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Research article

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Retrospective assessment of the association between co-morbid disease burden and biochemical parameters in hospitalized hypertensive COVID-19 patients

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Ethics Committee Approval
This study was approved by the Siirt University non-interventional research ethics committee (No: 2021/01.01).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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Abstract

Background/Aim: Hypertension (HT) was examined as a risk factor affecting the progression of the 2019 novel coronavirus disease (COVID-19). In COVID-19 patients, it can be found in many co-morbid diseases, along with hypertension. It is not clear whether the co-morbid burden of the disease affects the prognosis in hypertensive COVID-19 patients and which biochemical parameters may be indicative of this. Therefore, this study was designed to determine the effect of co-morbid disease burden on biochemical parameters in hospitalized hypertensive COVID-19 patients.

Methods: After receiving approval from the University Ethics Committee, demographic, clinical, radiological, and laboratory data of 250 hospitalized hypertensive COVID-19 patients between May 2020 and Sept 2020 were screened. Patients with missing records and unclear history of hypertension drug use were excluded from the study. A total of 215 patients were included in the study. Patients were divided into four groups according to the co-morbidity status: (1) HT alone (Group HT0), (2) HT+ Diabetes Mellitus (DM) (Group HTDM1), (3) HT+one co-morbidity exclude DM (Group HT2), and (4) HT+at least two co-morbidities (Group HT3).

Results: We analyzed the data of 105 female and 110 male patients. Of the 215 patients whose data were evaluated in this study, 15 patients died. Two hundred people were discharged with recovery. The mortality rate was 7%. Of the hypertension patients, 34.9% had DM, 32.6% had coronary artery disease (CAD), 30.2% had chronic obstructive pulmonary disease (COPD), 16.3% had heart failure (HF), 23.3% had chronic kidney failure (CKD), and 9.3% had cerebrovascular disease (CVD). Twenty-five percent were smokers. Urea, creatinine, direct bilirubin (DBil), and Troponin-I values were significantly higher in the Group HT3 compared to the Group HT0, Group HTDM1, and Group HT2 ($P < 0.001$, $P < 0.001$, $P < 0.001$, $P = 0.002$ respectively). Glomerular filtration rate (GFR) and albümin levels were significantly lower in Group HT3 than in Group HT0, Group HTDM1, and Group HT2 ($P < 0.001$ and $P < 0.001$, respectively). The logistic regression model was statistically significant ($\chi2(7) = 69.088$ and $P < 0.001$); advanced age, decrease in GFR and plateletcrit (PCT) levels, and increase in D-dimer and DBil levels were observed as predictive parameters of mortality in all hospitalized COVID-19 HT patients.

Conclusion: We determined that SARS-CoV-2 pneumonia patients with HT plus at least two co-morbidities were more serious than other patient groups in terms of organ damage and biochemical variables. In our study, we observed an increase in urea, creatinine, D-dimer, Dbil, and Troponin-I values and a decrease in GFR and albumin values as the co-morbidity burden increased in hypertensive COVID-19 patients. However, a decrease in GFR and hemogram PCT levels and an increase in D-dimer and DBil levels could be risk factors for mortality.

Keywords: COVID-19, Hypertension, CRP, Comorbidities, Troponin, Dimer

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Introduction

Coronavirus disease 2019 (COVID-19), which is brought on by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first discovered in Wuhan City, Hubei province, China, in December 2019 [1]. The World Health Organization proclaimed COVID-19 a pandemic on March 11, 2020, as soon as it met the epidemiological requirements (infection in more than 100,000 people in 100 countries) [2]. The virus is mostly spread by contaminated respiratory droplets and close contact with an infected individual. It is extremely infectious, and the incubation period can last up to 2 weeks [3]. The mean R0 of COVID-19 was shown to be around 2.68 (95% CI: 2.47–2.86). The risk of person-to-person transfer has been highlighted by an increasing number of epidemics of familial transmission [4]. Fever, dry cough, dyspnea, myalgia, lethargy, hypo lymphoma, and radiographic indications of pneumonia were the most prevalent signs of COVID-19. In extreme cases, complications [such as acute respiratory distress syndrome (ARDS), arrhythmia, shock, acute cardiac damage, secondary infection, and acute renal injury] and death may ensue [5].

A positive nasopharyngeal swab and respiratory pathogen nucleic acid test using high-throughput sequencing or real-time reverse transcriptase-polymerase chain reaction resulted in COVID-19 (RT-PCR) diagnosis. With better sensitivity, chest computed tomography (CT) imaging plays an important role in the surveillance and diagnosis of COVID-19 viral pneumonia [6]. Notably, it has been established that 2019-nCoV and SARS-CoV both enter cells through the same cell entry receptor, angiotensin-converting enzyme II (ACE2) [7]. Angiotensin receptor blockers (ARB) and ACE inhibitors (ACEi) may upregulate ACE2, increasing vulnerability to the virus, according to some evidence, as the ACE2 receptor is the route through which SARS-CoV2 enters the body. The lung-protective action of ACE2, an angiotensin II inhibitor, is potentiated by ACEi/ARB, according to previous investigations [8]. Medication affects ACE2 production, expression, and activity, with potentially significant implications for COVID-19 prevention, infection, severity, and therapy. Hypertension (HT) affects 1.39 billion people globally, with 349 million living in high-income nations and 1.04 billion in low- and middle-income countries. However, there are huge disparities in antihypertensive medication exposure worldwide; awareness, treatment, and control concern 67%, 56%, and 28% of patients in high-income nations, and 37%, 29%, and 7.7% of patients in low- and middle-income countries, respectively [9].

The European Society of Cardiology Council on Hypertension, European Society of Hypertension, and American Heart Association urge patients to continue on ACEi and ARB because no strong data support either a benefit or a risk [10]. Unfortunately, several studies have demonstrated that patients with underlying cardiovascular co-morbidities, such as HT and coronary artery disease (CAD), are more likely to get a severe COVID-19 infection that necessitates intensive care unit (ICU), have complications including ARDS, and ultimately die [11]. Adult inpatients with COVID-19 were also shown to have higher levels of age, lymphopenia, leucocytosis, lactate dehydrogenase (LDH), high-sensitivity cardiac troponin I, creatine kinase (CK), D-dimer, serum ferritin, IL-6, prothrombin time, creatinine, and procalcitonin [12].

Although there are many evaluations that HT and CAD adversely affect the prognosis of COVID-19, there are no publications in the literature showing how the prognosis is affected by additional co-morbid diseases (DM, CAD, COPD, HF, CVD, CKD) in hypertensive COVID-19 patients. The primary aim of this retrospective study was to evaluate the relationship between biochemical markers and groups separated by co-morbidity severity. The second aim was to determine the independent variables that could predict mortality by comparing the biochemical markers of those hypertensive COVID-19 patients who died and those that recovered.

Materials and methods

This study is a retrospective cohort study conducted with patients who had COVID-19 and also had HT and co-morbidities. After receiving approval from the Ethics Committee, demographic, clinical, radiological, and laboratory data of 250 hospitalized hypertensive COVID-19 patients were screened between May 2020 and Sept 2020. Patients with missing records and unclear history of hypertension drug use were excluded from the study. A total of 215 patients were included in the study. This study was approved by the Siirt University non-interventional research ethics committee (No:15.05.2020/06.01). Demographic, clinical characteristics, laboratory and radiological findings, and treatment protocols of the patients were obtained from hospital information system records. Information on demographic data, symptoms, pre-existing chronic co-morbidities, and laboratory results were collected. All data were checked by physicians who are experts in cardiology. The time from onset of illness to hospitalization was also recorded. All patients participating in this study were laboratory-confirmed COVID-19 patients, and the diagnostic criteria for COVID-19 were based on the positive detection of viral nucleic acids.

Leukocytes, neutrophils (NE), lymphocytes (LY), albumin, C-reactive protein (CRP), fasting blood glucose (FBG), LDH, urea, creatinine, sodium (Na), potassium (K), creatine kinase isoenzyme MB (CK-MB), total (TBil) and direct bilirubin (DBil), alanine aminotransferase (ALT), aspartate transaminase (AST), and D-dimer were determined for each patient. All medical laboratory data were measured by the clinical laboratory of Siirt State Hospital. HT disease was defined from the medical history of the patients.

Throat swab specimens from patients' upper respiratory tracts were kept in a viral-transport medium. The respiratory sample RNA isolation kit retrieved total RNA in less than 2 h. RT-PCR was used to look for SARS-CoV-2, as previously described.

The following criteria were satisfied by each COVID-19 patient: a history of epidemiology, fever or other respiratory symptoms, a typical viral pneumonia-related abnormality on a CT scan, and a positive RT-PCR result for SARS-CoV-2 RNA are all indicators of viral pneumonia. Patients were divided into four groups according to the co-morbidity status: (1) HT alone (Group HT0), (2) HT + Diabetes Mellitus (DM) (Group

HTDM1), (3) HT + one co-morbidity exclude DM (Group HT2), and (4) HT + at least two co-morbidities (Group HT3).

Statistical analysis

The statistical program SPSS for Windows, version 22.0, was used to conduct all statistical analyses (SPSS, Chicago, Illinois, USA). Continuous variables were presented as means and standard deviations, whereas categorical variables were specified as percentages. The distribution of continuous variables was examined for normality using the Shapiro-Wilk or Kolmogorov-Smirnov tests. Differences in mean values between two groups were analyzed using the independent t-test and the Mann-Whitney test, and four groups were tested using the analysis of variance (ANOVA) test. When ANOVA revealed significant differences between means, the post hoc test, Games-Howell, was used to examine them. Additionally, binary logistic regression analyses were carried out. *P*-values < 0.05 were judged statistically significant.

Results

The study was conducted with 215 patients, of whom 105 were females and 110 were males. The enrolled patients were classified into four groups: Group HT0 (n: 63; 29.3%), Group HTDM1 (n: 42; 19.5%), Group HT2 (n: 25; 11.6%), and Group HT3 (n: 85; 39.5%). Fifteen of them died. Two hundred people were discharged with recovery. The mortality rate was 7%. All deceased patients were in Group HT3. Of the COVID-19 HT patients, 34.9% had diabetes mellitus (DM), 32.6% had CAD, 30.2% had chronic obstructive pulmonary disease (COPD), 16.3% had heart failure (HF), 23.3% had chronic kidney disease (CKD), and 9.3% had the cerebrovascular disease (CVD). The proportion of smokers was 25.6%. Of the COVID-19 HT patients, 165 were using ACE/ARB, and 50 were using non ACE/ARB HT drugs (Table 1). In addition, 15 patients who died had been using ACE/ARB class drugs. No deaths were observed in patients using non ACE/ARB drugs.

Table 1: General demographic and clinical characteristics of the COVID-19 HT patients

		mean (SD)
Age		63.79 (10.97)
		n (%)
Gender	Male	110 (51.2)
	Female	105 (48.8)
Co-morbidity groups	Group HT0	63 (29.3)
	Group HTDM1	42 (19.5)
	Group HT2	25 (11.6)
	Group HT3	85 (39.5)
Result	Deceased	15 (7)
	Discharged	200 (93)
DM	Yes	75 (34.9)
	No	140 (65.1)
CAD	Yes	70 (32.6)
	No	145 (67.4)
COPD	Yes	65 (30.2)
	No	150 (69.8)
HF	Yes	35 (16.3)
	No	180 (83.7)
CKD	Yes	50 (23.3)
	No	165 (76.7)
CVD	Yes	20 (9.3)
	No	195 (90.7)
Smoking	Yes	55 (25.6)
	No	160 (74.4)
HT Drug Class	ACE i /ARB	165 (76.7)
	Non ACE i /ARB	50 (23.3)

Age was significantly different between Group HT0, Group HTDM1, and Group HT3 ($P < 0.001$). FBG level was statistically significantly higher in Group HTDM1 than in Group HT0 and Group HT2 ($P < 0.001$ for all). Urea level was significantly higher in Group HT3 than in Group HT0, Group HTDM1, and Group HT2 ($P < 0.001$ for all). Also, the urea level was higher in Group HT2 than in Group HT0 ($P = 0.009$). The creatinine level was significantly higher in Group HT3 than in Group HT0, Group HTDM1, and Group HT2 ($P < 0.05$ for all). Additionally, creatinine level was significantly higher in Group HT2 than in Group HT0 and Group HTDM1 ($P < 0.001$ for all). Glomerular filtration rate (GFR) level was significantly lower in Group HT3 than in Group HT0, Group HTDM1, and Group HT2 ($P < 0.001$ for all). AST level was significantly higher in Group HT3 than Group HT2 ($P = 0.012$) and higher in Group HTDM1 than Group HT2 ($P = 0.029$). Na level was significantly lower in Group HTDM1 than in Group HT3 and Group HT2 ($P = 0.003$ and $P = 0.006$, respectively). The K level was significantly higher in Group HT3 than in Group HT0 ($P = 0.006$). Also, the K level was higher in Group HT2 and Group HTDM1 than in Group HT0 ($P < 0.001$ and $P = 0.003$, respectively). The TBil level was significantly higher in Group HT3 than in Group HTDM1 and Group HT2 ($P < 0.001$ for all). Also, the TBil level was higher in Group HT0 than in Group HTDM1 and Group HT2 ($P = 0.006$ and $P = 0.017$, respectively). The DBil level was significantly higher in Group HT3 than in Group HT0, Group HTDM1, and Group HT2 ($P < 0.001$ for all). The albumin level was significantly lower in Group HT3 than in Group HT0, Group HTDM1, and Group HT2 ($P < 0.05$ for all). CK-MB level was significantly higher in Group HT3 than in Group HTDM1 ($P = 0.035$). CRP level was significantly higher in Group HT3 ($P < 0.001$), Group HT2 ($P < 0.001$), and Group HTDM1 ($P < 0.001$) than Group HT0, respectively (Table 2).

Table 2: Comparision of laboratory parameters of four groups

Laboratory findings	Group HT0	Group HTDM1	Group HT2	Group HT3	*P*-value [a]
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
Age	59.71 (10.56)	61.19 (11.27)	57.80 (6.10)	69.86 (9.37)	<0.001
GFR (ml/min)	77.66 (13.44)	75.07 (8.37)	67.31 (14.03)	52.08 (21.25)	<0.001
FBG (mg/dL)	108.32 (38.76)	174.24 (104.34)	98.68 (8.91)	163.67 (83.79)	<0.001
CRP (mg/dL)	15.85 (17.33)	77.95 (71.76)	49.67 (37.30)	70.46 (55.01)	<0.001
Urea (mg/dL)	31.90 (8.51)	32.40 (9.25)	36.89 (5.46)	49.43 (17.28)	<0.001
Creatinine (mg/dL)	0.95 (0.16)	0.96 (0.14)	1.18 (0.22)	1.59 (1.08)	<0.001
TBil (mg/dL)	0.54 (0.34)	0.037 (0.18)	0.40 (0.06)	0.64 (0.35)	<0.001
DBil (mg/dL)	0.15 (0.11)	0.10 (0.08)	0.11 (0.03)	0.24 (0.18)	<0.001
ALT (U/L)	32.68 (27.02)	42.93 (34.67)	32.36 (24.18)	38.69 (47.97)	0.495
AST (U/L)	35.08 (23.07)	42.33 (20.98)	30.120 (13.99)	43.40 (29.10)	0.041
LDH (U/L)	254.13 (80.71)	305.12 (179.60)	283.08 (115.23)	259.80 (84.61)	0.095
Na (mmol/L)	137.29 (3.09)	136.40 (2.24)	139.04 (3.28)	138.19 (3.37)	0.002
K (mmol/L)	4.09 (0.45)	4.49 (0.60)	4.64 (0.22)	4.41 (0.70)	<0.001
CK-MB (U/L)	13.90 (7.85)	10.74 (6.57)	17.67 (13.50)	15.63 (13.56)	0.047
Albumin (g/dL)	40.37 (4.33)	41.16 (5.20)	40.08 (4.45)	36.39 (4.92)	<0.001

[a] One Way ANOVA test

Red blood cell (RBC) level was significantly lower in Group HT3 than in Group HT2 ($P = 0.005$). White blood cell (WBC) level was significantly higher in Group HT3 ($P < 0.001$) than Group HT0 and also higher in Group HT2 ($P = 0.012$) than Group HT0, respectively. Platelet (PLT) level was significantly higher in Group HTDM1 ($P = 0.005$) than Group HT0 and higher in Group HT2 ($P = 0.005$) than Group HT0, respectively. Also PLT level was higher in Group HT2 than in Group HT3 ($P = 0.040$). Plateletcrit (PCT) level was significantly higher in Group HTDM1 ($P = 0.027$) than Group HT0 and higher in Group HT2 ($P < 0.001$) than Group HT0, respectively. Also, the PCT level was lower in Group HT3 than in Group HT2 ($P = 0.022$). NE level was significantly higher in Group HT3 ($P < 0.001$) than Group HT0 and higher in Group HT2 ($P = 0.008$) than Group HT0, respectively. LY level was significantly lower in Group HT3 than in Group HT0 ($P = 0.010$). Hemoglobin

(HGB) level was significantly lower in Group HT3 ($P < 0.001$) than Group HT0 and lower in Group HTDM1 ($P < 0.001$) than Group HT0, respectively. Hematocrit (HCT) percentage was significantly lower in Group HT3 ($P = 0.010$) than Group HT0 and lower in Group HTDM1 ($P < 0.001$) than Group HT0, respectively. Also, the HCT percentage was significantly lower in Group HTDM1 than in Group HT2 ($P = 0.016$). D-dimer level was significantly higher in Group HT3 ($P < 0.001$), Group HT2 ($P = 0.003$), and Group HTDM1 ($P = 0.002$) than Group HT0 respectively. Troponin-I level was significantly higher in Group HT3 than Group HT0 ($P = 0.012$), Group HTDM1 ($P = 0.011$), and Group HT2 ($P = 0.010$), respectively (Table 3).

Table 3: Comparision of hemogram parameters, some coagulation factors and markers of four groups

Laboratory findings	Group HT0 Mean (SD)	Group HTDM1 Mean (SD)	Group HT2 Mean (SD)	Group HT3 Mean (SD)	*P*-value [a]
RBC (10^3/mL)	4.65 (0.37)	4.69 (0.71)	5.03 (0.67)	4.48 (0.73)	0.002
WBC (10^3/mL)	6.22 (1.87)	7.35 (3.27)	9.02 (4.04)	7.83 (2.26)	<0.001
PLT (10^3/mL)	221793.6 (74195.3)	293761.9 (120449.5)	327120 (136688.6)	245011.8 (93931.8)	<0.001
MPV (fl)	9.88 (1.02)	10.17 (2.42)	10.03 (1.92)	9.93 (0.88)	0.767
PCT (%)	0.22 (0.07)	0.27 (0.09)	0.31 (0.11)	0.24 (0.09)	<0.001
NE (10^3/mL)	3.78 (1.39)	4.71 (2.97)	6.48 (3.76)	5.62 (1.98)	<0.001
LY (10^3/mL)	1.88 (0.55)	1.90 (0.99)	1.61 (0.92)	1.54 (0.78)	0.020
HGB (g/dL)	13.39 (1.16)	11.61 (1.59)	12.540 (1.61)	11.89 (2.05)	<0.001
HCT (%)	41.95(3.39)	38.45 (4.01)	42.168 (5.07)	39.39 (6.31)	<0.001
D-dimer (mg/L)	635.24 (440.58)	994.69 (509.87)	1141.60 (611.43)	1594.39 (1300.38)	<0.001
Troponin I (ng/mL)	0.0196 (0.021)	0.016 (0.012)	0.011 (0.010)	0.403 (1.122)	0.002

[a] One Way ANOVA test

When comparing COVID-HT patients who died versus those who were discharged according to age ($P < 0.001$), urea ($P < 0.001$), creatinine ($P = 0.046$), DBil ($P < 0.001$), Troponin-I ($P = 0.036$), D-dimer ($P = 0.031$), and hospitalization day ($P < 0.001$), all parameters were higher in the deceased group than the discharged group. On the other hand, GFR ($P < 0.001$), LDH ($P = 0.008$), HGB ($P = 0.013$), PLT ($P = 0.021$), PCT ($P = 0.040$), and LY ($P = 0.005$) levels were lower in deceased group than discharged group (Table 4). The logistic regression model was statistically significant ($\chi2(7) = 69.088$, $P < 0.001$) and decreases in PCT and GFR levels, increases in D-dimer and DBil levels, and advanced age were assessed as predictive factors for mortality (Table 5).

Table 4: Comparison of some biochemical and clinical data of deceased and discharged patients

	Deceased Median (Min-Max)	Discharged Median (Min-Max)	*P*-value [a]
Age	76 (71-83)	63 (39-87)	<0.001
Urea (mg/dl)	47.08 (40.66-68.48)	36.38 (17.12-92.02)	<0.001
Creatinine (mg/dl)	1.13 (1.07-1.22)	1.05 (0.61-4.54)	0.046
GFR (ml/min)	56.82 (43.13-59.77)	69.83 (10.41-100.96	<0.001
LDH (U/L)	210 (106-259)	248.5 (104-751)	0.008
DBil (mg/dl)	0.43 (0.05-0.58)	0.12 (0.03-0.64)	0.010
HGB (g/dl)	11.4 (10.8-12.6)	12.65 (8-15.8)	0.013
HCT (%)	39.5 (37.7-44.9)	39.95 (26.8-49.9)	0.914
PLT (10^3/mL)	178 (139-287)	251.5 (79-541)	0.021
PCT (%)	0.161 (0.137-0.304)	0.246 (0.092-0.436)	0.040
LY	1 (0.72-1.85)	1.79 (0.49-4.10)	0.005
Troponin I (ng/ml)	0.028 (0.014-0.660)	0.020 (0-4.79)	0.036
D-dimer (mg/L)	1190 (993-1320)	794.5 (245-5140)	0.031
Hospitalization day	15 (5-17)	7 (2-15)	<0.001

[a] Mann Whitney U test

Table 5: Predictors of mortality in binary logistic regression model

	B	SE	Wald	*P*-value [a]
GFR (ml/min)	-0.182	0.076	5.668	0.017
Age	0.506	0.189	7.197	0.007
D-dimer (mg/L)	0.008	0.003	7.235	0.007
DBil (mg/dl)	18.374	7.643	5.779	0.016
Troponin I (ng/ml)	-0.237	0.533	0.197	0.657
PCT %	-39.751	15.109	6.922	0.009
Comorbidity groups	2.611	2.395	1.188	0.276

[a] Binary Logistic Regression

Discussion

In our study, we observed an increase in urea, creatinine, D-dimer, Dbil, and troponin values and a decrease in GFR and albumin values as the co-morbidity burden increased in hypertensive COVID-19 patients. According to data from a different meta-analysis, HT was independently linked to a considerably higher incidence of critical COVID-19 and in-hospital COVID-19 mortality [13]. The severity of sickness, ICU hospitalization, death, and other organ damage was several times greater in COVID-19 patients with cardiac injuries than in infected individuals without them [14]. It is concluded that HT worsens the severity of COVID-19 due to underlying endothelial dysfunction and coagulopathy. Due to ACE2 downregulation, COVID-19 may exacerbate HT problems. The use of ACEIs or ARBs in the treatment of hypertensive individuals with COVID-19 might be advantageous [15]. In addition to the effect of HT on ACE-2 receptors alone, the co-morbidity burden may enable the virus to enter the cell more easily and damage the cell by influencing the ACE-2 receptor expression and providing the release of viral proprotein convertase [16]. As the co-morbidity burden increased in our patients, the deterioration in renal (urea, creatine and GFR), hepatic (DBil and albumin), and cardiac (Troponin-I) biochemical markers may have been due to these effects of co-morbidities. According to one investigation, prior exposure to ACEIs or ARBs was not related to a higher risk of hospitalization or all-cause death from COVID-19 infection [17]. For this reason, it can be thought that the use of ACEIs and ARBs may be beneficial in terms of prognosis as co-morbidities increase in hypertensive COVID-19 patients.

In previous studies, it has been stated that the presence of Type 2 DM is a risk factor for poor prognosis in COVID-19 infection. The disruption of insulin secretion from the pancreas due to the direct cytotoxic effect of the virus and the glucocorticosteroid group drugs taken may cause hyperglycemia. It is thought that hyperglycemia also increases the penetration of the virus by causing hyperglycosylation of ACE-2 receptors, which is the natural receptor of the virus and may cause more serious infection with increasing virulence [17]. In studies performed on COVID-19 patients with and without Type 2 DM, it was found that the group with Type 2 DM was more prone to severe disease than the group without DM, and inflammatory markers (CRP, ferritin, LDH, procalcitonin, and D-dimer) were significantly higher in this group [18]. In our study, when we compared the DM group (Group HTDM1) with the non-DM co-morbidities group (Group HT2) in hypertensive COVID-19 patients, we did not observe any significant difference in inflammatory markers (CRP, LDH and D-dimer). Observation of significant increases in inflammatory markers in Group HT3, where co-morbidity is higher, reveals that DM should be considered together with other additional disorders, not alone. Major cardiovascular risk factors and other co-morbidities (HT, DM, obesity, immunosuppression and end-stage kidney disease) increase the risk of dying in patients with COVID-19. The presence of two or three co-morbid diseases showed a stronger association with mortality than each co-morbid disease alone compared to the absence of them [20].

Similarly, another study showed that COVID-19 mortality risk sharply increased in patients with two or more co-

morbid diseases (obesity, DM, HT, and CAD) in Mexico [21]. In a retrospective study in Egypt, patients with DM, liver cirrhosis, HT, hepatitis C virus (HCV), and CKD tended to have more severe COVID-19; it has been suggested that it may be associated with ALT, AST, CRP, serum ferritin levels, FBG, segmented % and neutrophil/lymphocyte ratio (NLR) [22]. In another study on COVID-19 mortality, mortality for patients in the older age group and those patients who were admitted to the ICU was higher. Additionally, six laboratory measurements had a favorable correlation with the likelihood of dying: WBC count, NE, CK-MB, CRP, urea, and LDH [23].

In a study comparing laboratory parameters according to the severity of pneumonia involvement in CT, it was observed that COVID-19 had a worse prognosis in male patients and patients with HT and CAD, while no difference was found in terms of disease severity in patients with DM and COPD. In addition, it has been suggested in this study that the relationship between D-dimer and ferritin may indicate the severity of COVID-19 [24]. In our study, however, the increase in Troponin-I was significantly higher in Group HT3 (HT and at least two co-morbidities) compared to all other groups, and D-dimer values were found to be significantly higher as the co-morbidity increased. At the same time, these two parameters were significantly higher in patients who died, in hypertensive COVID-19 patients with a high co-morbid disease burden. It makes us think that it would be useful to evaluate Troponin-I and D-dimer together in the prognosis of COVID-19 patients. The fact that DM and CAD were higher than other diseases in our study group may have been responsible for the increase in Troponin-I and D-dimer, which was observed in hypertensive COVID-19 patients as co-morbidity increased, especially by causing silent ischemia in the coexistence of the two diseases.

In our study, it was seen that low GFR might be predictive in terms of mortality. Especially the hemodynamic changes experienced during viral sepsis, the nephrotoxic effects of the treatments used in co-morbid patient groups, and the development of acute tubular damage due to systemic inflammation suggest that low GFR may be a mortality indicator related to the severity of the disease. In this respect, fluid management, administration of anti-inflammatory and antiviral drugs, and avoidance of acute tubular damage by close hemodynamic monitoring can play a vital role, especially in patients with impaired renal function [25].

An endogenous byproduct of heme catabolism, known as bilirubin, is a protective bioactive molecule with potent antioxidant and anti-inflammatory properties and other critical physiological activities [26]. In our study, it was seen that DBil might have a predictive role in mortality. The use of ACE2 receptors expressed in the liver and bile ducts by SARS-CoV2 to increase viral replication may cause direct cytotoxicity. Again, with an immune-mediated mechanism, severe inflammation may cause cell damage in the liver and biliary tract [27]. These two mechanisms may be potential mechanisms of DBil increase in hypertensive COVID-19 patients with high co-morbidity, which we demonstrated in our study.

In a study comparing the COVID-19 pneumonia group to the control group, there was no discernible difference between the PCT value of advanced COVID-19 patients and mild COVID-19 patients, while the PCT value was discovered to have been considerably lower in the COVID group as compared to the control group [28]. In our study, decreased PCT value was determined as a predictive factor in HT COVID-19 patients, especially in mortality. In a study by Gao et al. [29] on hemogram parameters in septic shock patients, PCT values and a decrease in PLT were shown to be associated with mortality. On the other hand, D-Dimer is a well-known biomarker that has an important place in predicting the prognosis of COVID-19 and shows COVID-related coagulopathy [30]. We also showed that high D-dimer levels are associated with mortality. In this respect, using D-dimer and PCT to predict prognosis may be more effective in clinical decision-making, especially in patients with a high co-morbidity burden with hypertensive COVID-19 patients.

Our study has some limitations. First, hypertensive COVID-19 patients who were hospitalized were included in the study. Different results can be obtained in outpatients. Secondly, since our study was designed in a retrospective style, only patients using drugs for HT could be included from the records. Different results could be achieved with prospective, randomized, multicenter, and longer-term studies. A final limitation is that independent outcomes and variables may be affected in hypertensive COVID-19 patients, depending on metabolic status.

Conclusion

In this study, we determined that SARS-CoV-2 pneumonia patients with hypertension plus at least two co-morbidities were more serious than other patient groups in terms of organ damage and biochemical variables. In our study, we observed an increase in urea, creatinine, D-dimer, Dbil, and Troponin-I values and a decrease in GFR and albumin values as the co-morbidity burden increased in hypertensive COVID-19 patients. However, a decrease in GFR and hemogram PCT levels and an increase in D-dimer and DBil levels could be risk factors for mortality. Studies in larger patient numbers by different research groups are needed to contribute to these findings.

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