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Septic shock in patients admitted to intensive care unit with COVID-19 pneumonia

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Abstract:

BACKGROUND: The aim of this study was to determine mortality rates and to evaluate clinical features of coronavirus disease 2019 (COVID-19) patients with septic shock in intensive care unit (ICU).

MATERIALS AND METHODS: The medical records of COVID-19 patients requiring ICU admission were retrospectively reviewed over a 3-month period.

RESULTS: Forty patients with COVID-19 admitted to the ICU were screened. Two patients died within 24 h after ICU admission. After these patients were excluded, septic shock was detected in 11 (28%) of 38 patients during the 30-day follow-up period. Ten (91%) of the 11 patients with septic shock died in the ICU. Eight (72%) of the 11 patients had nosocomial infection during 30-day follow-up period. Six (54%) of 11 septic shock patients had positive culture results for bacterial pneumonia on the day of septic shock. The median time from symptom onset to septic shock was 14 (5–34) days. The median duration from ICU admission until septic shock was 8 (1–28) days. All of the patients with septic shock underwent invasive mechanical ventilation (IMV).

CONCLUSION: COVID-19 patients with septic shock have higher mortality rates, percentage of nosocomial infection, and IMV requirement.

Keywords:

Acute disease, COVID-19, critical illness, intensive care, septic shock

Introduction

Coronavirus disease 2019 (COVID-19) has affected more than 20,000,000 individuals and caused nearly 770,000 deaths as of late August 2020.[1] Five percent of patients may require intensive care unit (ICU) admission and mechanical ventilation (MV).[2-6]

The frequency of shock in patients with COVID-19 ranges between 1% and 35%.[3,4] The real incidence of septic shock in COVID patients is unknown. In one study, 70% of nonsurvivors of

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COVID-19 patients had septic shock indicating that septic shock is a common cause of death in COVID-19 patients with critical illness.[5]

There are limitations of the available data on risk factors associated with shock.[7-9] However, older age, comorbidities as hypertension, diabetes mellitus, and cardiac diseases, and lymphocytopenia have been considered as risk factors associated with shock.[2,4,8,9] Studies on septic shock in patients with COVID-19 are lacking. The aim of this study was to determine mortality rates and evaluate clinical features of COVID-19 patients with septic shock.

Materials and Methods

Patients

We retrospectively reviewed the records of all patients admitted to the ICU of a tertiary referral hospital between March 15, 2020, and June 15, 2020, with a diagnosis of COVID-19. Patients with clinical and radiological features of COVID-19 and positive real-time polymerase chain reaction (PCR) and/or positive antibody test results for coronavirus were included in the study. Patients who died within 24 h of ICU admission were excluded from the study.

Clinical data were obtained from medical and radiological imaging records. These data included age, sex, Acute Physiology and Chronic Health Evaluation (APACHE) II scores, Sequential Organ Failure Assessment (SOFA) scores, Glasgow Coma Scores, comorbidities, nosocomial infections, medications, duration of invasive mechanical ventilation (IMV), time from symptom onset to ICU admission and septic shock, duration of hospital and ICU stay, laboratory tests (blood chemistry, procalcitonin [PCT], C-reactive protein (CRP), arterial blood gas, and complete blood count), culture results of blood, bronchial secretions, urine samples, and medications. The study was approved by the local ethics committee of Tepecik Training and Research Hospital (no: 2020/6-1).

Definitions

Medical records of the patients were reviewed by an infectious disease specialist and intensivist. Patients were screened whether they had septic shock and concomitant nosocomial infections during the 30-day of ICU stay or until dead or discharge. Patients were divided into two groups as COVID-19 infection with septic shock and without septic shock. Nosocomial infection and types of nosocomial infection were defined according to the "Center for Disease Control and Prevention" recommendations on definition for specific types of infection.[10] Septic shock was defined according to "The Third International Consensus Definitions for Sepsis and Septic Shock."[11]

Statistical analysis

Data were presented as number of cases, percentage, and median (minimum and maximum). Categorical comparisons were performed by Chi-square test. The Mann–Whitney *U*-test was applied to compare continuous variables. The Wilcoxon signed-rank test was used to test differences of paired data. A $P < 0.05$ was considered statistically significant. Data analysis was performed using SPSS software version 15.0 (SPSS Inc., Chicago, IL, USA).

Results

During the 3-month period, forty COVID-19 patients were admitted to our ICU. Two patients died within 24 h after ICU admission. After these patients were excluded, 38 COVID-19 patients were included in the study. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) real-time PCR test was positive in 36 patients of the study population. In two patients whose SARS-CoV-2 real-time PCR test, results were negative had positive immunoglobulin M antibody test results for coronavirus. Septic shock was detected in 11 (28%) of 38 patients during the 30-day follow-up period.

The characteristics and clinical features of COVID-19 patients with or without septic shock are shown in Table 1. The median age of the patients with septic shock was 74 (57–79) years. Four of these patients were male and seven were female. There was no differences in age and gender between patients with septic shock and without septic shock. The median APACHE II score was 18 (11–31) in patients with septic shock and 13 (10–29) in patients without septic shock ($P = 0.07$). The median SOFA score was 5 (3–11) in patients with septic shock and 4 (2–13) in patients without septic shock ($P = 0.05$). Of the 11 patients with septic shock, four had hypertension, two had diabetes, three had cardiac disease, two had malignancy, two had neurologic disease, and one had chronic obstructive lung disease history. Eight (72%) patients in septic shock group and five (18%) without septic shock had nosocomial infections during ICU stay ($P < 0.01$). Eleven (100%) patients with septic shock and 7 (26%) without septic shock received IMV during the 30-day follow-up period ($P < 0.01$). Ten (91%) patients with septic shock and 4 (14%) without septic shock died in the ICU ($P < 0.01$).

The clinical and laboratory features of COVID-19 patients with septic shock on the 1st day of ICU stay and on the day of septic shock are shown in Table 2. SOFA score, leukocyte, neutrophil levels, PCT, CRP, and creatinine were higher on the day of septic shock ($P < 0.01$, $P < 0.01$, $P < 0.01$, $P < 0.01$, $P = 0.02$, and $P = 0.02$, respectively). Among SOFA score determinants, renal

Table 1: Baseline characteristics of Coronavirus disease 2019 patients with and without septic shock

	Without septic shock (*n*=27)	Septic shock (*n*=11)	*P*
Age	69 (39-92)	74 (57-95)	0.20
Sex (male/female)	16/11	4/7	0.20
Comorbidity, *n*			
Hypertension	12	4	0.72
Diabetes	1	2	1.00
Cardiovascular disease	8	3	1.00
COPD	3	1	1.00
Malignancy	4	2	0.40
Neurologic disease	3	2	1.00
APACHE II score	13 (10-29)	18 (11-31)	0.07
SOFA score	4 (2-13)	5 (3-11)	0.05
Hemoglobin (g/dL)	11.8 (9.4-15)	10.7 (8.7-13.7)	0.32
Leukocytes (/μL) $\times 10^9$	8.6 (4-39)	7.7 (5-13)	0.52
Lymphocytes (/μL) $\times 10^9$	0.7 (0.4-2.9)	0.7 (0.2-2.6)	0.58
Neutrophil (/μL) $\times 10^9$	7.6 (3.1-32)	6.4 (2.4-11)	0.42
Albumin (g/dL)	3 (2.4-3.8)	2.9 (2.4-3.4)	0.50
Aspartate transaminase (U/L)	35 (18-87)	56 (27-124)	0.06
Alanine aminotransferase (U/L)	28 (7-100)	35 (15-92)	0.11
Creatinine (mg/dl)	0.81 (0.4-4.8)	0.9 (0.4-1.5)	0.84
CRP (mg/L)	121 (23-302)	156 (15-253)	0.65
PCT (ng/ml)	0.11 (0.03-17)	0.1 (0.01-0.39)	0.40
Lactate dehydrogenase (U/L)	496 (137-1044) (*n*=21)	564 (220-817) (*n*=9)	0.24
Time from symptoms to admission (day)	7 (2-20) (*n*=19)	6.5 (2-10) (*n*=10)	0.28
Nosocomial infections during ICU stay yes/no (%)	5/22 (18)	8/3 (72)	<0.01
IMV during ICU stay yes/no (%)	7/20 (26)	11/0 (100)	<0.01
Treatment			
Favipiravir	18	10	0.22
Hydroxychloroquine	23	10	1.00
Azithromycin	11	3	0.48
Lopinavir-ritonavir		2	
IVIG	1	4	0.01
Convalescent plasma	6	1	0.64
Steroids	3	7	<0.01
Tocilizumab	2	5	0.01
Cytokine adsorption	2	1	1.00
Mortality yes/no (%)	4/23 (14)	10/1 (91)	<0.01
Length of stay in ICU (day)	10 (1-43) (*n*=26)	16 (8-62)	0.08

Data are presented as number of cases (%) and median (minimum-maximum). COPD: Chronic obstructive pulmonary disease, APACHE: Acute physiology and chronic health evaluation, SOFA: Sequential organ failure assessment, ICU: Intensive care unit, IVIG: Intravenous immunoglobulin, IMV: Invasive mechanical ventilation, PCT: Procalcitonin, CRP: C-reactive protein

and cardiovascular score was higher on the day of septic shock detected. Hemoglobin and albumin were lower on the day of septic shock ($P = 0.02$ and $P < 0.01$, respectively). The median time from symptom onset to septic shock was 14 (5–34) days. The median duration from ICU admission until initiation of septic shock was 8 (1–28) days. The median duration from IMV to septic shock was 3 (1–20).

Eight (72%) of 11 septic shock patients had nosocomial infection including bacteremia and ventilator-associated pneumonia, hospital-acquired pneumonia, candidemia, and aspergillosis during the 30-day follow-up period [Table 3]. Six (54%) of 11 septic shock patients had positive culture results including *Acinetobacter* spp., *Corynebacterium* spp., *Klebsiella pneumonia, Pseudomonas aeruginosa*, and *Haemophilus influenzae* on the day of septic shock [Table 3].

Discussion

In our retrospective study, COVID-19 patients with septic shock had higher nosocomial infection, MV requirement, and mortality rates compared to COVID-19 patients who did not develop septic shock.

Twenty-eight percent (11/38) of critically ill COVID-19 patients developed clinical signs of shock including hypotension requiring vasopressor and high lactate level. These patients met the diagnostic criteria

Table 2: The clinical features of Coronavirus disease 2019 patients with septic shock on the 1st day of intensive care unit stay and on the day of septic shock

	First day of ICU stay	On the day of septic shock	*P*
Total SOFA score	5 (3-11)	10 (6-15)	<0.01
SOFA-respiratory score	4 (2-4)	4 (2-4)	0.18
SOFA-hematologic score	0 (0-4)	0 (0-4)	1.00
SOFA-hepatic score	0 (0-1)	0 (0-2)	0.15
SOFA-cardiovascular score	0 (0-3)	3 (2-4)	<0.01
SOFA-renal score	0 (0-1)	1 (0-3)	0.02
Hemoglobin (g/dL)	10.7 (8.7-13.7)	9.1 (8.1-12)	0.02
Leukocytes (/μL) $\times 10^9$	7.7 (5-13)	18 (6-29)	<0.01
Lymphocytes (/μL) $\times 10^9$	0.7 (0.2-2.6)	0.7 (0.2-1.5)	0.58
Neutrophil (/μL) $\times 10^9$	6.4 (2.4-11)	14.4 (5.1-27)	<0.01
Albumin (g/dL)	2.9 (2.4-3.4)	2.1 (1.7-3.1)	<0.01
Aspartate transaminase (U/L)	56 (27-124)	55 (44-139)	0.97
Alanine aminotransferase (U/L)	35 (15-92)	37 (29-115)	0.64
Creatinine (mg/dl)	0.9 (0.4-1.5)	1.2 (0.6-3.9)	0.02
CRP (mg/L)	156 (15-253)	232 (100-384)	0.02
PCT (ng/ml)	0.1 (0.01-0.39)	1.9 (0.29-40)	<0.01
Lactate dehydrogenase (U/L)	564 (220-817) (*n*=9)	551 (350-986) (*n*=10)	0.76
pH	7.46 (7.31-7.53)	7.40 (7.19-7.53)	0.34
Blood lactate (mmol/L)	1.4 (0.8-4.3)	2.3 (2.1-5)	0.02
Hypotension yes/no (%)	4/7 (36)	11/0 (100)	<0.01
IMV yes/no (%)	7/4 (63)	11/0 (100)	<0.01
Time from symptoms to septic shock (day)	-	14 (5-34)	
Time from ICU admission to septic shock (day)	-	8 (1-28)	
Time from IMV to septic shock (day)	-	3 (0-20)	

Data are presented as number of cases (%) and median (minimum-maximum). SOFA: Sequential organ failure assessment, ICU: Intensive care unit, IVIG: Intravenous immunoglobulin, IMV: Invasive mechanical ventilation, PCT: Procalcitonin, CRP: C-reactive protein

for septic shock according to the "Third International Consensus Definitions for Sepsis and Septic Shock."[11] SOFA score reflects state of organ dysfunctions.[11] The total SOFA score determinanats include respiratory, renal, hepatic, cardiovascular, hematologic, and neurologic status scores. Among these, besides cardiovascular score, renal score was higher on the day of septic shock than at the admission in our septic shock patients, indicating that these patients are susceptible to acute kidney injury.

In a retrospective study, Zhou *et al*. found that COVID-19 patients who died had statistically significant prevalence of sepsis (100% vs. 42%) and septic shock (70% vs. 0%) compared to patients who survived ($P < 0.0001$ and $P < 0.0001$).[5] As 91% ($n = 10$) of our COVID-19 patients with septic shock died in ICU, septic shock seems to be a leading cause of death in our COVID-19 patients.

Secondary infections are not uncommon among the patients with COVID-19.[3,6-8] The contribution of secondary infections to outcomes in patients with COVID-19 is still not well known. Huang *et al*. reported that 10% (4/41) of COVID-19 patients had secondary infection.[6] Yu *et al*. found that 49% of COVID-19 patients in ICU had hospital-acquired bacterial infection or fungal infection.[7] In another study, 16% (11/68) of COVID-19 patients who died had secondary infection.[8] In a study in Wuhan, China, 50% of the patients who died in hospital ($n = 54$) had secondary infection.[5] In our study, 13 of 38 patients had secondary infection, and percentage of secondary infection in septic shock group was higher than patients without septic shock.

In previous studies, microorganisms that cause sepsis have been identified in 59%–69% of septic patients.[12-15] Seventy percent of documented sepsis is attributable to bacterial organisms.[13-15] Critically ill patients are susceptible to nosocomial bacterial infections,[16] and secondary bacterial infections may occur after viral infections; therefore, it is difficult to determine whether the cause of septic shock is viral or secondary/nosocomial bacterial infection in critically ill patients with pneumonia due to viral infection.[7,15] However, in contrast to viral infections, elevated PCT levels are expected to be seen in bacterial infections.[17] Increase in PCT and neutrophil count was found in our septic shock patients. In addition, high percentage of positive culture results for bacteria shows that nosocomial bacterial infection may be an important cause of septic shock in our patients.

Table 3: Clinical features of Coronavirus disease 2019 patients with septic shock admitted to intensive care unit

Patient	Age	Sex	Comorbidity	APACHE II	Nosocomial infection	Positive culture on the day of septic shock	IMV on admission	Septic shock on admission	Time from ICU admission to septic shock (day)	Time from IMV to septic shock (day)	Specific treatment	Outcomes
1	64	Male	CAD	13	VAP (*Corynebacterium*)	Yes	No	No	28	19	Favipiravir, hydroxychloroquine, Azithromycin, tocilizumab, IVIG, convalescent plasma, steroid	Exitus
2	67	Male	COPD, DM	11	-	No	No	No	6	3	Favipiravir, hydroxychloroquine, tocilizumab, steroid	Exitus
3	79	Female	HT	15	VAP (*Acinetobacter* spp.)	Yes	Yes	No	7	7	Favipiravir, hydroxychloroquine, IVIG	Exitus
4	57	Female	HT, DM	17	-	No	No	No	11	8	Favipiravir, hydroxychloroquine, azithromycin, tocilizumab, IVIG, cytokine adsorbtion, Steroid	Exitus
5	70	Male	CVD	18	VAP (*Klebsiella, Pseudomonas aeruginosa*)	Yes	Yes	No	18	18	Favipiravir, hydroxychloroquine, azithromycin	Exitus
6	95	Female	HT	18	VAP (*Acinetobacter* spp.)	Yes	Yes	No	21	20	Favipiravir, hydroxychloroquine	Exitus
7	86	Female	HT, dementia	21	-	No	Yes	Yes	1	1	Lopinavir-ritonavir	Exitus
8	69	Female	Hypothyroidism	18	VAP (*Klebsiella, Acinetobacter* spp.) Candidemia (*Candida parapsilosis*) UTI (*K. pneumonia*)	No	yes	Yes	2	2	Favipiravir, hydroxychloroquine, tocilizumab, steroid	Exitus
9	76	Male	CAD	17	HAP (*Haemophilus influenzae*)	Yes	No	No	8	1	Favipiravir, hydroxychloroquine, steroid	Exitus
10	74	Female	ITP, CLL	23	HAP (*K. pneumonia*) Bacteremia (*K. pneumonia*)	Yes	Yes	Yes	2	2	Favipiravir, hydroxychloroquine IVIG, steroid	Exitus
11	75	Female	CAD	31	*Aspergillosis pneumonia*	No	Yes	Yes	1	1	Lopinavir-ritonavir, favipiravir , hydroxychloroquine, tocilizumab, steroid	Discharged

CAD: Coronary artery disease, COPD: Chronic obstructive pulmonary disease, DM: Diabetes mellitus, HT: Hypertension, CVD: Cerebrovascular disease, *K. pneumonia*: *Klebsiella pneumonia*, ITP: Immune thrombocytopenic purpura, CLL: Chronic lymphocytic leukemia, IVIG: Intravenous immunoglobulin, VAP: Ventilator associated pneumonia, UTI: Urinary tract infection, HAP: Hospital acquired pneumonia, IMV: Invasive mechanical ventilation, ICU: Intensive care unit, APACHE: Acute physiology and chronic health evaluation

Lymphocytopenia has been found to be associated with an increased risk of acquired infection in ICU, the probability of 28-day septic shock and 28-day mortality in previous studies.[18,19] It is widely known that lymphocytopenia is a commoon finding in COVID-19 patients.[2-6] In our study, low lymphocyte count was found in most of patients and remain unchanged on the day of septic shock when compared with the lymphocyte count on the 1st day.

All of the patients who had septic shock received MV in our patients. Ventilatory support is a risk factor for ICU-acquired infections including ventilator-associated pneumonia.[16] Not surprisingly, in a report from the USA, bacteremia and requirement of vasopressor support were found to be high in mechanically ventilated COVID-19 patients (11% vs. 1.8% and 95.4% vs. 1.5%, respectively).[20] The mortality rate in our COVID-19 patients with septic shock requiring MV admission was higher compared to patients without septic shock.

Conclusion

COVID-19 patients with septic shock have higher mortality rates and percentage of nasocomial infections and IMV requirements. Although it is difficult to distinguish from viral septic shock, nosocomial bacterial infection may be an important cause of septic shock development in COVID-19 patients.

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Conflicts of interest
There are no conflicts of interest.

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