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# Cardiovascular markers and COVID-19

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## ARTICLE INFO

## ABSTRACT

COVID-19 is an emerging viral disease with incompletely elucidated pathogenesis, a heterogeneous clinical profile, and significant interindividual variability. The major cardiovascular complications of COVID-19 include acute cardiac injury, acute myocardial infarction (AMI), myocarditis, arrhythmia, heart failure, and venous thromboembolism (VTE)/pulmonary embolism (PE). Elevated BNP /NT-proBNP, troponin and D-dimer levels has been found in a significant proportion of patients since the first data analysis, suggesting that myocardial damage is a likely pathogenic mechanism contributing to severe disease and mortality. The level of these markers is now associated with a risk of adverse outcome, namely mortality. The aim of our study is to highlight the importance of these biomarkers for the prediction of cardiovascular complications and their potential role in the evolution of COVID-19.
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## 1. Introduction

COVID-19 is an emerging viral disease with incompletely elucidated pathogenesis, a heterogeneous clinical profile, and significant interindividual variability [1]. The course of the disease can be mild or severe with associated pulmonary and multivisceral damage that can lead to death [2]. The major cardiovascular complications of COVID-19 include acute cardiac injury, acute myocardial infarction (AMI), myocarditis, arrhythmia, heart failure, and venous thromboembolism (VTE)/pulmonary embolism (PE) [3]. COVID-19 may cause cardiovascular complications or deterioration of coexisting cardiovascular disease by direct or indirect mechanisms, including viral toxicity, deregulation of the renin-angiotensin-aldosterone system (RAAS), endothelial cell damage and thrombo-inflammation, cytokine storm and oxygen supply/demand mismatch [4]. It has been speculated that COVID-19 infection may cause thrombus formation with hypercoagulability. Up to 20 % of patients with COVID-19 have abnormal coagulation, which may be caused by myocardial injury [5]. In addition, it has been established that patients with COVID-19 have the potential to develop severe heart failure and are at risk of sudden cardiac death [6]. Thus, several studies and analyses have been performed to determine whether the measurement of cardiac troponin, pro-

BNP and D-dimer measurements can help predict clinical severity in patients with COVID-19. The purpose of this review is to present the current data on using cardiovascular markers as COVID-19 prognostic factors.

## 2. Materials and methods

A literature search was done on PubMed, SCOPUS, and Google Scholar to detect articles discussing biomarkers in this review and its clinical implications on COVID-19 based on the Preferred Reporting Items for Systematic Reviews and meta-analysis (PRISMA) guidelines. Key words used were 'COVID-19′, 'cardiovascular markers', 'BNP /NT-proBNP', 'troponin' and 'D-dimer'. Studies were included if they have reviewed a correlation between a biomarker and the severity of COVID-19. While, exclusion criteria were studies with no particular definition of the role of biomarkers in COVID-19.

## 3. BNP and NT-proBNP

A retrospective cohort study of consecutive adults (N = 679; median age 59 years; 38.7 % female), reported that NT-proBNP at admission was categorized using the age-specific criteria of the European Society of Cardiology Heart Failure Association for acute presentations. They examined mortality and the composite of death or mechanical ventilation and the number of days without

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hospitalization, without intensive care unit and without ventilator at 28 days. 417 patients (61.4 %) had low, 141 (20.8 %) borderline, and 121 (17.8 %) high NTproBNP. Mortality was 5.8 %, 20.6 % and 36.4 % for patients with low, borderline and high NT-proBNP, respectively. Elevated NT-proBNP level was associated with a higher mortality rate hazard ratio (HR) [2.15; 95 % confidence interval (CI) 1.06–4.39; P = 0.034] and a higher composite endpoint rate (HR) [1.66; 95 % CI 1.04–2.66; P = 0.035 composite end point (HR 1.66; 95 % CI 1.04–2.66; P = 0.035)]. Patients with elevated NT-proBNP levels had 32 %, 33 % and 33 % fewer days without hospitalization, intensive care and ventilation than their counterparts with low NT-proBNP. The results were consistent across age, sex, and race, and independent of coronary artery disease or hypertension, except for a stronger mortality signal with elevated NTproBNP in women. In conclusion, in patients with COVID-19 and without a history of heart failure, a high NT-proBNP level at admission is associated with higher mortality and health care resource utilization [7]. Another conducted retrospective, single-center cohort study, showed that the median age of the patients was 61 years (IQR, 47–69), and 39 (43.0 %) of them were men. 25.3 % had NT-proBNP levels above 300 pg/ml. Higher NT-proBNP levels were associated with poorer PSI (pneumonia severity index) and CT (chest computed tomography) scores. The natural logarithm of NT-proBNP level was positively correlated with PSI and CT scores (PSI score: rS = 0.396; CT score: rS = 0.440). Patients with NT-proBNP levels $\geq$ 300 pg/ml had a potential risk of mortality than patients with NT-proBNP levels < 300 pg/ml (mortality rate, 8.7 % vs 0 %). In conclusion, this study revealed that the plasma NT-proBNP level of NT-proBNP in COVID-19 patients was significantly related to the severity of pneumonia, indicating that heart failure should be evaluated in this disease. Plasma NT-proBNP analysis should be performed in COVID-19 patients to cardiac dysfunction [8]. A study of 3080 consecutive patients with confirmed SARS-CoV-2, reported that 192 (48.5 %) had NT-proBNP levels above the recommended threshold for identifying heart failure. Patients with higher NT-proBNP levels on admission had more frequent admission was more likely to have bleeding, arrhythmias and heart failure. NT-proBNP was associated with mortality both in the overall study population and after exclusion of patients with heart failure. A multivariable Cox model confirmed that NT-proBNP was independently associated with mortality after adjustment for all relevant confounding factors (hazard ratio 1.28, 95 % confidence interval 1.13–1.44, per log unit). In conclusion, NT-proBNP is frequently elevated in the COVID-19 study. It is strongly and independently associated with mortality after adjustment for relevant confounders including chronic heart failure and acute heart failure. therefore, its use could improve early prognostic stratification in this condition [9]. Table 1 summary BNP/NT-proBNP concentrations between COVID-19 patients with low vs high severity or survivor vs non-survivor status in several studies.

## 4. Troponin

A *meta*-analysis was performed on studies conducted in China and included that a total number of 341 patients of which 123 (36 %) had severe disease. Although heterogeneity was significantly high (I2 98 %; p < 0.001), the HS cTnI values were found to be significantly increased in COVID-19 patients with severe disease compared with those with moderate disease (MDS: 25.6 ng/L; 95 % CI, 6.8–44.5 ng/L) [3]. Han et al reported higher concentrations of some biomarkers, such as myohaemoglobin (Mb), CK-MB isoenzyme, NT-proBNP and cardiac troponin cTnI. Rates were related to severity and mortality in patients infected with COVID-19. HS troponin was above normal in 27 patients, these data indicated that some patients with COVID-19 developed an acute cardiac injury. They concluded that increased venous blood concentrations of Mb, TnI-ultra and NT-proBNP were associated with the severity of COVID-19 [17]. A cohort analysis showed that 82 patients (19.7 %) had a cardiac lesion. These patients had more complications (impaired renal function, ARDS with non-invasive mechanical ventilation, hydroelectrolytic disorders, coagulation disorders) and were more susceptible to mortality than those without cardiac injury, with very high values of inflammatory and cardiac markers [18]. On the other hand, a multicenter retrospective study, 3219 patients diagnosed with COVID-19 admitted to 9 hospitals, aims to estimate the associations and prognostic power of circulating cardiac lesion markers with poor prognosis. The adjusted hazard ratio for 28-day mortality for HS-cTnI was 7.12 ([95 % CI 95 %: 4.60–11.03] P < 0.001), NT-proBNP was 5.11 ([95 % CI: 3.50–7.47] P < 0.001), CK MB was 4.86 ([95 % CI, 3.33–7.09] P < 0.001), and Mb was 4.50 ([95 % CI 3.18–6.36] P < 0.001). The threshold for these cardiac biomarkers for effective prognosis of 28-day mortality for COVID-19 were found to be much lower than for ordinary heart disease at approximately 19 % to 50 % of currently recommended thresholds. Patients with elevated cardiac injury markers above newly established thresholds were associated with a significantly increased risk of death by COVID-19. They also found that elevations in cardiac biomarkers were significantly associated with death at 28 days in patients with COVID-19 [19]. Huiqi Guo and Yunzhi Shen studied myocardial injury in patients with severe and critical COVID-19. They reported that myocardial injury is evident and associated with a poor prognosis, including long ventilation time, incidence of malignant arrhythmia incidence and mortality [20]. The various kinds of cTn studies are shown in Table 2.

## 5. ᴅ-dimer

A study conducted by Huang et al reported that ᴅ-dimer values were almost five times higher in those with severe disease (median: 2.4 mg/L; IQR: 0.6–14.4 mg/L) than in those without severe

**Table 1**
BNP/NT-proBNP concentrations between COVID-19 patients with low vs high severity or survivor vs non-survivor status.

| | Study design | Low severity or survivor | | High severity or non-survivor | |
| | | n | BNP pg/mL (Mean ± SD | N | BNP pg/mL (Mean ± SD |
| --- | --- | --- | --- | --- | --- |
| Chen et al. [10] | Not reported | 1651 | 67 ± 93 | 208 | 685 ± 987 |
| Gottlieb et al. [11] | Retrospective | 7190 | 33 ± 35 | 1483 | 73 ± 74 |
| Cui et al. [12] | Retrospective | 699 | 153 ± 158* | 137 | 1244 ± 1649* |
| Ma et al. [13] | Retrospective | 429 | 180 ± 273 | 94 | 663 ± 641 |
| He et al. [14] | Retrospective | 530 | 83 ± 95* | 501 | 381 ± 498* |
| Ciceri et al. [15] | Not reported | 291 | 206 ± 259* | 95 | 1583 ± 2176* |
| Tao et al. [16] | Retrospective | 202 | 198 ± 352* | 20 | 811 ± 1367* |

*: NT-proBNP.

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**Table 2**
Several studies on Cardiac troponin and COVID-19 [21].

| References | Number of patients | Type of study | Results |
|---|---|---|---|
| Tanboğa et al. [22] | 14,855 | Retrospective | cTn-negative = 13,828 (N), cTn-positive = 1027 (N |
| Ali et al. [23] | 466 | Retrospective | High cTnI level N = 168 (36.05 % |
| Puntmann et al. [24] | 207 | Prospective | Elevated TnT levels, was significantly correlated with native T1 |
| Shi et al. [18] | 187 | Case Series | Elevated TnT levels, patients with high TnT levels had more severe respiratory dysfunction |
| Guo et al. [25] | 187 | Retrospective | Elevated TnT levels in 52 patients |
| Wei et al. [26] | 101 | Retrospective | Almost half of whom had aN hs-TnT value fivefold more than the normal upper limit |
| Zhu et al. [27] | 49 | Retrospective | 12 % Elevated TnT levels |
| Kermali et al. [28] | 25 | Retrospective | Elevated CRP, cTnI, D-dimer, LDH, and lactate levels |

**Table 3**
Studies detailing correlations between D-dimer levels and progression of patients hospitalized with COVID-19 [33].

| | Survivors, not hospitalized in ICU | | Non-survivors, hospitalized in ICU | |
|---|---|---|---|---|
| | N | D-Dimer levels ng/mL, median (range) | N | D-Dimer levels ng/mL, median (range) |
| Huang et al.[6] | 28 | 500 (300–1300) | 13 | 2400 (600–14,400)* |
| Han et al.[34] | 49 | 214 ± 288[a] | 45 | 1960 ± 3400[a] |
| Zhou et al.[31] | 137 | 600 (300–1000) | 54 | 5200 (1500–21,000)** |
| Tang et al.[30] | 162 | 610 (350–1290) | 21 | 2120 (770–5271)* |
| Tang et al.[35] | 315 | 1470 (780–4160) | 134 | 4700 (1420–21,000)* |
| Wu et al.[36] | 117 | 520 (330–930) | 184 | 1160 (460–5370)*** |
| Feng et al.[37] | 352 | 510 (320–1080) | 70 | 1110 (510–4000)** |
| Chen et al.[38] | 161 | 600 (300–1300) | 113 | 4600 (1300–21,000)* |
| Middeldrop et al.[39] | 123 | 1100 (700–1600) | 75 | 2000 (800–8100)* |
| Fogarty et al.[40] | 50 | 804 (513–1290) | 33 | 1003 (536–1782)* |
| Wang et al.[32] | 102 | 1660 (1010–2850) | 36 | 4140 (1910–13,240)* |

ICU: intensive care unit. *<0.001; **<0.0001; *** with or without ARDS. a Mean (standard deviation).

disease (median: 0.5 mg/L; IQR: 0.3–0.8 mg/L; p = 0.004) [6]. Tang et al also studied 183 patients with COVID-19 and found that D-dimer values were approximately 3.5 times higher in patients with severe disease (median: 2.12 mg/L; IQR: 0.77 to 5.27 mg/L) than in non-severe patients (median: 0.61 mg/L; IQR: 0.35–1.29 mg/L; p < 0.001). They pointed out that the vast majority of COVID-19 patients who died stay met the diagnostic criteria for disseminated intravascular coagulation disseminated intravascular coagulation [29]. Wang et al studied 138 patients hospitalized for COVID-19, D-dimer values were 2.5 times higher in patients with severe disease (median: 4.14 mg/L; IQR: 1.91–13.2 mg/L) than in non-severe patients (median: 1.66 mg/L; IQR: 1.01–2.85 mg/L; p < 0.001) [30]. Zhou et al studied 191 patients with COVID-19 and found that D-dimer values were almost nine times higher in patients who died (median: 5.2 mg/L; IQR: 1.5–21.1 mg/L) than in those who survived (median: 0.6 mg/L; IQR: 0.3–1.0 mg/L; p < 0.001) [31]. A retrospective study of 248 consecutive cases of COVID-19, showed that A D-dimer level > 2000 g/L at admission was the only variable associated with an increased probability of mortality. An elevation D-dimer elevation ≥ 500 g/L was observed in 74.6 % of patients. Pulmonary embolism and deep vein thrombosis were excluded in patients with a high probability of thrombosis. D-dimer levels increased significantly with increasing severity of COVID-19. D-dimer level's median in non-survivors (n = 17) was significantly higher than in survivors (n = 231) [6.21 (3.79–16.01) mg/L versus 1.02 (0.47–2.66) mg/L, P = 0.000]. A D-dimer level > 2140 g/L predicted in-hospital mortality with a sensitivity of 88.2 % and a specificity of 71.3 % [32]. The following table (Table 3) summary several studies, detailing correlations between D-dimer levels and progression of patients hospitalized with COVID-19.

## 6. Conclusion

Overall, we note that the values of D-dimer, troponin, pro-BNP and NT-proBNP are significantly higher in patients with severe COVID-19 than in those with milder forms of the disease. As a result, the level of these markers is now associated with a risk of adverse outcome, namely mortality. Our literature review showed their importance in the management of patients with severe forms of COVID-19 progressing to towards critical forms. The validation of clinical-biological scores would therefore allow a standardization of practices with a correct prescription of biological analyses.

## Data availability

No data was used for the research described in the article.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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