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Research article

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A prospective study on the relationship between COVID-19 disease progress and cardiovascular damage

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The study was approved by Harran university Ethics Committee (date:27.04.2020 and number: HRU/20.08.23)
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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No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Covid-19 is a new coronavirus disease with high mortality that has reached all parts of the world. This study aimed to prospectively compare individual characteristics, echocardiographic findings, and laboratory findings in patients with Covid-19 according to the need for intensive care unit (ICU) admission and mortality.

Methods: In this single-center prospective cohort study, patients hospitalized with the diagnosis of Covid-19 between June and November 2020 were examined in terms of echocardiographic and laboratory results. Early in-hospital findings that might affect mortality, cardiac injury and thrombotic complications were evaluated and compared.

Results: A total of 214 patients who were hospitalized due to Covid-19 were included in our study, 80 (37.3%) of which needed hospitalization in the ICU and 134 (62.6%) of which did not. The mean ages of patients treated in the ICU unit and the ward were 69.5 (57.5-80.5) years and 40 (29-58) years, respectively (P<0.001). Among patients hospitalized in the ICU, mean Troponin T on Day 1 (27.12 ng / L, range: 10.48-70.51, P<0.001), mean Troponin T on Day 3 (31.5ng / L, range: 10.24 - 114.5, P<0.001) and mean D-dimer (2.84ng / L, range: 1.1-8.22, P<0.001) levels of those who died were significantly higher compared to survivors. These parameters were important markers of mortality along with right ventricular end-diastolic diameter (RVDD) (3.3 cm (2.8-3.7) P<001).

Conclusion: While cardiac damage and high D-dimer values suggest the possibility of pulmonary microembolism in those who need ICU hospitalization, the relationship between RVDD and mortality supports the possibility of pulmonary embolism.

Keywords: Covid-19, D-dimer, Cardiac damage, ICU, RVDD

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Introduction

Covid-19 disease caused by the SARS2-CoV-2 viral infection that started in Wuhan in December 2019 was declared a pandemic by the World Health Organization (WHO) [1]. The SARS-CoV-2 is an enveloped virus of the Coronavirus (CoV) family, with a characteristic genome composed of RNA. Its clinical severity may range from asymptomatic to symptomatic (including fever, cough, shortness of breath, malaise, muscle pain and diarrhea). More importantly, it can cause a disease of the respiratory tract which may progress to acute respiratory distress syndrome (ARDS) and fatal organ failure [2]. The disease has greater infectivity than influenza, in addition to its higher mortality rate. The high infectivity and relatively high rate of serious complications have caused Covid-19 to become a serious public health threat worldwide [3, 4]. The disease may also cause arrhythmia through some proinflammatory mediators [5]. Despite cardiac manifestations being reported in the literature, mortality and complications are primarily related to respiratory involvement in patients with Covid-19 [6]. Several studies have shown that, along with respiratory tract defects, heart damage is observed in 20-30% of hospitalized patients and may be associated with mortality in up to 40% [7-9].

In the present study, the effects of echocardiographic examination, cardiac injury markers and laboratory parameters on mortality were investigated prospectively among hospitalized Covid-19 patients, with analyses based on comparing patients hospitalized in the ICU and the ward, and respective survival and mortality rates.

Materials and methods

Study population

Patients who presented to Şanlıurfa Mehmet Akif İnan Training and Research Hospital with Covid-19 symptoms and were hospitalized after diagnostic confirmation with positive real-time reverse transcription polymerase chain reaction (RT-PCR) between June-November 2020 were included in this prospective study. They were assessed in two groups according to intensive care requirement. The echocardiographic examination and laboratory findings of patients who required admission to the intensive care unit (ICU) (n = 80) and those who were hospitalized without need of ICU admission (n = 134) were evaluated and compared. We also compared patient characteristics based on fatal disease progression.

All hospitalized patients received routine medical treatment, in-line with WHO recommendations as per the current treatment guidelines prepared by the Turkish Ministry of Health. Patients with chronic renal or heart failure, acute coronary syndrome, coronary artery disease and a history of previous cerebrovascular events were excluded from the study.

Demographic characteristics (age, gender), smoking status, and hypertension (HT) and diabetes mellitus (DM) histories were recorded as part of patient history. Laboratory findings, including glucose, urea, creatinine, sodium, potassium, calcium, D-dimer, procalcitonin, fibrinogen, ferritin, CKMB, hemoglobin, lymphocyte, neutrophil, and troponin (cTnT) were measured from blood samples obtained on days 1 and 3 of hospitalization. cTnT values being above the 99th percentile was considered a marker of newly developed cardiac injury, regardless of echocardiographic findings. To validate Covid-19, a Viral nucleic acid Kit was used to extract nucleic acids from clinical samples, in accordance with the kit instructions. The study was approved by the Harran university Ethics Committee (date:27.04.2020 and number: HRU/20.08.23) and carried out in accordance with the Helsinki Declaration.

Echocardiographic evaluation

All patients included in the study underwent echocardiography in isolated wards and ICUs. Examinations in the parasternal long-axis view and the apical 4-chamber plane were conducted with patients in the left lateral decubitus position. A Philips EPIQ 7 system (Philips EPIQ7, Bothell, WA, USA) 3.5 MHz transducer was used for echocardiographic evaluation, during which two-dimensional instant and color Doppler evaluations were performed with standard techniques. Left atrium (LA) size, left ventricle (LV) end-diastolic diameter (LVDD) and LV end-systolic diameter (LVSD), right ventricular end-diastolic diameter (RVDD) were measured using the M-mode method. Pulmonary arterial pressure (PAB) was measured from the tricuspid valve. LV ejection fraction (LVEF) was calculated using Simpson's method.

Statistical analysis

All analyses were performed on SPSS v21 (SPSS Inc., Chicago, IL, USA). Shapiro-Wilk test was used for normality check. Data are presented as median (1st quartile – 3rd quartile) for continuous variables, and as frequency (percentage) for categorical variables. Non-normally distributed variables were analyzed with Mann-Whitney *U* test, and categorical variables were analyzed with the Pearson's chi-square test. Logistic regression analysis (forward conditional method) was performed to identify the risk factors of mortality and ICU requirement. Variables that were statistically significant in univariate analyses were included in the regression models. Two-tailed *P*-values of less than 0.05 were considered statistically significant.

Results

Gender, age, WBC, hemoglobin, glucose, sodium, calcium, creatinine (1st day), alanine aminotransferase (ALT), aspartate aminotransferase (AST), albumin, CRP, INR, creatine kinase-MB (CKMB) (1st and 3rd day), troponin (1st and 3rd day), ferritin, D-dimer, procalcitonin, ejection fraction percentage (EF%), PABs, fever, cough, diarrhea, dyspnea, myalgia, fatigue, hypertension, diabetes mellitus were significantly associated with ICU need (Table 1).

Age, ICU need, WBC, hemoglobin, glucose, sodium, creatinine (1st and 3rd day), AST, albumin, CKMB (1st and 3rd day), troponin (1st and 3rd day), ferritin, D-dimer, procalcitonin, EF%, RVDD, PABs, dyspnea, diabetes mellitus, and cancer were significantly associated with mortality (Table 2).

Table 1: Clinical variables compared with respect to ICU need

	ICU need		
	Absent	Present	*P*-value
Gender			
Male	87 (67.97%)	41 (32.03%)	0.048
Female	47 (54.65%)	39 (45.35%)	
Age	40 (29 - 58)	69.5 (57.5 - 80.5)	<0.001
White blood cell	7.38 (5.91 - 10.72)	11.8 (8.69 - 15.93)	<0.001
Hemoglobin	14.75 (13.4 - 15.7)	12.55 (10.7 - 14)	<0.001
Platelet	255 (195 - 289)	239 (185.5 - 281.5)	0.247
Glucose	112 (99 - 144)	163.5 (123.5 - 225)	<0.001
Sodium	140 (137 - 141)	137 (133 - 140)	<0.001
Potassium	4.39 (4.1 - 4.68)	4.6 (4.13 - 5.09)	0.015
Calcium	9.11 (8.73 - 9.44)	8.6 (8.18 - 8.9)	<0.001
Creatinine (1st day)	0.93 (0.77 - 1.08)	1.1 (0.78 - 1.67)	0.002
Creatinine (3rd day)	0.9 (0.77 - 1)	1 (0.68 - 1.5)	0.208
ALT	17.8 (11.4 - 26.4)	24 (12.3 - 39.5)	0.041
AST	20.1 (15 - 25.9)	30.85 (20.5 - 49.5)	<0.001
Albumin	43.93 (39.16 - 46.29)	31.92 (30 - 35.92)	<0.001
CRP	11.16 (2.85 - 41.33)	94.99 (35.8 - 188.33)	<0.001
INR	1.08 (1.02 - 1.15)	1.1 (1.05 - 1.3)	0.002
CKMB (1st day)	1.19 (0.83 - 1.99)	1.72 (0.95 - 2.81)	0.014
CKMB (3rd day)	1.5 (1 - 2.5)	2.17 (1.3 - 3.3)	0.001
Troponin (1st day)	3 (3 - 5.14)	27.12 (10.48 - 70.51)	<0.001
Troponin (3rd day)	3.39 (3 - 6.23)	31.5 (10.24 - 114.5)	<0.001
Fibrinogen	3 (2 - 4)	3.2 (2.3 - 4.8)	0.077
Ferritin	78 (56 - 133)	536 (213 - 1256)	<0.001
Procalcitonin	0.13 (0.04 - 0.27)	0.4 (0.15 - 1.2)	<0.001
D-dimer	0.23 (0.14 - 0.5)	1.55 (0.61 - 4)	<0.001
EF%	60 (55 - 65)	55 (50 - 60)	<0.001
LA	3.55 (3.4 - 3.7)	3.6 (3.45 - 3.7)	0.390
LVDD	4.5 (4.4 - 4.7)	4.6 (4.5 - 4.7)	0.071
RVDD	2.8 (2.5 - 3)	2.6 (2.5 - 3.1)	0.212
PABs	25 (24 - 32)	35 (29 - 45)	<0.001
Fever	73 (53.68%)	63 (46.32%)	<0.001
Cough	102 (57.95%)	74 (42.05%)	0.002
Diarrhea	3 (16.67%)	15 (83.33%)	<0.001
Chest pain	9 (45.00%)	11 (55.00%)	0.087
Dyspnea	43 (36.75%)	74 (63.25%)	<0.001
Myalgia	30 (32.97%)	61 (67.03%)	<0.001
Fatigue	34 (35.79%)	61 (64.21%)	<0.001
Headache	15 (71.43%)	6 (28.57%)	0.379
Sore throat	32 (71.11%)	13 (28.89%)	0.185
Hypertension	21 (38.18%)	34 (61.82%)	<0.001
Diabetes mellitus	16 (30.19%)	37 (69.81%)	<0.001
Cancer	5 (45.54%)	6 (54.55%)	0.227
Smoking	35 (62.50%)	21 (37.5%)	0.983

Data are given as median (1st quartile – 3rd quartile) for continuous variables, and frequency (percentage) for categorical variables.

Table 2: Clinical variables compared among patients who survived and those who died

	Result		
	Survived	Died	*P*-value
Gender			
Male	120 (93.75%)	8 (6.25%)	0.596
Female	79 (91.86%)	7 (8.14%)	
Age	53.00 (33.00 - 69.00)	62.00 (51.00 - 79.00)	0.044
ICU need			
Absent	134 (100.0)	0 (0%)	<0.001
Present	65 (81.25%)	15 (18.75%)	
White blood cell	8.79 (6.28 - 11.99)	14.12 (7.7 - 18)	0.014
Hemoglobin	14.2 (12.5 - 15.4)	12 (10.3 - 12.8)	0.001
Platelet	245 (194 - 285)	232 (167 - 330)	0.700
Glucose	120 (101 - 174)	173 (127 - 291)	0.003
Sodium	139 (136 - 141)	134 (130 - 138)	0.002
Potassium	4.45 (4.1 - 4.74)	4.7 (4.21 - 5.6)	0.095
Calcium	8.93 (8.5 - 9.3)	8.63 (8.2 - 9.2)	0.117
Creatinine (1st day)	0.95 (0.77 - 1.11)	1.5 (0.89 - 1.8)	0.003
Creatinine (3rd day)	0.9 (0.75 - 1.07)	1.26 (1 - 2.15)	0.002
ALT	18.5 (11.4 - 31)	21 (14 - 64)	0.296
AST	22.1 (16 - 32.5)	38 (21 - 69.7)	0.003
Albumin	40.1 (33 - 45.09)	32.9 (27.25 - 37)	0.001
CRP	23.18 (4.04 - 90.01)	73 (5.21 - 182.67)	0.065
INR	1.1 (1.02 - 1.2)	1.2 (0.93 - 1.8)	0.297
CKMB (1st day)	1.23 (0.84 - 2.17)	2.8 (1.6 - 4.08)	0.006
CKMB (3rd day)	1.7 (1 - 3)	3.2 (2 - 5)	0.003
Troponin (1st day)	4.7 (3 - 14.6)	46.1 (26.57 - 162.2)	<0.001
Troponin (3rd day)	6 (3 - 20)	98 (29 - 145)	<0.001
Fibrinogen	3.05 (2 - 4.4)	2.9 (1.76 - 3.4)	0.092
Ferritin	98.5 (67 - 353)	456 (138 - 936)	0.003
Procalcitonin	0.16 (0.05 - 0.44)	0.45 (0.16 - 4.1)	0.003
D-dimer	0.42 (0.18 - 1.3)	2.84 (1.1 - 8.22)	<0.001
EF%	60 (55 - 60)	50 (45 - 60)	0.008
LA	3.6 (3.4 - 3.7)	3.6 (3.4 - 3.9)	0.763
LVDD	4.5 (4.4 - 4.7)	4.5 (4.2 - 4.5)	0.063
RVDD	2.7 (2.5 - 3)	3.3 (2.8 - 3.7)	<0.001
PABs	27 (24 - 35)	45 (34 - 50)	<0.001
Fever	125 (91.91%)	11 (8.09%)	0.414
Cough	162 (92.05%)	14 (7.95%)	0.244
Diarrhea	17 (94.44%)	1 (5.56%)	0.801
Chest pain	17 (85.00%)	3 (15.00%)	0.142
Dyspnea	105 (89.74%)	12 (10.26%)	0.041
Myalgia	82 (90.11%)	9 (9.89%)	0.156
Fatigue	88 (92.63%)	7 (7.37%)	0.854
Headache	20 (95.24%)	1 (4.76%)	0.671
Sore throat	42 (93.33%)	3 (6.67%)	0.919
Hypertension	48 (87.27%)	7 (12.73%)	0.054
Diabetes mellitus	45 (84.91%)	8 (15.09%)	0.008
Cancer	7 (63.64%)	4 (36.36%)	<0.001
Smoking	52 (92.86%)	4 (7.14%)	0.964

Data are given as median (1st quartile – 3rd quartile) for continuous variables, and frequency (percentage) for categorical variables.

We performed Cox regression analysis to determine significant factors associated with mortality. Sodium level (OR: 0.806, 95% CI: 0.703-0.924, P=0.002), AST level (OR: 1.015, 95% CI: 1.004-1.026, P=0.007), and RVDD (OR: 19.662, 95% CI: 5.371-71.971, P<0.001) were associated with mortality, while other variables included in the model, namely, age (P=0.281), WBC (P=0.485), hemoglobin (P=0.507), glucose (P=0.210), 1st day creatinine (P=0.278), 1st day CKMB (P=0.665), 1st day troponin (P=0.870), ferritin (P=0.742), D-dimer (P=0.090), procalcitonin (P=0.074), dyspnea (P=0.205), diabetes mellitus (P=0.617), PAB (P=0.874), cancer (P=0.178), ejection fraction (P=0.374), and ICU need (P=0.994) were not (Table 3).

Table 3: Significant factors of death, multiple logistic regression analysis (Forward conditional, step 5)

	β coefficient	Standard Error	Wald	*P*-value	Exp(β)	95.0% CI for Exp(β)	
Sodium	-0,216	0.070	9.541	0.002	0.806	0.703	0.924
AST	0,015	0.006	7.291	0.007	1.015	1.004	1.026
RVDD	2,979	0.662	20.243	<0.001	19.662	5.371	71.971
Constant	-1.843	8.730	3.834	0.050			

CI: Confidence Interval, Dependent Variable: Death, Nagelkerke R^2=0.464

Multiple logistic regression analysis revealed that age (OR: 1.072, 95% CI: 1.039-1.106, P<0.001), AST level (OR: 1.049, 95% CI: 1.019-1.080, P=0.001), 1st day troponin level (OR: 1.018, 95% CI: 1.004-1.032, P=0.013), dyspnea (OR: 9.762, 95% CI: 2.871-33.196, P<0.001), fatigue (OR: 4.727, 95% CI: 1.828-12.225, P=0.001) were associated with ICU need, while gender (P=0.808), WBC (P=0.265), hemoglobin (P=0.439), glucose (P=0.683), sodium (P=0.190), calcium (P=0.051), ALT (P=0.459), albumin (P=0.074), CRP (P=0.093), 1st day CKBM (P=0.557), ferritin (P=0.894), D-dimer (P=0.613), procalcitonin (P=0.697), fever (P=0.989), cough (P=0.168), headache (P=0.844), hypertension (P=0.540), and diabetes mellitus (P=0.537) were not (Table 4).

Table 4: Significant factors of ICU need, multiple logistic regression analysis (Forward conditional, step 10)

	β coefficient	Standard Error	Wald	*P*-value	Exp(β)	95.0% CI for Exp(β)	
Age	0.069	0.016	19.124	<0.001	1.072	1.039	1.106
AST	0.048	0.015	10.355	0.001	1.049	1.019	1.080
1st day troponin	0.018	0.007	6.116	0.013	1.018	1.004	1.032
Dyspnea	2.279	0.624	13.313	<0.001	9.762	2.871	33.196
Fatigue	1.553	0.485	10.265	0.001	4.727	1.828	12.225
Constant	-8.721	1.381	39.861	<0.001			

CI: Confidence Interval, Dependent Variable: ICU need, Nagelkerke R^2=0.744

Discussion

This study shows that mortality among hospitalized patients with Covid-19 was significantly related to cTnT, RVDD, and especially D-dimer (as shown by logistic regression). In previous studies, high troponin levels and myocardial damage were identified with infection, in addition to varying degrees of electrocardiographic and echocardiographic abnormalities [8, 10]. Such relationships have become more remarkable with the increasing number of cases all over the world. As of November 21, while there was a total of more than 440,000 Covid-19 cases in Turkey, and more than 58 million laboratory-confirmed cases around the world.

Severe respiratory distress (as in ARDS) is considered the main cause of death in Covid-19; therefore, severe pneumonia was associated with mortality regardless of admission to the intensive care unit, or the need of mechanical ventilation [11]. Co-morbidities, such as advanced age, diabetes, hypertension, and coronary artery disease, are well established as factors that

increase the possibility of being infected with Covid-19 and related mortality [12]. Similarly, in our study, advanced age, diabetes, and hypertension were risk factors in terms of ICU requirement, but this risk was not found in smokers. Significant differences in age, diabetes, hypertension, cTnT, D-dimer, ferritin and procalcitonin in patients in need of ICU (compared to those without) suggests that factors other than primary lung infection may also contribute to disease progression in these patients. While 7.2% of the patients hospitalized with the diagnosis of Covid-19 developed acute heart injury, overall, cardiac injury was observed at a higher frequency in patients who were hospitalized in the ICU compared to those who were not (22.2%) [13]. Although it was revealed that there was a strong relationship between ICU need and cardiac injury, a meta-analysis showed that high cTnT is associated with cardiac injury [7]. In another meta-analysis including 341 patients, increased cTnT levels were associated with fatal Covid-19 infection [14]. In a study examining 191 patients, hs-cTnI (high-sensitivity Troponin I) increased in more than half of the hospitalized patients who died due to Covid-19 disease. In these patients, hs-cTnI levels were higher than 28pg/ml in 46%, whereas this rate was around 1% in survivors, indicating a considerable association between hs-cTnI levels and mortality [15]. This was further exemplified by a study evaluating 416 patients, among which 19.7% had cardiac injury. The requirement for invasive or non-invasive ventilation was observed to a greater degree in these patients, especially those with high cTnT values [16]. In our study, a significant correlation was observed between cardiac damage and clinical disease severity. The significant correlation between ICU requirement decreased LVEF and increased cTnT on days 1 and 3 suggests a role of cardiac injury in ICU need. A single-center study with a similar design to ours reported cardiac injury in 19% of patients hospitalized with Covid-19; moreover, cardiac damage was closely associated with in-hospital mortality [7]. In our study, the significant relationship between ICU need and cTnT levels (as a marker of cardiac damage) on both the first and third days supports this hypothesis and provides further evidence for the notion that a close relationship between cardiac damage and mortality exists.

There was a significant relationship between D-dimer, ferritin and procalcitonin levels and the need for ICU admission. In a similar study, the finding that D-dimer levels were greater than 500 ng/ml in patients who died (compared to survivors) was put forward as an independent indicator of the prothrombotic process [17]. Systemic microvascular thrombosis is common in critical patients infected with Covid-19 and has been associated with death [18,19]. In addition, infection-induced coagulopathy and hyperfibrinolysis are common in severe cases [20]. In our study, high D-dimer levels, in addition to indicating that the course of the disease would be critical, were associated with mortality. Again, in a retrospective study in which 343 patients were included, D-dimer > 2.0 n/ml was associated with in-hospital mortality in patients infected with Covid-19, and it was shown that D-dimer was an effective marker in determining treatment approach [21]. The relationship between pulmonary embolism and RVDD has been previously shown [22]. In our study, the significant increase in right ventricular pressures (PABs) and right ventricular diameters (RVDD) together with the elevation of D-dimer in patients who required ICU care supports the presence of a prothrombotic effect which may lead to pulmonary embolism. The observation of a significant relationship between increased RVDD and mortality in patients needing ICU treatment supports this notion [23]. The increase in RVDD values in our study may have caused an increase in cTnT, which possibly led to the deterioration in right ventricular functions secondary to pulmonary embolism. The relationships between mortality and parameters such as RVDD, PAB and D-dimer may suggest that mortality due to Covid-19 may develop in relation with microvascular thrombosis. Unlike many studies in the literature, echocardiographic findings in our prospective study are important in terms of showing microembolic complications in Covid-19 infection, despite the use of antiaggregant and antithrombotic therapy.

Limitations

Our study has some limitations. First, the research was conducted in a single center and the number of patients, especially in the mortality group, was low. Second, the current state of routine practice (due to Covid-19) prevented the evaluation of a greater number of echocardiographic analyses and longitudinal follow-up. Third, brain natriuretic peptide levels could not be evaluated.

Conclusion

While significant relationships were found between various parameters, co-morbid factors and the requirement of ICU or the development of mortality in patients with Covid-19, regression analyses demonstrated that significant factors were much fewer than suggested by univariate analyses. Of note, interestingly, smoking was not a factor that increased ICU admission or death, a finding that has been mirrored in some studies. Prospective data obtained from our study support the significant relationship between mortality and the levels of cTnT, RVDD and D-dimer, and show that these may indicate the formation of end-stage cardiac injury, microvascular thrombosis and pulmonary embolism in patients admitted to the ICU. The RVDD and PAB values might be valuable markers that could predict mortality, which warrants further studies on this subject to elucidate these relationships and aid physicians in the management of patients with Covid-19.

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