Cardiac biomarkers and mortality in COVID-19 infection: A review

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Abstract

Lots of meta-analyses emphasize that a great number of hospitalized patients with moderate and severe forms of COVID-19 developed acute myocardial damage, defined as an increase of cardiac biomarkers, such N-terminal pro-B-type natriuretic peptide (NT-pro-BNP), creatine kinase-myocardial band (CK-MB) and of all type of troponins. The highest mortality rate is related with progressively increasing biomarkers levels and with a history of cardiovascular disease. In fact, the biomarkers dosage should be considered as a prognostic marker in all patients with COVID-19 disease at admission, during hospitalization and in the case of clinical deterioration. The purpose of this review is to evaluate cardiovascular prognostic factors in COVID-19 disease throughout the analysis of cardiac biomarkers to early identify the most serious patients and to optimize their outcomes.

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Introduction

Coronavirus disease 2019 (COVID-19), is caused by an enveloped, non-segmented, single-stranded, positive-sense RNA virus belonging to the Coronaviridae family (SARS-CoV-2) [1], emerged in China's region Wuhan [2] , spreading worldwide and becoming one of the most lethal pandemic with a rapid increase of affected people. The SARS-CoV-2 infection clinical progression is mostly characterized by acute lung injury. Yet, some COVID-19 patients showed also neurological signs, acute myocardial injury, heart failure, myocarditis and hypercoagulability, such as pulmonary embolism [3]. Cardiac biomarkers can play an essential role in the diagnosis, management, and prognosis of COVID-19. In fact, during hospitalization, these patients develop biochemical abnormalities, with increasing of all troponins (TnT), B-type natriuretic peptide (NT-pro-BNP) and creatine kinase-myocardial band (CK-MB) levels. This situation helps us to predict adverse outcomes, especially in patients with cardiovascular comorbidities or risk factors. Despite initially COVID-19 was identified above all as a respiratory disease with severe interstitial pneumonia and risk of acute respiratory distress syndrome, data emerged demonstrated a myocardial involvement which determines a high risk of adverse events and increasing of mortality. According to Danwang *et al*. [4], COVID-19 patients are divided into mild, moderate, severe, and critical classifications basing on biochemical parameters.

The aim of our review is to evaluate data on the predisposition to worse outcomes, comparing the severity of COVID-19 and levels of biomarkers.

Troponin T

Previous coronavirus were associated with arrhythmias, cardiomegaly, cardiac arrest, sub-clinical diastolic impairment and acute-onset heart failure [5-7]. The possible role of troponin-T (TnT) in the prognosis of COVID-19 patients has been reported in numerous clinical studies (Table 1). In China all patients reporting elevated TnT values, have developed a myocardial injury. Among these, the mortality rate at one month was more than 50% in those who had elevated TnT [8,9] and it was also shown that high levels of this biomarker were a negative prognostic factor, predicting sometimes even death of patients [10,11]. Therefore, increased

blood levels of TnT were correlated with increased severity of infection from COVID 19 and its higher mortality rate [12].

Studies conducted in Italy have shown that the presence of elevated troponin levels was an independent variable associated with in-hospital mortality and an increased risk of cardiovascular complications, especially in patients with a previous history of heart disease.

Importantly, a correlation with heart failure, renal failure, pulmonary embolism and major bleeding was observed. In fact, half of COVID-19 patients with elevated troponins, with a history of cardiovascular disease and / or the presence of heart damage, have died [13,14]. Therefore, to better stratify the prognosis of these patients, it becomes important to evaluate TnT at hospitalization and during hospitalization, up to discharge [13-15].

In the United States it has also been demonstrated the correlation between the changes of ECG with an increased risk of death, especially in the presence of atrial fibrillation, atrial flutter, or both [16,17].

B-type natriuretic peptide

The system of natriuretic peptides (NP) counteracts the cardiovascular and renal effects related to the activation of renin-angiotensin-aldosterone system (RAAS) [18-20]. NPs, however, are predictors of an adverse outcome in acute myocardial damage because their concentrations increase immediately after myocardial damage, reducing only to clinical improvement [21]. A retrospective study conducted in China demonstrated that markedly higher concentrations of CK, lactate dehydrogenase, TnT, and B-type natriuretic peptide (NT-proBNP) were seen in deceased patients than in recovered patients [9]. Also Caro-Codòn *et al*. findings support the hypothesis that natriuretic peptides are highly associated with prognosis in COVID-19 patients [22]. A recent meta-analysis including 13 observational studies and 2248 patients (most of them also from the early COVID-19 outbreak in China) also supported the idea that NT-proBNP assessment may improve the discrimination of high-risk patients [23]. Yang *et al*. retrospectively analyzed 224 patients with confirmed diagnosis of SARS-CoV-2 infection and definite outcomes (discharge or death), consisting of 145 patients who recovered and 58 patients who died. In their analysis, 53% of non-survivors had elevated NT-proBNP [10]. Finally, according to Gao *et al*. [24], plasma NT-proBNP level and the risk of in-hospital death in severe COVID-19 patients was directly proportioned. Severe COVID-19 patients with high NT-proBNP levels tended to be older with increased cardiac injury markers and higher levels of systematic inflammation markers, and that with high NT-proBNP (>88.64 pg/mL) level had lower cumulative survival rate. After adjusting for potential cofounders in separate modes, NT-proBNP presented as an independent risk factor of in-hospital death for 30 patients with severe COVID-19.

Also thanks to others Italian studies, it has been demonstrated NT-proBNP levels were eight times higher at the time of hospitalization in non survivors versus survivors [13,14]. Therefore, despite cardiac injury is a common condition among hospitalized patients with COVID-19, association with high level of Nt-pro BNP was associated with higher risk of in-hospital mortality (Table 2).

Creatine kinase-myocardial band

Creatine kinase-myocardial band (CK-MB) is mostly found in the myocardium and is a diagnostic marker for myocardial damage [25], It may have a prognostic value in COVID-19 infection because patients with high levels require urgent intervention and had poor prognosis [3,21]. Elevated serum CK-MB, in fact, might indicate

Table 1. Involvement of the cardiopulmonary system in COVID-19 in patients with elevated troponin values.

Study	Region	Dates of study	Age	Male (%)	TnT elevation (%)	Arrhythmia (%)	Death (%)
Guo *et al.* [8]	China	23 January-3 February 2020	59±15	48.7	27.8	16.7	23.0
Chen *et al.* [9]	China	January-February 2020	59±16	56.0	14.7	—	7.3
Yang *et al.* [10]	China	10 January-29 February 2020	62 (49-69)	56.7	50	—	28
Zhou *et al.* [11]	China	29 December 2019-31 January 2020	56 (46-67)	62.3	16.6	—	28.3
Han *et al.* [12]	China	1 January-18 February 2020	58.95±10.80	71	80	—	42.31
Inciardi *et al.* [13]	Italy	4-25 March 2020	67±12	81.0	48	40	36
Lombardi *et al.* [14]	Italy	1 March-9 April 2020	64	70.8	45.3	—	24.1
Stefanini *et al.* [15]	Italy	March-April 2020	66 (55-75)	67	43	—	23.2
Poterucha *et al.* [16]	USA	1 March-3 April 2020	64±17	58	43	5	23
Aggarwal *et al.* [17]	USA	April 2020	67 (28-95)	75	14	6	19

Table 2. COVID-19 infection and mortality in patients with high levels of NT-pro-BNP.

Study	Region	Dates of study	Age	Male (%)	NT-pro-BNP (median value) and mortality
Chen *et al.* [9]	China	January-February 2020	59±16	56.0	800.0 (389.8-1817.5)
Yang *et al.* [10]	China	10 January-29 February 2020	62 (49-69)	56.7	109 (50-299)
Gao *et al.* [24]	China	——	60.4±16.1	54	88.64
Inciardi *et al.* [13]	Italy	4-25 March 2020	67±12	81.0	2584 (206-4546)
Lombardi *et al.* [14]	Italy	1 March-9 April 2020	64	70.8	882 (196-3170)

more organ damages and a higher immune response in patients with COVID-19, so additional monitoring should be conducted on these patients with abnormal serum CK-MB levels [26].

A meta-analysis of relation of CK-MB to risk of mortality in COVID-19 [27], shown that patients with severe pneumonia have varying degrees of myocardial injury due to hypoxemia and toxicity of the pathogen [28,29]. Furthermore, overall results showed that the elevated levels of CK- MB were significantly associated with an increased risk of the mortality in COVID-19 infected patients. Also a previous meta-analysis by Li *et al.* [30] observed that the elevated CK-MB levels were associated with the severity of COVID-19 patients. Other Chinese studies showed patient with COVID-19 infection had high CK-MB levels associated with in-hospital death, compared to non-hospitalized patients [8,10,31,32] (Table 3).

Discussion

Results of aforementioned studies underline how cardiac biomarkers, such as TnT, NT-pro-BNP and CK-MB are associated with severe form of COVID-19 infection. Above all, higher levels of these biomarkers are significantly associated with an increased risk of the mortality in COVID-19 infected patients (Table 4). Therefore, has been demonstrated COVID-19 infection is more severe in those patients with a previous history of arterial hypertension, cardiovascular diseases [8,9,13-15,31].

In addition to classical laboratory parameters evaluated in COVID-19 infection, such as C-reactive protein (CRP), D-dimer, and lactate dehydrogenase (LDH), which are currently used in clinical practice, other biomarkers could potentially be useful for screening, clinical management, and prevention of serious complications.

Among the biomarkers mentioned above, the most important parameter to consider as a prediction of mortality is TnT. In fact the highest mortality was found in patients with progressively increasing troponin levels and a history of cardiovascular disease [8,9,31,33]. Moreover, some pathophysiological bases have been hypothesized regarding the elevation of TnT levels in patients with COVID-19 infection: the instability of pre-existing atherosclerotic plaques resulting from the phenomenon of cytokine storm with a characteristic clinical picture of type 1 myocardial infarction [34,35], a marked increase in oxygen demand by cardiomyocytes, in a situation of tissue hypoxia, with consequent ischemia that configures a picture of type 2 myocardial infarction [34]; a direct myocardial damage with a picture of fulminant myocarditis (coronary artery disease) [36,37], effect of sepsis / cytokine storm and endothelial damage [38]. These hypotheses were proposed following the absence of viral genomes in cardiomyocytes and the presence of mononuclear inflammatory cells from autopsy findings [30]. Therefore, it is clinically significant that fluctuating levels of myocardial biomarkers are closely monitored and patients with high levels of myocardial biomarkers are treated promptly to improve prognosis [39-41].

At the end, on basis of symptoms and cardiac biomarkers patients could be divided as follows:

Mild: patient has mild symptoms (fever, cough, headache, anosmia and/or ageusia) and possible or not pneumonia on X-ray imaging with normal cardiac biomarkers.

Severe: patient with respiratory distress, respiratory rate≥30 beats/min in a resting state, mean oxygen saturation ≤93%, and an arterial blood oxygen partial pressure (PaO_2)/oxygen concen-

Table 3. COVID-19 infection and CK-MB levels in patients with or without myocardial injury.

Study	Region	Dates of study	CK-MB (median value) with cardiac injury	CK-MB (median value) without cardiac injury
Guo *et al.* [8]	China	23 January-3 February 2020	3.34	0.81
Yang *et al.* [10]	China	10 January-29 February 2020	7.27	0.77
Shi *et al.* [31]	China	20 January-10 February 2020	3.2	0.9
Wang *et al.* [32]	China	1 January-3 February 2020	18	13

Table 4. Relationship between mortality and myocardial injury in COVID-19 infection.

Study	Myocardial injury	Underlying cardiovascular disease	Mortality
Guo *et al.* [8]	27%	32.7%	59.6%
Chen *et al.* [9]	44%	61%	77%
Shi *et al.* [31]	19%	29.3 %	51.2%
Inciardi *et al.* [13]	48%	—	36 %
Lombardi *et al.* [14]	45.3%	15 %	37.4%
Wei *et al.* [44]	15.8%	18.8%	18.8%
Zhou *et al.* [11]	17%	—	OR 80.1
Stefanini *et al.* [15]	85.7%	10.7%	39.3%
Poterucha *et al.* [16]	43%	10%	49%
Yang *et al.* [10]	50%	4.4%	67%
Ghio *et al.* [45]	21%	65%	51.4%
Han *et al.* [12]	9.9%	—	22.8%
Aggarwal *et al.* [17]	25%	19%	60%

tration (FiO_2) ≤300 mm Hg with normal or high cardiac biomarkers. In this situation, an increase in the levels of cardiac biomarkers worsens the prognosis.

Critical: patient is characterized by respiratory failure and required mechanical ventilation, the occurrence of shock, and the combined failure of other organs that required Intensive Care Unit (ICU) monitoring and treatment with significantly elevated cardiac biomarkers. In this case, elevated cardiac biomarkers are an independent risk factor for in-hospital death [42,43].

The values of cardiac biomarkers in COVID-19 infection have been studied on the first variant ("alpha").

More research is needed to determine the relationship between cardiac biomarkers and new COVID-19 infection variants.

Limitations

Our review analyzed the relationship only between the classic COVID-19 infection ("alpha") and cardiac biomarkers. Further investigations will be needed to evaluate the impact of cardiac biomarkers on the new variants of COVID-19.

Conclusions

Biomarkers of acute myocardial injury play an important role in predicting worsening prognosis for COVID-19 patients with and without myocardial injury. Elevated TnT, CK-MB and NT-pro-BNP levels correlate with more severe symptoms of COVID-19. There are in fact not only predictive of disease severity, but are also helpful for therapeutic management, based on drugs preventing the activation of coagulation processes. It is important, above all, to identify a laboratory score, made by hematological, inflammatory, biochemical (above all TnT, NT-pro-BNP and CK-MB) and immunological parameters, may help to stratify COVID-19 positive patients into risk categories for deciding therapeutic management, thus avoiding cardiac compromise which, as we have previously analyzed, is an indication of a poor prognosis.

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