ABSTRACT

INTRODUCTION: Novel coronavirus disease (COVID-19) may lead to diffuse pulmonary intravascular thrombosis that can lead to a sudden right ventricular stress by causing an acute elevation in pulmonary artery pressure. We aim to evaluate this right ventricular stress due to COVID-19 with the electrocardiography (ECG) score

METHODS: One hundred and forty-one patients hospitalized with COVID-19, whose ECGs were obtained ECG at admission, were included in the study. ECG score was calculated for each patient from the ECGs taken during admission.

RESULTS: In-hospital mortality was significantly higher in COVID-19 patients with an ECG score of ≥10 (15% vs 0%, p=0.001). Univariate regression analysis reveals neutrophil and lymphocyte counts, creatinine kinase, D-dimer, fibrinogen, C-reactive protein (CRP), cardiac biomarkers, ferritin and procalcitonin levels as significant predictors of ECG score of ≥10. The ECG score was found as a significant predictor of mortality (odds ratio 0.33, 95% confidence interval 0.14-0.77, p=0.01) in COVID-19 patients. According to multivariate regression analysis, CRP (odds ratio 1.03, 95% confidence interval 1.00-1.05, p=0.02) and high-sensitive cardiac troponin I (odds ratio 1.00, 95% confidence interval 0.99-1.00, p=0.009) are significant independent predictors of ECG score of ≥10 and mortality in COVID-19 patients, respectively.

DISCUSSION AND CONCLUSION: ECG score appears to be associated with the severity and mortality of the COVID-19 infection.

Keywords: COVID-19, electrocardiography score, right ventricular stress, pulmonary hypertension
INTRODUCTION

The increased incidence of cardiac dysfunction and hypercoagulability has been reported in especially critically ill hospitalized patients with 2019 novel coronavirus disease (COVID-19) (1-3). In a recent published case series sudden severe hemodynamic instability associated with acute right ventricular failure, which was also confirmed by the echocardiography findings of right ventricular dilatation and systolic dysfunction, was reported in patients with COVID-19 (3). This observation is also supported by the findings of Argulian et al, who demonstrated right ventricular dilatation in patients with COVID-19 infection and significant association between the right ventricular enlargement and in-hospital mortality in these patients (4). In the light of increasing data, the right heart appears to be primarily affected by COVID-19 infection compared to the left. This could be explained by the elevated right ventricular afterload related to extensive pulmonary vascular thrombosis with microangiopathy and increased pulmonary vascular resistance induced by the vasoconstriction due to hypoxemia (5-7). We aim to assess the right ventricular stress induced by the increased right ventricular afterload in COVID-19 infection with the ECG scoring system (8) developed to evaluate the severity of pulmonary hypertension in pulmonary embolism.

MATERIALS AND METHODS

Study population

In the present single-center retrospective study, we recruited consecutive adult patients hospitalized with the diagnosis of COVID-19 infection according to the results of laboratory tests between April 1 and April 30, 2020. Patients whose 12-lead ECG was not taken at the time of admission to the emergency department or before starting any treatment were excluded from the study.

The study complied with the Declaration of Helsinki and was approved by the Institutional Review Board and the Locals Ethics Committee. All patients or their guardians gave written informed consent while retrospective data were gathered.

COVID-19 infection induced right ventricular stress was calculated by the ECG score according to the following criteria: (1) sinus tachycardia (> 100 beats/minute) [2 points]; (2) incomplete right bundle branch block [2 points]; (3) complete right bundle branch block [3 points]; (4) T-wave inversion, scored by magnitude [in lead V1 < 1 mm 0, 1-2 mm 1, > 2 mm 2 points; in lead V2 < 1 mm 1, 1-2 mm 2, > 2 mm 3 points; in lead V3 < 1 mm 1, 1-2 mm 2, > 2 mm 3 points]; (5) T-wave inversion in leads V1 through V4 [> 2 mm 4 points]; (6) components of the S1Q3T3 pattern [S wave in lead I 0, Q wave in lead III 1, T-wave inversion in lead III 1 point]; (7) the complete S1Q3T3 pattern [2 points]. The maximum calculable score was 21. ECG scores were calculated independently by two experienced cardiologists blinded to patient data from admission ECGs of COVID-19 patients. Then, patients were classified according to the ECG score cut-off value of ≥ 10 points, which was found highly specific for the determination of severe pulmonary hypertension due to pulmonary embolism by Daniel et al. (8).

We collected epidemiological, demographic and clinical outcome data, radiological findings, clinical characteristics, cardiac biomarkers (creatinine kinase, creatinine kinase-myocardial brain fraction [CK-MB] and high-sensitive troponin I [hs-TnI]), C-reactive protein (CRP), procalcitonin, ferritin, d-dimer, fibrinogen and other routine laboratory test results from the patient’s electronic medical records. Clinical outcomes of the patients were followed up to May 25, 2020. These collected data were independently checked by two researchers. In addition, the study patients who had pulmonary embolism based on the chest computed tomography findings were excluded.

Statistical Analysis

Descriptive statistics were performed using mean ± standard deviation (SD) for normally distributed or median and interquartile ranges (IQR) for skewed distributed continuous variables and percentage for categorical variables. The distribution of variables was assessed by the Kolmogorov-Smirnov test. Continuous variables were compared by the independent-samples t test when normally distributed or the Mann-Whitney U
test when not normally distributed. The analyzes were carried out by classification of the hospitalized COVID-19 patients as those with and without ECG score ≥ 10 and who died in hospital and survived. We used the independent sample t test or Mann-Whitney U test whenever appropriate to compare the differences in continuous variables between the patients with ECG score ≥ 10 and <10 as well as patients who died and those who were discharged from the hospital. The differences in categorical variables between patients with ECG score ≥ 10 and <10 and those who died and were discharged from the hospital were compared using the X2 test or Fisher's exact test, when appropriate. Univariate logistic regression analysis was used to identify significant predictors of both in-hospital mortality and the ECG score ≥10 in patients with COVID-19. Variables with p values < 0.05 on univariate analysis were included in the multivariate logistic regression analysis to determine independent predictors of both in-hospital mortality and the ECG score ≥ 10 in patients with COVID-19. The odds ratios (OR) were given with 95% confidence intervals (CI) and p values. A p value < 0.05 was considered as statistically significant. All statistical analyses were performed using IBM SPSS software version 26.0 (IBM Corp, Armonk, NY).

RESULTS

After excluding 26 patients whose diagnosis of COVID-19 was not confirmed by the laboratory tests, 61 patients whose ECG was not obtained at the time of admission, 4 patients with simultaneous pulmonary embolism as well as 14 patients whose medical data were inadequate in electronic records, we included 141 hospitalized patients with COVID-19 infection in the study. During the hospitalization, 5 patients died and 136 patients were discharged. The mean age of the patients was 63 ± 12 and 40% were female. None of the study patients showed evidence of atrial fibrillation or acute myocardial infarction.

Of 141 patients, 36 (26%), 44 (31%), 27 (19%), 5 (3.5%) and 2 (1.4%) had underlying diabetes, hypertension, coronary artery disease, chronic obstructive pulmonary disease, and cancer, respectively.

The comparison of clinical and demographic characteristics, laboratory and radiological findings between the patients with an ECG score of ≥ 10 and <10 as well as those who died in hospital and survived are presented in Table I. There is no significant difference in the comorbidities, age, gender, laboratory findings including kidney and liver function tests, hemoglobin levels, platelet and leukocyte counts between the patients with an ECG score of ≥10 and <10 as well as those who died, and survivors (Table I). However, smoking rate is significantly higher in COVID-19 patients who died in hospital compared with those who survived (14% vs 40%, p = 0.04; Table I).

The prevalence of bilateral pneumonia is significantly more frequent in patients with an ECG score of ≥10 compared in those with ECG score of <10 (100% vs 49%, p < 0.001), while it is statistically similar in patients who died in hospital and those who survived (100% vs 60%, p = 0.16). In addition, the lymphocyte count is significantly lower in patients with an ECG score of ≥ 10 (median [IQR], 0.9 [0.8-1.0] ×10³/μL vs 1.1 [0.9-1.3] ×10³/μL, p < 0.001) and those who died in hospital (median [IQR], 0.8 [0.3-0.9] ×10³/μL vs 1 [0.88-1.2] ×10³/μL, p = 0.002). Creatinine kinase, D-dimer, fibrinogen, CRP, CK-MB, hs-cTnI, ferritin and procalcitonin levels are significantly elevated in COVID-19 patients who died in hospital and those with an ECG score of ≥10 (Table I). In-hospital mortality is significantly higher in COVID-19 patients with an ECG score of ≥10 than in those with ECG score of <10 (15% vs 0%, p = 0.001).

Univariate and multivariate logistic regression results are detailed in Table II and Table III. In univariate analysis, neutrophil and lymphocyte counts, levels of creatinine kinase, D-dimer, fibrinogen, CRP, CK-MB, hs-cTnI, ferritin and procalcitonin are the significant predictors of the ECG score ≥10 in COVID-19 patients (Table II). ECG score, neutrophil count, levels of creatinine kinase, D-dimer, fibrinogen, CRP, CK-MB, hs-cTnI, ferritin and procalcitonin are determined as the significant predictors of mortality in hospitalized patients with COVID-19 by univariate logistic regression analysis (Table III). Multivariate logistic regression analysis reveals that CRP was the only significant independent predictor of the
ECG score ≥10 in COVID-19 patients (OR 1.03, 95% CI 1.00 to 1.05, p = 0.02). High-sensitive cardiac troponin I is found to be the only significant independent predictor of in-hospital mortality in patients with COVID-19 infection by the multivariate logistic regression analysis (OR 1.00, 95% CI 0.99 to 1.00, p = 0.009).

Table 1. Epidemiological, demographic, clinical characteristics, laboratory and radiological findings of patients with COVID-19 infection on admission

| Characteristics                | All patients (n=141) | ECG score ≥10 (n=33) | ECG score <10 (n=108) | P | Death in hospital (n=5) | Survived (n=136) | p |
|--------------------------------|----------------------|----------------------|-----------------------|---|------------------------|-----------------|---|
| Age                            | 63 ±12               | 67 ± 14              | 62 ± 12               | 0.06† | 64 (58-76)              | 63 ± 12         | 0.47† |
| Female patients                | 57 (40%)             | 17 (52%)             | 40 (37%)              | 0.14† | 1 (20%)                 | 56 (41%)        | 0.34† |
| Smoking                        | 21 (15%)             | 6 (18%)              | 15 (14%)              | 0.74† | 2 (40%)                 | 19 (44%)        | 0.04† |
| Diabetes                       | 36 (26%)             | 9 (27%)              | 27 (25%)              | 0.60† | 2 (40%)                 | 34 (25%)        | 0.33† |
| Hypertension                   | 44 (31%)             | 11 (33%)             | 33 (31%)              | 0.28† | 2 (40%)                 | 42 (31%)        | 0.73† |
| CAD                            | 27 (19%)             | 6 (18%)              | 21 (19%)              | 1.0†  | 1 (20%)                 | 26 (19%)        | 1.0†  |
| COPD                           | 5 (3.5%)             | 1 (3%)               | 4 (4%)                | 1.0†  | 1 (20%)                 | 4 (3%)          | 0.43† |
| Cancer                         | 2 (1.4%)             | 1 (3%)               | 1 (0.9%)              | 0.41† | 0 (0%)                  | 2 (2%)          | 1.0†  |

**Chest CT Findings**

| Unilateral pneumonia          | 55(39.0%)            | 0 (0%)               | 55 (51%)              | <0.001† | 0 (0%)                  | 55 (40%)        | 0.16† |
| Bilateral pneumonia           | 86 (61.0%)           | 33 (100%)            | 53 (49%)              |         | 5 (100%)                | 81 (60%)        |     |

**Laboratory Findings**

| Leukocyte count >10³/µL       | 6.8 (5.5 - 8.5)      | 7.7 (5.8 - 9.9)      | 6.6 (5.4 - 8.3)       | 0.066†  | 8.1 (5.9 - 10.5)        | 6.6 (5.5 - 8.5) | 0.32† |
| Neutrophil count >10³/µL      | 4.9 (3.5 - 6.6)      | 6.0 (4.3 - 8.3)      | 7.7 (3.3 - 6.0)       | 0.002†  | 6.5 (4.8 - 9.2)         | 4.8 (3.5 - 6.5) | 0.1†  |
| Lymphocyte count <10³/µL      | 1.0 (0.86 - 1.22)    | 0.9 (0.8 - 1.0)      | 1.1 (0.9 - 1.3)       | <0.001‡ | 0.8 (0.3-0.9)           | 1 (0.88 - 1.2) | 0.002‡ |
| Platelets >10³/µL             | 220 (166 - 272)      | 205 (161 - 307)      | 222 (167 - 265)       | 0.798‡  | 174 (144 - 185)         | 225 (167 - 280) | 0.05‡ |
| Hemoglobin, g/dL              | 12 (11 - 13)         | 12 (11.9 - 13)       | 12 (12 - 13)          | 0.30‡   | 11 (9.1 - 13.6)         | 12 (11 - 13)   | 0.47‡ |
| AST, U/L                      | 32 (24 - 42)         | 44 (30 - 53)         | 30 (23 - 38)          | 0.34‡   | 47 (34 - 81)            | 32 (24 - 41)   | 0.06‡ |
| ALT, U/L                      | 31 (23 - 45)         | 35 (23 - 56)         | 31 (23 - 45)          | 0.22‡   | 43 (16 - 62)            | 31 (23 - 45)   | 0.78‡ |
| Albumin, g/L                  | 34 (30 - 36)         | 32 (27 - 36)         | 34 (32 - 36)          | 0.15‡   | 30 (22 - 34)            | 34 (31 - 36)   | 0.05‡ |
| Creatinine kinase, U/L        | 50 (39 - 112)        | 112 (64 - 198)       | 50 (36 - 80)          | <0.001† | 89 (71 - 514)           | 55 (38 - 109) | 0.04† |
| LDH, U/L                      | 305 (264 - 368)      | 365 (280 - 531)      | 308 (263 - 350)       | 0.003‡  | 420 (332 - 575)         | 311 (264 - 364) | 0.06‡ |
| Creatinine, mg/dL             | 0.9 (0.77 - 1.1)     | 1.2 (0.8 - 1.4)      | 0.9 (0.75 - 1.1)      | 0.11‡   | 1.5 (0.9 - 2.1)         | 0.9 (0.9 - 1.1) | 0.16‡ |
| D-dimer, µg/mL                | 0.85 (0.38 - 2.04)   | 3.6 (2.1 - 4.5)      | 0.5 (0.26 - 1.0)      | <0.001† | 6.3 (5.8 - 7.1)         | 0.8 (0.36 - 1.62) | <0.001† |
| Fibrinogen, mg/dL             | 523 (429 - 632)      | 740 (650 - 799)      | 487 (420 - 561)       | <0.001† | 854 (804 - 893)         | 518 (518 - 621) | <0.001† |
| CRP, mg/L                     | 90 (50 - 154)        | 217 (152 - 244)      | 49 (47 - 108)         | <0.001† | 263 (250 - 269)         | 87 (76 - 149)  | <0.001† |
| CK-MB, µg/L                   | 4 (3 - 9)            | 18 (11 - 27)         | 3 (2 - 5)             | <0.001† | 68 (36 - 75)            | 4 (3 - 8)      | <0.001† |
| hs-cTnI, ng/L                 | 18 (15 - 67.5)       | 360 (169 - 467)      | 16 (13 - 19)          | <0.001† | 2100 (1816 - 2616)      | 17 (14 - 50)   | <0.001† |
| Ferritin, µg/L                | 400 (280 - 672)      | 980 (704 - 1077)     | 339 (254 - 456)       | <0.001† | 1120 (985 - 1231)       | 392 (278 - 630) | <0.001† |
| Procalcitonin, µg/L           | 0.36 (0.05 - 3.6)    | 6.7 (3.9 - 12.4)     | 0.11 (0.03 - 0.84)    | <0.001† | 12.2 (8.6 - 13.6)       | 0.3 (0.05 - 0.4) | <0.001† |

**ECG score, ≥7 ± 5**

| Death in hospital             | 5 (3.5%)             | 5 (15%)              | 0 (0%)                | 0.001‡  | 19 ± 1                   | 6 ± 4           | <0.001† |

Data are given as mean ± SD, median (interquartile range) or n (%). ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; CAD = coronary artery disease; CK-MB = creatinine kinase-myocardial brain fraction; COPD = chronic obstructive pulmonary disease; CRP = C-reactive protein; CT = computed tomography; ECG = electrocardiography; hs-cTnI = high-sensitive cardiac troponin I; LDH = Lactate dehydrogenase.

† Compared using the independent sample t test
‡ Compared using the Mann-Whitney U test
§ Compared using the X² test
\* Compared using the Fisher’s exact test
**DISCUSSION**

As far as we know, the present study is the first to investigate the usefulness of an ECG scoring system that is used to detect severe pulmonary hypertension due to pulmonary embolism in predicting the severity and prognosis of an infection such as COVID-19, which primarily affects the lower respiratory tract. A significant association between the cardiac injury and in-hospital mortality has been previously reported in patients with COVID-19 infection (9,10). Recently, it has been reported that right ventricular dilatation and dysfunction are associated with cardiac injury and increased mortality in patients with COVID-19 infection (4,11). The mechanism of this observation can be explained as follows. Presumably, both an extensive immune response and endothelial damage caused by the intracellular severe acute respiratory syndrome coronavirus 2 can induce diffuse intravascular thrombosis in lungs (6,7). This widespread vascular thrombosis, which has been shown in the lungs of COVID-19 patients [7], leads to an acute increase in pulmonary arterial pressure and in right ventricular afterload. In addition, an increase in pulmonary vascular resistance due to hypoxemia, which induces vasoconstriction in COVID-19 patients, contributes to the increase in both pulmonary artery pressure and right ventricular afterload. Then, the process proceeds to acute right ventricular insufficiency and right ventricular enlargement, also called acute cor pulmonale, which is related with increased mortality in patients with acute respiratory distress syndrome (5,6). Based on these observations, we suggest that ECG, which is a safe, easy applicable and inexpensive test, might indicate acute right ventricular stress secondary to acute increase in
pulmonary hypertension and thus may give an opinion about the severity and the prognosis of the COVID-19 disease.

We have observed significantly higher levels of creatinine kinase, D-dimer, fibrinogen, CRP, CK-MB, hs-cTnI, ferritin, procalcitonin and neutrophil count and significantly lower lymphocyte count in COVID-19 patients with an ECG score of ≥ 10 than in those with an ECG score of < 10. Additionally, the prevalence of bilateral pneumonia and in-hospital mortality rate are significantly higher in COVID-19 patients with an ECG score of ≥ 10. The univariate analysis has showed that ECG score was a significant predictor of in-hospital mortality in patients with COVID-19. On the other hand, neutrophil and lymphocyte counts, levels of creatinine kinase, D-dimer, fibrinogen, CRP, CK-MB, hs-cTnI, ferritin and procalcitonin are found to be significantly associated with the ECG score of ≥ 10 by the univariate logistic regression analysis in patients with COVID-19 infection. Moreover, CRP has appeared determined as the only independent predictor of the ECG score ≥10 in hospitalized COVID-19 patients in the multivariate logistic regression analysis. Our findings have revealed that there is a relationship between the ECG score, which can be calculated from ECG taken at the time of hospital admission, and the severity as well as the prognosis of the COVID-19 disease.

According to the univariate analysis, neutrophil count, levels of creatinine kinase, D-dimer, fibrinogen, CRP, CK-MB, hs-cTnI, ferritin and procalcitonin are significantly associated with in-hospital mortality in patients with COVID-19 infection. However, our multivariate logistic regression analysis has demonstrated that hs-cTnI is the only strong and significant independent predictor of in-hospital mortality in COVID-19 patients. This result is also compatible with the previous reports that indicating association between the cardiac injury and in-hospital (9,10).

The present study has some limitations that need to be mentioned. Firstly, we have examined the relatively small number of patients in a single center. Secondly, as a nature of retrospective study, some specific investigations such as ECG monitoring to observe potential changes in ECG scores during the course of COVID-19 disease or echocardiographic examinations are lacking in our study. The final limitation is that our study consisted only of COVID-19 patients and there was no control group to compare in terms of ECG scores.

**CONCLUSION**

Our results suggest that viral infections such as influenza A and coronavirus infections that are complicated to intravascular thrombosis and pulmonary microembolism (12) can be monitored through the ECG scoring system that is developed to assess the right ventricular stress due to pulmonary hypertension. Moreover, we found significant relationships between the ECG score and the severity and the mortality of the COVID-19 disease. Finally, with an ECG scoring system that quantities right ventricular stress, an ECG can be a useful prognostic tool in the COVID-19 disease. Further large-scale clinical trials are required to confirm our findings.

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