	0.397*
Biochemical				
Glucose+ (mg/dL)	175.5 (84.8)	159 (81)	186 (86.6)	**<0.0001***
Sodium (mmol/L)	139.4 ± 6.8	140.7 ± 6.5	138.9 ± 6.9	**0.008**
LDH+ (IU/L)	517 (382.5)	436.2 (401.7)	540 (373.2)	**0.006***
Amylase+ (IU/L)	81.7 (104.2)	82 (87)	81.5 (106.5)	0.877*
Lipase+ (IU/L)	26.5 (58.3)	23.7 (45.6)	27.5 (58.2)	0.067*
Ferritin+ (mg/dL)	752.3 (1156.7)	566.5 (1407.6)	752.3 (1137.2)	0.522*
CK+ (IU/L)	132 (258)	210.7 (265.7)	124 (247)	**0.049***
Albumin (g/dL)	2.7 ± 0.4	2.6 ± 0.5	2.8 ± 0.4	**0.013**
Procalcitonin+ (ng/dL)	3.2 (6.1)	5.4 (14.2)	1.1 (4.4)	**<0.0001***
CRP+ (mg/dL)	120 (152)	86.3 (130.2)	132 (148)	**0.001***

ICU: intensive care unit; SD: standard deviation; WBC: white blood cell; LDH: lactate dehydrogenase; CK: creatine kinase; CRP: C-reactive protein
*Values presented as median (interquartile range) and comparisons made using the Mann-Whitney U test.

follow-up was significantly higher in Group 2 ($p<0.0001$). When the averages of the electrolyte parameters were examined, Group 1 had significantly higher sodium and chlorine values, and Group 2 had a significantly higher calcium value ($p<0.0001$, $p=0.002$, and $p=0.006$, respectively). Comparing the first-week averages of bilirubin,

Table 4. Comparison of the mechanical parameters at ICU admission

Parameters (mean ± SD)	Total n = 717	Non-COVID-19 sepsis n = 303 (42.3%)	COVID-19 sepsis n = 414 (57.5%)	p
Mechanical ventilation				
$ETCO_2$ (mmHg)	50.7 ± 16	47.2 ± 15.6	52.3 ± 16	**0.033**
Horowitz+ (PaO_2/FiO_2)	174 (125)	168.5 (148.6)	175.6 (110.4)	0.543*
RR_{set} (min)	14.2 ± 1.9	13.9 ± 2.1	14.4 ± 1.7	**0.001**
PEEP (cmH_2O)	8.2 ± 2	7.8 ± 2	8.6 ± 1.8	**<0.0001**
P_{mean} (cmH_2O)	14.3 ± 3.1	13.5 ± 3	15 ± 3	**<0.0001**
Tidal volume/ideal weight	6.9 ± 1.4	7.3 ± 1.6	6.6 ± 1.2	**<0.0001**
P_{peak} (cmH_2O)	24.1 ± 4.7	22.8 ± 4.8	25 ± 4.4	**<0.0001**
$P_{plateau}$ (cmH_2O)	24.1 ± 4.4	24.4 ± 4.2	23.9 ± 4.5	0.700
WOB (j/L)	1.2 ± 0.2	1.1 ± 0.2	1.2 ± 0.2	**0.001**
I/E	0.6 ± 0.2	0.5 ± 0.2	0.7 ± 0.2	**<0.0001**
DP (cm H_2O)	15.2 ± 3.6	14.8 ± 3.5	15.5 ± 3.6	**0.018**

ICU: intensive care unit; SD: standard deviation; PaO_2: partial arterial oxygen pressure; $ETCO_2$: end-tidal carbon dioxide; FiO_2: fraction of inspired oxygen; RR_{set}: set respiratory rate; PEEP: positive end-expiratory pressure; P_{mean}: mean airway pressure; P_{peak}: peak airway pressure; $P_{plateau}$: plateau airway pressure; WOB: work of breathing; I/E: inspiratory/expiratory ratio; DP: driving pressure
*Comparisons made using the Mann-Whitney U test

Table 5. Comparison of the first-week averages of the hemodynamic parameters

Parameters (mean ± SD)	Total n = 717	Non-COVID-19 sepsis n = 303 (42.3%)	COVID-19 sepsis n = 414 (57.5%)	p
Peak heart rate (beat/min)	90.2 ± 19.8	95 ± 21.8	86.6 ± 17.4	**<0.0001**
ABP_{sys} (mmHg)	118.6 ± 17.5	116.2 ± 22.4	119.9 ± 14	**0.026**
ABP_{dias} (mmHg)	59 ± 10.9	56.7 ± 13.3	60.3 ± 9.1	**<0.0001**
ABP_{mean} (mmHg)	78.1 ± 11.6	75.5 ± 14.9	79.6 ± 9.1	**<0.0001**
Adrenalin+	20 (17.3)	30.5 (37.6)	14.2 (9.4)	**<0.0001***
Noradrenalin+	45 (49.3)	78.9 (63.5)	35.2 (43.5)	**<0.0001***
Dopamine+	1394.6 (1194.4)	2000 (2147)	1128.4 (738.6)	**<0.0001***
Dobutamine+	675 (1266)	1150 (3057)	375 (250)	**0.047***
Urine volume (cc/day)	1292.4 (1228.2)	1440 (1373)	1254.6 (1077)	**0.037***
APACHE II, admission+	22 (10)	22 (11)	22 (10)	0.449*
APACHE II, mortality+	42 (34)	42 (37)	42 (34)	0.448*
CRRT	199 (27.8)	40 (13.2)	159 (38.4)	**<0.0001**
ICU stay+(day)	9.9 (13)	9.7 (15.3)	10 (11.8)	**0.823***
Number of days on MV+	7.5 (11.1)	6.6 (11.8)	8.3 (10.3)	**0.018***
Number of days without MV+	1.2 (3.6)	1.7 (4)	1.1 (3.4)	**0.001***
Mortality, n (%)	299 (41.7)	130 (42.9)	169 (40.8)	0.592*

ABP_{sys}: systolic arterial blood pressure; ABP_{dias}: diastolic arterial blood pressure; ABP_{mean}: mean arterial blood pressure; APACHE: acute physiology and chronic health evaluation; CRRT: continuous renal replacement therapy; ICU: intensive care unit; MV: mechanical ventilation
*Comparisons made using the Mann-Whitney U test. Values presented as median (interquartile range)

Table 6. Comparison of the first-week averages of the laboratory parameters

Parameters (mean ± SD)	Total n = 717	Non-COVID-19 sepsis n = 303 (42.3%)	COVID-19 sepsis n = 414 (57.5%)	p
Hemogram				
WBC (10^3/uL)	16.1 ± 7.9	19.5 ± 7.4	15 ± 7.7	**<0.0001***
Hemoglobin (g/dL)	10.5 ± 2	9.9 ± 1.9	10.7 ± 2	**<0.0001**
Hematocrit (%)	32 ± 6.3	31.4 ± 6.2	33.5 ± 6.3	**0.001**
Platelet$^+$ (10^3/uL)	226.7 (154.3)	200 (155.6)	231.3 (162.8)	**0.002***
Lymphocyte$^+$ (10^3/uL)	0.9 (0.7)	0.9 (0.8)	0.8 (0.7)	**0.008***
Lymphocyte percentage$^+$	6.9 (5.8)	5.9 (5.6)	7.3 (5.9)	**0.004***
Neutrophil (10^3/uL)	14.9 ± 7.1	17 ± 6.8	12.9 ± 6.9	**<0.0001**
Neutrophil/lymphocyte$^+$	13.3 (13.4)	16.6 (15.6)	12.3 (12.4)	**<0.0001***
Biochemical				
Glucose$^+$ (mg/dL)	164 (58)	148.8 (59.6)	169.7 (58.3)	**<0.0001***
Calcium (mg/dL)	8.1 ± 0.6	8 ± 0.7	8.2 ± 0.5	**0.006**
Sodium (mmol/L)	138.9 ± 5.7	140.7 ± 6.4	138.2 ± 5.2	**<0.0001**
Potassium (mmol/L)	4.3 ± 0.6	4.3 ± 0.7	4.3 ± 0.5	0.504
Chloride (mmol/L)	101.1 ± 5.5	102.6 ± 6.5	100.6 ± 5	**0.002**
Creatinine$^+$ (mg/dL)	1.1 (1.3)	1.3 (1.2)	1 (1.3)	0.171*
Bilirubin$^+$(mg/dL)	0.7 (1)	0.7 (0.8)	0.8 (1.1)	0.002*
AST$^+$ (IU/L)	50.4 (75.1)	44 (86.6)	55.8 (71.7)	**0.035***
ALT$^+$ (IU/L)	37.2 (73.2)	25.4 (56.7)	45.7 (77.8)	**<0.0001***
LDH$^+$ (IU/L)	466.8 (375)	439 (440)	474.8 (364.1)	0.083*
Amylase$^+$ (IU/L)	82.5 (104.9)	73 (91)	87 (112.7)	0.173*
Lipase$^+$ (IU/L)	32 (68.8)	25.5 (62.6)	36.5 (68.8)	**0.009***
Ferritin$^+$ (g/L)	740 (1304.2)	823.4 (1646)	696.6 (1301)	0.896*
CK$^+$ (IU/L)	192 (437)	181 (414)	196.5 (438.2)	0.408*
Albumin (g/dL)	2.6 ± 0.4	2.5 ± 0.5	2.6 ± 0.3	0.077
Triglyceride$^+$ (mg/dL)	164.5 (141.2)	131 (115.3)	190 (152.1)	**0.002***
LDL$^+$ (mg/dL)	77 (64.7)	79.1 (87)	74 (61.7)	0.988*
HDL$^+$ (mg/dL)	26 (17.4)	25 (29)	27 (14)	0.757*
Cholesterol$^+$ (mg/dL)	140.5 (63)	125 (55)	144.2 (55.9)	**0.028***
CRP$^+$ (mg/dL)	105.4 (122.2)	79.5 (119)	120.7 (113.1)	**<0.0001***
Procalcitonin$^+$ (ng/mL)	3 (6.4)	5.4 (14.7)	1.3 (4.7)	**<0.0001***
Coagulation				
aPTT$^+$(sn)	40.2 (16.5)	40.8 (18.4)	39.9 (15.3)	0.943*
PT$^+$(sn)	1.2 (0.3)	1.2 (0.3)	1.2 (0.2)	0.163*
INR$^+$	1.2 (0.3)	1.3 (0.4)	1.2 (0.2)	**0.002***
Fibrinogen$^+$ (mg/dL)	455 (267.2)	392 (343.7)	491.3 (260.3)	**0.011***

SD: standard deviation; WBC: white blood cell; AST: aspartate aminotransferase; ALT: alanine aminotransferase; LDH: lactate dehydrogenase; CK: creatine kinase, LDL: low-density lipoprotein; HDL: high-density lipoprotein; CRP: C-reactive protein; aPTT: active partial thromboplastin time; PT: prothrombin time; INR: international normalized ratio
*Comparisons made using the Mann-Whitney U test. Values presented as median (interquartile range)

aspartate transaminase (AST), and alanine aminotransferase (ALT), which did not differ significantly at the time of ICU admission, significantly higher values were found in Group 2 ($p=0.002$, $p=0.035$, and $p<0.0001$, respectively). There was also a significant difference between the two groups in terms of the mean values of the lipase parameters, which did not show a significant difference at ICU admission ($p=0.009$). The comparison of the mean values of the lipid profile is shown in Table 6. Similar to the ICU admission parameters, the follow-up CRP was significantly higher in Group 2 and the procalcitonin valuewas significantly higher in Group 1 ($p<0.0001$ for both).

When the averages of the coagulation parameters were compared, the INR and d-dimer values were significantly higher in Group 1, and the fibrinogen value was significantly higher in Group 2 ($p=0.002$, 0.017, and 0.011, respectively). These data are detailed in Table 6.

Among the mean blood gas parameters, the lactate value was significantly higher in Group 2 ($p=0.028$). In addition, significant differences were observed in the set respiratory rate (RRset), positive end-expiratory pressure (PEEP), Pmean, minute ventilation, respiratory index, Ppeak, work of breathing (WOB), inspiratory/expiratory ratio (I/E), and driving pressure (DP) values. When the first-week averages of the RRset parameters were compared, significantly higher values were detected in Group 2 ($p=0.015$). The PEEP value was determined as 7.8 ± 2 mm H2O in Group 1 and 8.3 ± 1.6 mm H2O in Group 2, showing a significantly higher result for Group 2 ($p<0.0001$). The Pmean value was 13.5 ± 2.9 mm H2O in Group 1 and 14.9 ± 2.8 mm H2O in Group 2, indicating a significantly higher value in the latter ($p<0.0001$). When the first-week averages of the I/E values were compared, the result was significantly higher in Group 2 ($p<0.0001$). The DP values of Groups 1 and 2 were found to be 15 ± 3.3 and 15.6 ± 3.4 mm H2O in Group 2, respectively, and the difference between the group was statistically significant ($p=0.018$) (Table 7).

Table 7. Comparison of the first-week averages of blood gas and mechanical ventilation parameters

Parameters (mean ± SD)	Total n = 717	Non-COVID-19 sepsis n = 303 (42.3%)	COVID-19 sepsis n = 414 (57.5%)	p
Blood gas				
Lactate^{+}(mmol/L)	1.6 (1)	1.5 (1.1)	1.7 (0.9)	**0.028***
PaO_2^{+}	92.1 (31.7)	90.3 (49.3)	92.2 (24.5)	0.170*
SO_2	94.4 ± 4.6	94.4 ± 5.5	94.4 ± 3.9	0.931
Mechanical ventilation				
$ETCO_2$ (mmHg)	49.9 ± 13.4	49 ± 15.3	50.2 ± 12.7	0.480
FiO_2 (%)	53.3 ± 12.9	52.6 ± 13	53.8 ± 12.8	0.229
Horowitz^{+} (PaO_2/FiO_2)	187.2 (113.2)	183.7 (148.9)	187.6 (101.9)	0.338*
RR_{set} (min)	14.3 ± 1.9	14.1 ± 2.2	14.5 ± 1.6	**0.015**
PEEP (mm H_2O)	8.1 ± 1.8	7.8 ± 2	8.3 ± 1.6	**<0.0001**
P_{mean} (mm H_2O)	14.3 ± 2.9	13.5 ± 2.9	14.9 ± 2.8	**<0.0001**
MVE (L)	7.2 ± 1.6	7.4 ± 2	7 ± 1.2	**0.001**
Tidal volume/ideal weight	7 ± 1.3	7.4 ± 1.5	6.7 ±1.1	**<0.0001**
RI^{+}	9.6 (4.6)	13.2 (10)	9.2 (2.9)	**<0.0001***
P_{peak} (mm H_2O)	24.1 ± 4.5	23.2 ± 4.7	24.8 ± 4.3	**<0.0001**
$P_{plateau}$ (mm H_2O)	23.9 ± 4.1	23.6 ± 3.7	24 ± 4.2	0.711
WOB (j/L)	1.2 ± 0.2	1.1 ± 0.2	1.2 ± 0.2	**<0.0001**
Flow	0.4 ± 0.1	0.4 ± 0.1	0.4 ± 0.1	0.158
I/E	0.6 ± 0.2	0.6 ± 0.2	0.7 ± 0.2	**<0.0001**
DP (mm H_2O)	15.3 ± 3.4	15 ± 3.3	15.6 ± 3.4	**0.018**

SD: standard deviation; PaO_2: partial arterial oxygen pressure; SO_2: oxygen saturation; $ETCO_2$: end-tidal carbon dioxide; FiO_2: fraction of inspired oxygen; RR_{set}: set respiratory rate; PEEP: positive end-expiratory pressure; P_{mean}: mean airway pressure; MVE: minute ventilation; RI: respiratory index; P_{peak}: peak airway pressure; $P_{plateau}$: plateau airway pressure; WOB: work of breathing; I/E: inspiratory/expiratory ratio; DP: driving pressure
*Comparisons made using the Mann-Whitney U test. Values presented as median (interquartile range)

The mean SOFA score at the time of ICU admission was 8.2 ± 2.9 in Group 2 and 7.2 ± 3.7 in Group 1, indicating a significant difference (p<0.0001). The hematological and cardiovascular parameters were significantly higher in Group 1, and the Glasgow Coma Scale (GCS) score was significantly higher in Group 2 (p<0.0001, p<0.0001, and p=0.001, respectively).

When the follow-up SOFA scores were compared, there was a significant increase in Group 2 (p=0.002). Group 2 also had significantly higher seven-week averages of hepatic system scores (p=0.024) and neurological, renal, and cardiovascular scores (p=0.005, p=0.014, and p<0.0001, respectively) (Table 8).

Discussion

COVID-19 disease, caused by SARS-CoV-2, is a multisystemic syndrome that emerged in December 2019 and has, since then, had serious consequences on a global scale related to the development of acute respiratory distress syndrome (ARDS) and multiorgan failure, especially the lungs (3). In addition to meeting the criteria for sepsis-3 and being associated with high mortality rates, clinical findings specific to COVID-19 sepsis suggest that this disease may be a different phenotype of sepsis (8).

In our study, when the hemodynamic parameters were compared between the two groups, it was determined that vasoplegia was more pronounced at ICU admission, and the need for inotropic and vasopressor agents was higher during the follow-up in the non-COVID-19 sepsis group, which is consistent with the literature (7-9). The vasopressor requirement in COVID-19 patients may be associated with stronger sedation, high airway pressures, right ventricular dysfunction, and secondary infections rather than cytokine storm and sepsis-induced vasodilation (10).

The neutrophil and procalcitonin levels being significantly higher in the non-COVID-19 sepsis group of our study is consistent with the characteristics of bacterial infections. Although lymphocytes, which are cellular immunity elements, were found to be at a low level in both sepsis groups, lymphopenia was significantly more pronounced in the COVID-19 sepsis group during admission and follow-up, which is similar to the studies in the literature comparing bacterial and COVID-19 sepsis cases (11, 12). When compared to other sepsis agents, SARS-CoV-2 sepsis presents with milder hyperinflammation, T lymphocyte suppression and insufficient adaptive immune response, extensive macrophage infiltration in the lungs, and early fibrosis, indicating the presence of different phenotypic sepsis specific to this infection. Inappropriate and high-

Table 8. SOFA and SOFA component scores evaluated at ICU admission and on the seventh day

Parameters (mean ± SD)	Total n=717	Non-COVID-19 sepsis n = 303 (42.3%)	COVID-19 sepsis n = 414 (57.5%)	p
SOFA, admission	7.8 ± 3.3	7.2 ± 3.7	8.2 ± 2.9	**<0.0001**
Respiratory (Horowitz)	2.7 ± 0.9	2.7 ± 0.9	2.7 ± 1	0.995
Hepatic (bilirubin+)	0 (0)	0 (0)	0 (0)	0.509*
Hematologic (platelet+)	0 (0)	0 (1)	0 (0)	**<0.0001***
Neurologic (GCS+)	2.6 ± 1.5	2.2 ± 1.4	2.8 ± 1.5	**<0.0001***
Renal	2 (3)	3 (3)	2 (3)	0.296
Cardiovascular+	0 (0)	0 (0)	0 (0)	**<0.001***
SOFA, day 7	8.4 ± 4.5	7.8 ± 3.7	8.9 ± 4.9	**0.002**
Respiratory (Horowitz)	2.5 ± 1.1	2.5 ± 1.1	2.5 ± 1.1	0.525
Hepatic (bilirubin+)	0 (1)	0 (1)	0 (1)	**0.024***
Hematologic (platelet+)	0 (1)	0 (1)	0 (1)	0.549*
Neurologic (GCS)	2.4 ± 1.6	2.2 ± 1.4	2.6 ± 1.6	**0.005**
Renal+	1 (4)	1 (3)	1 (4)	**0.014***
Cardiovascular+	0 (0)	0 (0)	0 (2)	**<0.0001***

SOFA: sequential organ failure assessment; GCS: Glasgow Coma Scale
*Comparisons made using the Mann-Whitney U test. Values presented as median (interquartile range).

dose immunosuppressive treatments impair the immune response in these patients, and thus increase the risk of secondary infections, further complicating treatment with a clinical picture including more than one sepsis (sepsis^2, sepsis^3, etc.).

In a retrospective study of patients that died due to bacterial sepsis and severe COVID-19, Yu et al. reported that the activated partial thromboplastin time, prothrombin time, and INR values were lower and the fibrinogen and d-dimer levels were higher in the COVID-19 group (12). In another study, Leisman et al. showed that many acute phase reactants, including d-dimer, CRP, and ferritin, were similar or higher in patients with COVID-19 compared to those with sepsis or ARDS (13). As a result of the activation of different inflammatory cascades in COVID-19 sepsis, endothelial damage, hypofibrinolysis, immunomicrothrombus, and hypercoagulopathy are seen more frequently than non-COVID-19 sepsis cases. In addition, patients with COVID-19 sepsis require anticoagulant treatment at a higher rate and may present with microcirculation disorder, organ damage, and different clinical symptoms. In our study, the ICU admission and mean follow-up values of CRP, which is an acute phase reactant that plays a key role in the complement system and opsonization, were found to be significantly higher in the COVID-19 sepsis group. In addition, this group had significantly higher fibrinogen associated with inflammation and coagulopathy and significantly lower INR compared to the non-COVID-19 sepsis group. Considering that it is related to steroid treatment and the high incidence of diabetes in Covid-19 patients, the admission and mean glucose levels of our COVID-19 group were determined to be significantly higher.

When the parameters evaluating hepatic and gastrointestinal function were compared between the two groups, it was determined that the AST, ALT, bilirubin, and lipase values, which initially did not significantly differ, showed a significant increase in the COVID-19 sepsis group during the follow-up period. AST and ALT play an important role in the prognosis of COVID-19 [14]. Cai et al. reported that 76.3% of 417 patients with COVID-19 had impaired liver function test results, and 21.5% had liver damage at the time of hospitalization, while the ALT, AST, total bilirubin, and gamma-glutamyl transferase levels increased more than three times than the normal ranges (15). In a prospective observational study, Rasch et al. found increased lipase levels in 31% of patients with COVID-19-associated ARDS without evidence of pancreatitis (16). Similarly, during the one-week follow-up, we detected significantly elevated lipase values in the COVID-19 sepsis group. Lipasemia seen after SARS-CoV-2 infection can be explained by the direct damage of the virus to pancreatic cells and decreased organ perfusion due to microcirculation and endothelial damage (16). The significant increase in bilirubin levels in the COVID-19 sepsis group during the follow-up period also indicates effects on bile duct epithelial cells (cholangiocytes) with a higher angiotensin-converting enzyme (ACE)-2 expression than hepatocytes (17). Unlike inflammatory damage in sepsis, involvement and direct organ damage due to SARS-CoV-2 are more prominent in all cells and organs where ACE-2 receptors are common.

When the mechanical ventilation parameters were compared between the two groups, the number of days on mechanical ventilation was found to be significantly higher in the COVID-19 sepsis group. The higher PEEP and FiO2 levels and the lower tidal volume detected in our COVID-19 cases are consistent with the results of the study and FiO2 levels and are consistent with the review of 20 studies by Tsonas et al. in which they compared the mechanical ventilator parameters of non-COVID-19 and COVID-19 ARDS groups in 2021 (18). In the current study, hypercarbia, an indicator of a ventilation/perfusion mismatch, was found to be significantly higher in the COVID-19 sepsis group, although the minute respiratory frequency was adjusted higher. While primary pulmonary sepsis mostly causes ARDS as a result of alveolar epithelial damage, pulmonary endothelial and alveolar epithelial damage is seen together in ARDS associated with COVID-19. It has been argued that rather than using the term typical ARDS, it would be more appropriate to refer to COVID-19 lung involvement as acute vascular distress syndrome (AVDS), which is characterized by an intrapulmonary right-to-left shunt, increased pulmonary blood flow, and ventilation/perfusion mismatch (19, 20). The invasion of endothelial cells by SARS-CoV-2 via ACE-2 receptors and endotheliitis suggest a specific pulmonary vascular disorder induced by this virus, indicating AVDS rather than typical ARDS (21).

In our study, organ dysfunction in both sepsis groups with the primary focus of infection being the lungs were evaluated with ICU admission and seven-day follow-up SOFA scores, and these scores were found to be significantly higher in the COVID-19 sepsis group. In studies comparing SARS-CoV-2-related and non-COVID-19 organ damage in the literature, it was found that the SOFA scores were higher in the non-COVID-19 sepsis at the time of ICU admission, and organ dysfunction was also more prominent in this group (9, 11,12). However, in contrast to our study, previous research did not re-evaluate patients for organ dysfunction during the follow-up period. In a prospective cohort study by Remy et al. evaluating patients with COVID-19 and sepsis, the mean SOFA scores were reported to be similar between the two groups (22). In another prospective observational study conducted by Grigorescu et al. to compare bacterial sepsis and COVID-19 sepsis cases, organ dysfunction was evaluated over a five-day follow-up period, and although the SOFA scores were similar between the two groups at baseline, they significantly increased in the bacterial sepsis group after five days of follow-up compared to the COVID-19 sepsis group (23). The reason for the multi-organ failure seen in SARS-CoV-2 sepsis may be systemic endotheliitis, endovasculitis, and direct viral cytotoxic effect, as well as vascular dysfunction, which has a more chronic course of irregular inflammatory response compared to other sepsis agents through a mechanism that has not yet been elucidated (24).

In our study, organ dysfunction in the patients with sepsis was evaluated with ICU admission and seven-day follow-up SOFA scores. By evaluating each component of this scoring system, the effects of sepsis due to different pathogens on each organ system and their changes over time were determined. In the neurological evaluation using the GCS score as a component of SOFA, COVID-19 sepsis was found to have a significantly higher score. This can be explained by the requirement for stronger sedation and longer prone positioning times in COVID-19 cases.

The admission SOFA score, used to evaluate hematological and cardiac dysfunction, was found to be significantly higher in the non-COVID-19 sepsis group. However, in the COVID-19 sepsis group, hepatic, renal, and cardiac dysfunction was more pronounced according to the SOFA scores evaluated during the follow-up. Although the rate of chronic renal failure was higher in the non-COVID-19 group, CRRT requirement and renal dysfunction significantly increased in the COVID-19 sepsis group during the follow-up period. It remains unclear whether SARS-CoV-2 contributes to this damage by directly targeting organs with a high expression of alternative cell receptors, especially ACE-2 and L-SIGN, or through the expression of genes on the coagulation system and endothelial immunomicrothrombosis mechanisms (25–28).

The mortality rates reported by Eleni et al. in patients with COVID-19 requiring mechanical ventilation are similarly high when compared to the sepsis-related mortality data published before 2019 [8, 29]. In our study, the mortality rates were statistically similar between the two sepsis groups. In our study, we found that although the patients with COVID-19 sepsis were younger and had fewer comorbidities, this group had a similar mortality rate to the non-COVID pneumosepsis group. This finding reveals the destruction caused by COVID-19 viral sepsis with multisystemic involvement in healthy adults.

Our study has certain limitations. First, it had a single-center and retrospective design despite the large sample size of 717 patients. Second, although the causes of pneumosepsis in the non-COVID-19 group were similar to the literature, these factors were not differentiated. Third, admission and one-week follow-up values were evaluated to minimize hospital-acquired infections, but it was not possible to exclude cases complicated with culture-negative secondary infections. However, since pulmonary involvement mainly determines clinical presentation in patients with COVID-19 cases, the inclusion of primary pulmonary sepsis cases in the non-COVID-19 sepsis group and the examination of their effects on the organ system separately based on the idea that they can better define each other can be regarded as the strong aspects of our study. Another strength of the study is that data were obtained from the electronic recording system verified by the researchers.

Conclusion

Despite the patient population with lower mean age and less comorbidities, it was observed that organ dysfunction was higher in Covid-19 sepsis patients during admission to the intensive care unit and follow-up. Mortality rates were similar in the two sepsis groups. Although the definition of sepsis-3 is not pathogen-specific, SARS CoV-2-associated sepsis cases occur with different phenotypic features. While the pathogen causing sepsis can be controlled with rapid diagnosis and appropriate antimicrobial treatment, these patients become more susceptible to secondary infections due to the lack of appropriate antiviral treatment in Covid-19 sepsis, immunomicrothrombosis, secondary organ damage, and widespread immunosuppression.

Ethics

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of

University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital (decision no: 2021-20-17, date: 18.10.2021).

Informed Consent: Due to the pandemic condition, verbal informed consent was obtained from the relatives of the patients included in the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Ö.M.E., M.S.S., Concept: Ö.M.E., M.S.S., S.A., Y.P., G.O.H., Design: Ö.M.E., Z.Ç., S.A., Y.T.Ş., G.O.H., Data Collection and Process: Ö.M.E., Z.Ç., Y.T.Ş., Y.P., Analysis or Interpretation: Ö.M.E., Z.Ç., Y.T.Ş., Literature Search: Ö.M.E., M.S.S., Y.P., G.O.H., Writing: Ö.M.E., M.S.S., G.O.H.

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