Long-term predictive value of cardiac biomarkers in patients with COVID-19 infection

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Abstract. – OBJECTIVE: Several studies have investigated the association between cardiac biomarkers and short-term prognosis in the COVID-19 infection. However, the data on the predictive value of cardiac biomarkers to predict long-term prognosis in COVID-19 infection are limited. We aimed at determining the relationship between N-terminal brain-type natriuretic peptide (NT-proBNP) and high-sensitivity cardiac troponin I (hs-TnI) as cardiac biomarkers and in-hospital/long-term outcomes in COVID-19 infection.

PATIENTS AND METHODS: The study included a total of 916 patients with confirmed COVID-19 infection. The primary outcome was in-hospital and 1-year mortality. The secondary outcome was intensive care need at admission or the need to be transferred to the intensive care unit later on. RESULTS: The study included 498 (54.4%) males and 418 (45.6%) females with a mean age of 55.1±18.5 years. The patients with known heart failure (HF), COVID-19-related HF, acute renal failure (ARF), chronic kidney disease (CKD), diabetes mellitus, hypertension, coronary artery disease (CAD), chronic obstructive pulmonary disease (COPD)/asthma, high CO-RADS score (≥ 4), lower EF, higher hs-TnI, and NT-proBNP levels had increased in-hospital and 1-year mortality. After multivariate analysis, NT-proBNP, hs-TnI, CKD, ARF, diabetes mellitus, and CAD were independent predictors of in-hospital and 1-year mortality. After ROC analysis, NT-proBNP cut-off levels of 1022.50 (sensitivity 87.5%, specificity 87.1%) and 1008 (sensitivity 88.6%, specificity 88.0%) were found to predict in-hospital and 1-year mortality, respectively. Hs-TnI cut-off levels of 49.6 (sensitivity 88.6%, specificity 88.9%) and 34.10 (sensitivity 83.8%, specificity 84.1%) were found to predict in-hospital and 1-year mortality, respectively.

CONCLUSIONS: The current study suggests that NT-proBNP and hs-TnI can be used as valuable cardiac biomarkers to predict short-term and long-term parameters in COVID-19 infection.

Key Words: Cardiac biomarkers, High-sensitivity cardiac troponin I, hs-TnI, N-terminal brain-type natriuretic peptide, NT-proBNP, COVID-19.

Introduction

The coronavirus disease 2019 (COVID-19) outbreak has affected about 522 million people worldwide, causing more than 6 million deaths despite a total of 12 billion vaccine doses¹. Not only the respiratory system is affected in the short term, but also the cardiovascular, hematological, and central nervous systems may also be affected which may cause multiorgan dysfunction and death². Patients with comorbid diseases, such as hypertension, diabetes mellitus, coronary heart disease (CAD), heart failure, and chronic kidney disease (CKD) have a worse prognosis ³,⁴. Regardless of the severity of the disease in the acute phase, the disease may increase the risk of mortality in the long term, particularly in the elderly population⁵.

Recently, inflammatory/hematologic parameters, such as procalcitonin, albumin, C-reactive protein (CRP), lactate dehydrogenase (LDH), cardiac biomarkers, such as high-sensitivity cardiac troponin I (hs-TnI), D-dimer, creatinine kinase-myocardial band (CK-MB), Brain-type natriuretic peptide (BNP) and imaging scoring systems, such as the Coronavirus Disease 2019 (COVID-19) Reporting and Data System (CO-RADS) classification have been investigated regarding the severity of disease or predictors of short-term mortality⁴,⁶,⁷. However, studies⁸,⁹ on the effect of COVID-19 infection on long-term mortality are limited and include specific patient groups, such as the older population and CKD.

An increase of cardiac marker levels (mainly BNP and troponin) during the infection reflects the excessive amount of inflammation, viral load, cytokine storm, and atherothrombotic process that may cause direct or indirect cardiac damage in the body⁷. Therefore, those parameters can provide useful information about not only short-term but also long-term mortality risks after COVID-19 in-
fection. Since data on the parameters of the long-term mortality risk of COVID-19 are limited, we aimed at investigating the ability of the troponin and NT-proBNP levels to predict long-term mortality in the general population.

**Patients and Methods**

**Study Design and Clinical Parameters**

This single-center, case-control, and cross-sectional study was approved by the Local Ethics Committee of Kırıkkale University Hospital in terms of compliance with the Helsinki principles (Date: 27.01.2022, Decision number: 2022.01.29), and informed written consent was obtained from all participants. The study included a total of 916 patients having a history of COVID-19 infection confirmed by positive Real-Time Polymerase Chain Reaction (PCR) between April 2020 and April 2021. Patients who were asymptomatic, pregnant, younger than 18 years of age, and did not undergo computed tomography (CT) were excluded from the study. Non-euvolemic patients with known chronic renal failure or heart failure were also excluded from the study. Patients’ demographics, clinical characteristics, medical history, laboratory parameters, radiological and clinical outcome data were obtained through the electronic patient database.

**Cardiac Biomarkers**

The hs-TnI as a biomarker of myocardial injury and N-terminal proBNP (NT-proBNP) as a biomarker of cardiac stress were measured within the first 24 hours of hospital admission. Based on our institutional laboratory normal ranges, a value of 14 ng/L for hs-TnI and 100 pg/mL for BNP was considered above the upper limit of normal serum levels, and values above these limits were considered elevated.

**Thorax Computed Tomography Imaging**

All patients were imaged at presentation with multidetector computer tomography (CT) using the TOSHIBA Alexion/Advance Edition (Toshiba Medical Systems Corporation, Japan, 1.25 mm section thickness) with 64-detector rows. All scans were acquired without an intravenous contrast agent, with the patient in a supine position during end inspiration. CT indications were as follows: patients having moderate-to-severe respiratory symptoms and high index of clinical suspicion of COVID-19 infection, showing unexplained clinical deterioration and/or where other concurrent lung pathology needs exclusion, COVID-19-positive patients with associated co-morbidities (age >65 years, diabetes, hypertension, obesity, cardiovascular disease, chronic respiratory disease, immune-compromise, etc.) who, despite having mild symptoms and indeterminate CXR, record oxygen saturation of <93 percent at rest while breathing room air or de-saturate on six-minute walk test.

The CO-RADS classification was used to categorize the level of COVID-19 suspicion. According to that system, the degree of suspicion is classified into five levels from very low (CO-RADS 1) to very high (CO-RADS 5). The CO-RADS levels are summarized as follows: CO-RADS 1 (no suspicion: normal findings); CO-RADS 2 (low level of suspicion: absence of ground-glass opacities [GGO], the presence of tree-in-bud signs or endobronchial spread or bronchiolitis); CO-RADS 3 (indeterminate: unifocal GGO); CO-RADS 4 (high level of suspicion: unilateral multifocal GGO); and CO-RADS 5 (very high level of suspicion: multifocal bilateral GGO).

**Echocardiographic Measurement**

Standard 2-dimensional echocardiography was performed on all subjects lying in the left lateral decubitus position with a Vivid 7 Doppler echocardiographic unit (GE Vingmed Ultrasound, Horten, Norway) using a 3.5-MHz transducer. Echocardiographic measurements were made according to ACC and AHA standard protocols. We utilized two-dimensional and M-mode echocardiography to investigate ejection fraction (EF). An EF of less than 50% was defined as heart failure.

**Outcome**

The primary outcome was in-hospital and 1-year mortality after the diagnosis of the COVID-19 infection. The secondary outcome was the need for intensive care from the beginning of the hospitalization or the need to be transferred to the intensive care unit later on. In-hospital death was defined as death during the index hospital stay related or non-related to COVID-19. One-year mortality was defined as death related or unrelated to COVID-19 infection within 1 year from diagnosis.

**Statistical Analysis**

SPSS 25.0 (IBM Corporation, Armonk, NY, USA) program was used in the analysis of the variables. Quantitative variables with a normal
distribution were specified as the mean ± standard deviation and categorical variables were specified with number and percentage values. The conformity of quantitative data to normal distribution was assessed with the Kolmogorov-Smirnov test. Independent Samples t-test was applied in the comparison of continuous variables showing normal distribution. Odds ratio with 95% confidence intervals was used to determine how many effects were caused by those who were exposed to a risk factor than those who were not. Logistic regression analysis was applied in the univariate and multivariate analyses to determine the independent predictors of both in-hospital and 1-year mortality. The ROC curves were used to determine the cut-off values of cardiac biomarkers to predict mortality. A p-value of <0.05 was considered statistically significant.

### Results

A total of 916 patients were analyzed in our study, including 498 (54.4 %) males and 418 (45.6 %) females with a mean age of 55.1±18.5 years. Demographic, clinical, imaging, and laboratory characteristics of the patients were presented in Table I.

As presented in Table II, a significant association was found between higher levels of BNP and troponin values of the patients and ICU admission from the beginning, in-hospital mortality, and 1-year mortality rates (p < 0.001). Table III provides information about univariate and multivariate logistic regression analysis results of patients’ in-hospital and 1-year mortality. Univariate logistic regression analysis results revealed that patients with known heart failure, heart failure due to COVID-19 infection, acute renal failure (ARF), CKD, diabetes mellitus, hypertension, CAD, chronic obstructive pulmonary disease (COPD)/asthma (p = 0.001), high CO-RADS score (≥ 4), lower EF, higher troponin and NT-proBNP levels were associated with both higher in-hospital and 1-year mortality (p < 0.001). After the multivariate logistic regression analysis model-1, higher NT-proBNP (odds ratio (OR): 1.00; 95%
Long-term predictive value of cardiac biomarkers in patients with COVID-19 infection

Confidence interval (CI): 1.00-1.01; \( p = 0.009 \) and hs-TnI levels (OR: 1.02; 95% CI: 1.01-1.02; \( p < 0.001 \)) remained as significant predictors of in-hospital mortality, as well as CKD (OR: 3.57; 95% CI: 1.03-12.28; \( p = 0.043 \)), ARF (OR: 8.44; 95% CI: 1.73-41.8; \( p = 0.008 \)), diabetes mellitus (OR: 3.37; 95% CI: 1.39-8.19; \( p = 0.007 \)), and CAD (OR: 8.85; 95% CI: 2.15-36.37; \( p = 0.002 \)). Similarly, the multivariate logistic regression model-2 showed that higher NT-proBNP (OR: 1.00; 95% CI: 1.00-1.01; \( p < 0.001 \)) and troponin levels (OR: 1.02; 95% CI: 1.01-1.02; \( p < 0.001 \)), CKD (OR: 4.43; 95% CI: 1.03-12.28; \( p = 0.006 \)), ARF (OR: 20.11; 95% CI: 3.06-132.01; \( p = 0.002 \)), diabetes mellitus (OR: 3.59; 95% CI: 1.55-12.28; \( p = 0.006 \)), CAD (OR: 4.78; 95% CI: 1.55-14.59; \( p = 0.006 \)) were significant predictors of 1-year mortality.

As shown in Table IV, NT-proBNP and troponin parameters were able to predict in-hospital and 1-year mortality (\( p < 0.001 \) for all). NT-proBNP had a sensitivity of 87.5% and a specificity of 87.1% at a cut-off value of \( \geq 1022.50 \) in estimating in-hospital mortality.

### Abbreviations
- NT-proBNP: N-terminal brain-type natriuretic peptide
- ICU: Intensive care unit
- Independent Samples t-test (Bootstrap)
- Mean±standard deviation for normal distribution, and n (%) for categorical data

### Tables

**Table II.** The relationship of cardiac biomarkers with the intensive care unit need and mortality.

<table>
<thead>
<tr>
<th></th>
<th>n, %</th>
<th>NT-proBNP</th>
<th>p</th>
<th>Troponin</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ICU (at admission)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No 690 (75.3%)</td>
<td>690</td>
<td>451.59±1205.79</td>
<td>&lt;0.001</td>
<td>32.58±167.65</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Yes 226 (24.7%)</td>
<td>226</td>
<td>2796.15±4565.47</td>
<td>0.385</td>
<td>129.60±674.71</td>
<td>0.458</td>
</tr>
<tr>
<td><strong>Transferring to ICU</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No 752 (82%)</td>
<td>752</td>
<td>451.71±895.01</td>
<td>&lt;0.001</td>
<td>24.34±44.89</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Yes 164 (18%)</td>
<td>164</td>
<td>6741.72±5952.02</td>
<td>0.001</td>
<td>1045.30±1779.65</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>In-hospital mortality</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No 828 (90.3%)</td>
<td>828</td>
<td>451.71±895.01</td>
<td>&lt;0.001</td>
<td>24.34±44.89</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Yes 88 (9.7%)</td>
<td>88</td>
<td>6741.72±5952.02</td>
<td>0.001</td>
<td>1045.30±1779.65</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>1-year mortality</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No 811 (88.5%)</td>
<td>811</td>
<td>407.79±800.49</td>
<td>&lt;0.001</td>
<td>23.39±43.46</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Yes 105 (11.5%)</td>
<td>105</td>
<td>5836.26±5691.46</td>
<td>&lt;0.001</td>
<td>887.30±1667.60</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Table III.** Risk factors associated with in-hospital and 1-year mortality according to univariate and multivariate logistic regression analysis.

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>In-hospital mortality</th>
<th>1-year mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Model-1</td>
<td>Model-2</td>
</tr>
<tr>
<td>HF (known)</td>
<td>11.13 (6.70-18.42)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HF (new onset)</td>
<td>23.40 (10.13-54.01)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CKD</td>
<td>7.35 (4.01-13.45)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ARF</td>
<td>112.64 (37.52-338.14)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DM (Ref:Yok)</td>
<td>7.68 (4.83-12.21)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HT (Ref:Yok)</td>
<td>3.58 (2.28-5.65)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CAD (Ref:Yok)</td>
<td>9.27 (5.32-19.98)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>COPD/Asthma</td>
<td>2.28 (1.39-3.55)</td>
<td>0.001</td>
</tr>
<tr>
<td>CO-RADS (Ref:4)</td>
<td>19.95 (8.01-49.71)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>EF</td>
<td>0.87 (0.85-0.89)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NT-proBNP</td>
<td>1.01 (1.00-1.01)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>hs-TnI</td>
<td>1.02 (1.01-1.03)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Abbreviations: ARF: Acute renal failure; CAD: Coronary artery disease; CKD: Chronic kidney disease; CI: Confidence interval; COPD: Chronic obstructive pulmonary disease; CO-RADS: Coronavirus Disease 2019 (COVID-19) Reporting and Data System; DM: Diabetes mellitus; EF: Ejection fraction; HF: Heart failure; hs-TnI: High-sensitivity cardiac troponin I; HT: Hypertension; NT-proBNP: N-terminal brain-type natriuretic peptide; OR: Odds ratio.
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The sensitivity of troponin at a cut-off value of ≥ 49.60 was 88.6%, and the specificity was 88.9%. Similarly, NT-proBNP had a sensitivity of 88.6% and a specificity of 88.0% at a cut-off value of ≥ 1008 in estimating 1-year mortality. The sensitivity of troponin at a cut-off value of ≥ 34.10 was 83.8%, and the specificity was 84.1%. In the ROC analysis of NT-proBNP and troponin values designed to estimate in-hospital mortality, the area under the curve (AUC) values were 0.95 (95% CI: 0.940-0.972; p < 0.001) and 0.965 (95% CI: 0.950-0.980; p < 0.001), respectively. In the ROC analysis of NT-proBNP and troponin values designed to estimate 1-year mortality, the AUC values were 0.956 (% 95 CI: 0.941-0.971; p < 0.001) and 0.951 (% 95 CI: 0.935-0.967; p < 0.001), respectively (Figure 1). Finally, it was found that the factors explained 79% of the factors predicting in-hospital mortality (R²=0.79, -2 loglikelihood= 157.40) and 78% of the factors that predicting one-year mortality (R²=0.78, -2 loglikelihood= 182.90).

<table>
<thead>
<tr>
<th>Abbreviations:</th>
<th>AUC</th>
<th>95% CI</th>
<th>Cut-off</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-hospital mortality</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NT-proBNP</td>
<td>0.956</td>
<td>0.940-0.972</td>
<td>≥ 1022.50</td>
<td>87.5</td>
<td>87.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>hs-TnI</td>
<td>0.965</td>
<td>0.950-0.980</td>
<td>≥ 49.60</td>
<td>88.6</td>
<td>88.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>1-year mortality</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NT-proBNP</td>
<td>0.956</td>
<td>0.941-0.971</td>
<td>≥ 1008.00</td>
<td>88.6</td>
<td>88.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>hs-TnI</td>
<td>0.951</td>
<td>0.935-0.967</td>
<td>≥ 34.10</td>
<td>83.8</td>
<td>84.1</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

The main findings of this study are: i) NT-proBNP and hs-TnI were independent predictors of both in-hospital and 1-year mortality, as well as ACF, CKD, diabetes mellitus and CAD were other independent predictors; ii) NT-proBNP predicted in-hospital mortality at a cut-off value of ≥ 1022.50 with a sensitivity of 87.5% and a specificity of 87.1%. The sensitivity of troponin at a cut-off value of ≥ 49.60 was 88.6%, and the specificity was 88.9%; iii) NT-proBNP predicted 1-year mortality at a cut-off value of ≥ 1008 with a sensitivity of 88.6%, and a specificity of 88.0%. The sensitivity of troponin at a cut-off value of ≥ 34.10 was 83.8%, and the specificity was 84.1%; iv) Increased NT-proBNP and hs-TnI levels were associated with a higher need for ICU.

NT-proBNP is released from cardiac myocytes in response to an increase in wall stress in conditions, such as heart failure, acute coronary syn-

Discussion

Figure 1. ROC curves of NT-proBNP and troponin levels for in-hospital and one-year mortality. A, In-hospital mortality. B, One-year mortality.
drome, valvular heart disease, and stable coronary artery disease. In addition, it may increase without underlying cardiac diseases, such as sepsis and renal or respiratory failure. Troponin is another cardiac biomarker considered a significant indicator of cardiac injury, and these two cardiac biomarkers have been recognized as important prognostic parameters during the COVID-19 infection. By interacting with the cardiovascular system at various levels, COVID-19 causes myocardial injury and dysfunction not only in patients with underlying cardiovascular diseases but also in those without cardiovascular history. Although not fully understood, the possible direct and indirect effects of COVID-19 on the cardiovascular system are as follows: i) the virus enters the cell by targeting ACE2 receptors in myocytes, as well as in the lungs, directly causing degeneration and necrosis; ii) the host-immune dysregulation causing a direct and indirect myocardial injury by triggering a cytokine storm; iii) stress-induced cardiomyopathy; iv) microvascular dysfunction due to microthrombus, vascular injury or autonomic dysfunction; v) atherosclerotic plaque activation and thrombus formation due to severe inflammation; vi) demand-supply mismatch; vii) arrhythmias. Furthermore, acute renal failure, increased pulmonary vascular tonus due to mechanical ventilator support, and vasopressor drugs administered during hospitalization may exacerbate myocardial wall stress and cardiac injury.

Recently, several studies and meta-analyses have investigated the association between cardiac markers and the short-term prognosis of COVID-19 infection. Despite different cut-off values, it has been shown that there is a close relationship between mortality and high levels of cardiac markers at the time of diagnosis. In a study, Chehrazi et al. determined two cut-off levels of NT-proBNP as 331 and 11.126 and classified the patients as low, intermediate, and high risk according to these cut-off levels. They excluded the patients with heart failure from the study. Falco et al. found that mortality was higher in patients having NT-proBNP above the level of 511 ng/L. In a study involving 137 patients, Selcuk et al. investigated the prognostic value of NT-proBNP in patients without previous heart failure and found that in-hospital mortality was higher above the level of 260 ng/L. Karahan et al. investigated the association between myocardial injury and short-term prognosis. Myocardial injury was defined as a hs-TnI level above 19.9 ng/L above and it was found as an independent predictor of short-term mortality. According to a recent meta-analysis, acute cardiac injury during COVID-19 infection was significantly associated with increased mortality, the need of ICU, and severity of infection. In our study, unlike other studies, we investigated the effectiveness of cardiac biomarkers in predicting in-hospital and 1-year mortality as a primary outcome and the need for intensive care as a secondary outcome. We found that patients having the NT-proBNP levels of 1022.50 and 1008 and above had a significantly increased risk of in-hospital and 1-year mortality, respectively. Similarly, patients having the hs-TnI levels of 49.6 and 34.10 and above had a significantly increased risk of in-hospital and 1-year mortality, respectively. Increased cardiac biomarker levels were also associated with a higher need for ICU. To our best knowledge, this is the first study investigating the use of cardiac markers in predicting long-term mortality in the general population. The relatively higher NT-proBNP cut-off value in our study can be explained as follows: i) the study included patients with chronic/acute kidney failure, heart failure, and COPD, which may cause high NT-proBNP levels; ii) since the previous studies were conducted with relatively a smaller number of patients, very different cut-off values were found.

Our study has many different other aspects from previous studies. Several studies have suggested using imaging scoring systems to evaluate the pulmonary findings of COVID-19 infection more objectively. Moreover, it has been shown that patients having high imaging scores are independently associated with a worse prognosis. Differently from other studies investigating the association between cardiac biomarkers and prognosis, we used the CO-RADS scoring system to determine the severity of pneumonia more accurately and found that the imaging scores were 4 and above in correlation with the levels of cardiac markers in in-hospital or 1-year mortality group. Heart failure, whether secondary to infection or preexisting, is an important factor influencing mortality during COVID-19 infection. Therefore, the ejection fraction of the patients included in the study was evaluated and only euvolemic patients were included in the study to provide more accurate and objective results.

**Study Limitations**

Our study has several limitations. First of all, this was a retrospective and single-center study. Second, we did not present the treatment strategies that may affect the levels of cardiac biomarkers. Third, ECG findings of the patients could be
presented because arrhythmia may affect the level of cardiac biomarkers. Fourth, D-dimer levels could be presented as findings are closely related to thrombotic events. Fifth, we did not present the accurate cause of the deaths within one year after the diagnosis of COVID-19 infection.

**Conclusions**

NT-proBNP and hs-TnI are key laboratory parameters to predict intensive care need, in-hospital mortality, and 1-year mortality in COVID-19 infection.

**Conflict of Interests**

The authors declare that they have no conflict of interests.

**Ethics Approval**

The study as approved by the Local Ethics Committee of Kırıkkale University (Date: 27.01.2022, Decision number: 2022.01.29).

**Informed Consent**

Informed written consent was obtained from all participants.

**Availability of Data and Material**

Available.

**Authors’ Contributions**


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**References**


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