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ORIGINAL ARTICLE

Cardiac Biomarkers of High Risk of Complications and Death in Patients with SARS-COV-2 and CHF

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ABSTRACT

The review is devoted to investigate cardiovascular biomarkers in patients with SARS-CoV-2 associated with a high risk of complications and death. The article provides information on the main cardiovascular biomarkers and pro-inflammatory cytokines in relations to the processes of decompensation in patients with chronic heart failure complicated by ARVI, including the SARS-CoV-2.

MeSHwords: heart failure, troponin I, NT-proBNP, cytokines, SARS-CoV-2

INTRODUCTION

Despite the significant reduction in mortality from cardiovascular diseases, achieved through the timely provision of necessary assistance to patients with acute cardiac pathology, the problem of chronic heart failure remains extremely relevant. In connection with the improvement in the quality of medical care, an increase in life expectancy leads to an increase in the population of elderly and senile people who develop heart failure, including for other natural reasons. Including achievements in the field of combating cardiovascular diseases led to a decrease in the mortality of patients in the acute period of myocardial infarction, stroke. This has led to the fact that they naturally develop late complications, which include heart failure. Currently, in our country, about 10 million people have a diagnosis of chronic heart failure and more than 2 million patients of this number suffer from the final forms of this condition. It is impossible not to note the increase in the proportion of hospitalizations in the cardiology departments of patients in a state of decompensation of chronic heart failure during the Long COVID period, as well as an increase in the proportion of those suffering from this pathology with the manifestation of the disease over the past two years after suffering a new coronavirus infection caused by SARS-CoV-2[1,2].

Myocardial damage in viral infections (VI) can be asymptomatic and is detected only when conducting a series of laboratory studies to evaluate biomarkers showing the effect of VI on the cardiovascular system. In the pathogenesis of the development or progression of CVD in COVID-19, not only direct myocardial damage plays a role, but also hyperactivation of the inflammatory reaction, the appearance of an autoimmune response against its background, which also enhance myocardial damage. The mechanism of direct myocardial damage may be associated with the depletion of ACE2 due to the blocking of ACE2 receptors by the virus and leads to dysregulatory disorders of the CVS activity. Also, with VI, there is a sharp increase in the number of pro-inflammatory cytokines. Accumulated data show that cytokines play an important role in the pathogenesis of chronic heart failure. They have a negative inotropic effect, stimulate protein synthesis, increase capillary permeability, contribute to the progression of myocardial hypertrophy and participate in the processes of left ventricular remodeling.

Both mechanisms of myocardial damage are not completely independent, as direct myocardial damage causes violent activation and secretion of pro-inflammatory cytokines ("cytokine storm"). A cohort study in Wuhan found that inflammatory response markers, such as C-reactive protein, procalcitonin and white blood cells, were significantly elevated in patients who had suffered heart trauma. Activation or increased release of these inflammatory cytokines can lead to apoptosis or necrosis of myocardial cells, which can increase damage to the cardiovascular system and the severity of clinical manifestations. This phenomenon can be considered as one of the mechanisms of decompensation in patients with chronic heart failure complicated by ARVI, including the SARS-CoV-2 virus. [2]

A team of scientists from Wuhan reported that higher concentrations of certain biomarkers, such as myogemoglobin (MYO), the creatine kinase isoenzyme MB (CK-MB), N-terminal dank natriuretic peptide (NT-proBNP) and cTnI, biomarkers of inflammation were associated with the severity and frequency of deaths in patients with COVID-19 infection.

The determination of biomarkers of myocardial necrosis in patients with viral infections can provide prognostic information for assessing the progression of the disease and preventing the development of adverse events.

Much attention of clinicians among biomarkers of myocardial necrosis is riveted to Troponin I.

In one of the first studies in Wuhan, it was suggested that an increase in the level of highly sensitive cardiac TnI is associated with a worse prognosis. Among the 41 Covid-19 patients, 5 of them had troponin I (hs-cTnI) levels above 28 pg/ml, indicating myocardial damage. Patients with a significant increase in troponin were in severe (33.3%) and critical condition (100.0%). 4 out of 5 people with elevated hs-cTnI required hospitalization in ICU [3].

T. Guo et al. showed that an increase in the level of TnI in the blood has a direct relationship with death. Patients with CHF and high hs-cTnI have a higher mortality rate compared to patients without cardiovascular disease (59.6% vs. 8.9%). Patients with an elevated TnI and CVD history have the highest mortality rate (69.4%), while patients with only elevated TnI have a lower mortality rate (37.5%). However, the prognosis in patients with concomitant CVD, without myocardial damage, seems relatively favorable in comparison with patients without CVD and high TnT (mortality 13.3% vs. 37.5%) [4].

In the same study, plasma troponin levels were found to have a high positive correlation with levels of the N-terminal pro-B-type natriuretic peptide. Therefore, it is advisable to use the biomarkers hs-cTnt and NT-proBNP in the complex.

NT-proBNP is considered a common biomarker for HF, but there is also evidence of an increase in IT with SARS-CoV-2-19 infection.

In a study of the Cardiovascular Disease Registry of COVID-19 of the American Heart Association in patients with Covid-19 and HF in the anamnesis. It was obtained that elevated levels of NTproBNP predict a twofold increase in mortality. The incidence of deaths among 4675 patients was higher in patients with high levels of NT-proBNP (37% vs. 16%). The mean time to death was shorter with an increase in N-terminal natriuretic peptide (7 days vs. 9). It was noted that the risk of nosocomial mortality with an increase in Hs-TnT in the blood serum is the same in patients with previous HF and without it [5,6].

The efficacy of NT-proBNP for patients with a history of pre-existing CHF was determined in the Belarte-Tornero, L study. C. et al. The authors found that for patients in this group, the prognosis is less favorable. Against the background of COVID-19, decompensation of OSN (21%) developed, compared with 3.5% of patients without CHF, and in 50% of cases death occurred. According to the findings of the group of scientists, NT-proBNP can be used as a biomarker and become a risk factor for 30-day mortality in patients with CHF and COVID-19 [1,7].

An increase in the level of NT-proBNP is not necessarily specific to the disease, but rather may reflect a deterioration in hemodynamics, myocardial ischemia, and an increase in the contractile function of the heart.

In recent years, the role of the soluble ISOFORM ST2 in the pathogenesis of heart failure, which has become one of the most promising biomarkers for patients with this disease, has also been actively studied. In particular, recent studies suggest sST2 as a potential biomarker for COVID-19. Soluble SST2 is part of the interleukin-1 receptor family, which play a key role in triggering immunoinflammatory reactions. Its functional ligand is the cytokine Interleukin-33, synthesized by fibroblasts and having a cardioprotective effect.

When heart tissue is damaged, in response to mechanical stress, interleukin-33 (IL-33) binds to ST2, triggering a protective cascade, preventing fibrosis, cardiac remodeling and heart failure.

In a number of clinical studies, elevated levels of sST 2 have been shown to be associated with adverse outcomes in patients with CVD. This is confirmed by the Bonnie Ky study, which looked at the prognostic value of sST2 in patients with CHF. Among 1141 patients, the disease was more severe, with an increased risk of mortality and heart transplantation in patients with sST2 levels above normal values. The authors also found an association between an increase in sST2 levels and the severity of the disease in patients with Covid-19. Initial concentrations increased in proportion to the severity of the disease 43 (36-59) ng / ml for patients treated in wards, 67 (39–104) ng/mL for patients treated in the intensive care unit and 107 (72–116) ng/mL for non-survivors. Scientists noticed that adverse outcomes were independent of risk factors, inflammatory biomarkers and exceeded them [8].

Of great interest are clinical studies that involve the activation of the humoral immune system in response to myocardial damage. High titers of anti-myosin Ab have been reported to be widely found in serum patients in patients with myocardial infarction (16%-43%) and heart failure (20%-66%) [9].

An increase in ACA titers is also noted in patients with COVID-19 and can be regarded within the framework of immuno-inflammatory syndrome and LONG-COVID infection.

Blagova et al. conducted a study examining the correlation of the antibody spectrum with the clinical picture and prognosis in patients with COVID-19. It was found that the titers of all types of AKAt on average for a group of 86 patients exceeded the norm - to a greater extent this applied to AtK, AtGM and AtVPS. An increase in titers in the examined correlates with mortality (9.3% with a hospital stay of 14 days) and signs of myocardial damage. For AtGM with the presence of MA at admission ($r = 0.414$, $p<0.05$), for ANF and AtK with the presence and volume of effusion in the pericardial cavity ($r = 0.721$ and $r = 0.745$, respectively, $p<0.05$). There is also an association between ATE and AtK with CRP levels ($r= -0.466$, $p<0.01$, $r = 0.360$, $p<0.05$), which may reflect the overall activity and severity of the disease [10,11].

There is no doubt about the role of hypercoagulation in the pathogenesis of acute infection SARS-Cov 2.

Han H et al. Looked at changes in blood clotting in patients infected with COVID-19 with healthy controls. They reported that fibrinogen levels were higher in patients with mild to severe disease than in healthy patients. It was also noted that fibrinogen levels upon admission to the hospital may be a predictor of a survival rate of 4.51 (3.65-5.09) in 162 survivors; against 5.16 (3.74-5.69) in non-survivors [12]. However, Hayıroglu M reported in his study that fibrinogen cannot be prognostically significant as a stand-alone biomarker and must be evaluated together with a D-dimer for the correct predictive value [13].

The D-dimer is another biomarker closely related to fibrinolytic processes [14]. A study of 343 hospitalized patients with COVID-19 found that A D-dimer level of more than 2.0 µg/mL on admission was an independent predictor of all-cause mortality and a need for mechanical ventilation [15].

Huang et al. found that D-dimer levels upon admission could be used to triage patients in intensive care units [16]. It was found that the average level of D-dimer was higher in patients in ICU compared to patients not receiving ICU (2.4 mg/L vs. 0.5 mg/L;p=0.0042). These findings, along with previous research, suggest that D-dimer levels could be used as a prognostic marker and help clinicians monitor those who are likely to worsen earlier.

Although the D-dimer is well studied, it is not recommended to be used as a prognostic test for outcomes in patients with COVID-19. In a study by Selda Murat et al. of patients with HF, high DFR at admission was more specific in predicting clinical outcomes than D-dimer and fibrinogen. [17,18]. In their study, the high DFR value was significantly correlated with biomarkers that determine the prognosis of both inflammation and disease, such as procalcitonin, lactate, troponin, and ferritin.

Free iron is highly reactive and potentially toxic due to its role in the generation of reactive oxygen species (ROS). ROS react with cellular lipids, nucleic acids and proteins and damage them, followed by activation of acute or chronic inflammatory processes associated with a variety of clinical conditions. Moreover, iron-catalyzed lipid damage has a direct causal effect on non-apoptotic cell death (ferroptosis). Unlike apoptosis, ferroptosis is immunogenic and not only leads to increased cell death, but also contributes to a number of reactions, associated with inflammation, correlating with the level of pro-inflammatory cytokines.

The creatine phosphokinase-MB fraction is also of great prognostic importance for patients with CHF and viral infection, including COVID-19. It is suggested that an increase in CK-MB in the blood may indicate not only damage to cardiomyocytes, but also reflect a state of excess inflammation.

Mehrdad Sahranavard in his article examined the relationship of the biomarker CPK-MB and cardiac complications, in particular CHF, in COVID-19. In this cohort study of 4157 patients, the risk of developing heart failure was 22.24%. Among all patients with developed heart failure, elevated CK-CF levels were 10.92% (95% CI 5.36-20.96; $p <0.001$) [19]. Cardiac biomarkers, including CK-MB, are elevated in cases of COVID-19 infection, indicating myocardial damage in these patients. It is also noted that a high level of CK-MB on admission was associated with higher mortality.

In its meta-analysis, Huang et al. showed that CK-CF levels can be high in all COVID-19 patients (125 patients out of 135 had CK-MB levels above 200 IU/L on admission) [20].

An increase in myoglobin, a biomarker of early myocardial damage, may also be observed in patients with CHF and viral infections. Jennifer M McGoogan conducted studies and compared myoglobin and TnI levels. It was found that in patients with severe COVID-19, an increase in Mb was more common than an increased level of TnI [37.7 (23.3–52.1%) versus 30.7% (24.7–37.1%)], which is the gold standard among biomarkers of myocardial necrosis. It was also noted that the level of myoglobin is a predictor of the severity of the course (Mb, OR = 13.75 (10.2-18.54)), as well as mortality (Mb, OR = 13.49 (9.3-19.58)) [21].

Commented [1]: describe ferritin data??

There is evidence that increased levels of pro-inflammatory cytokines tumor necrosis factor (TNF)-α, C-reactive protein (CRP), interleukin (IL)-1, and IL-6 are strongly associated with adverse CHF outcomes. [22,23]

Yook Chin Chia in his research found the relationship of IL-6 with the development of HF. A cohort of 961 people of different sexes and ages with HF of various etiologies was studied [24]. The il-6 level was determined once. The evaluation found that IL-6 levels were significantly associated with preserved ejection fraction heart failure (HFpEF) (95% CI 2.06–3.39; p <0.001). Whereas IL-6 was not significantly associated with heart failure with reduced ejection fraction (HFrEF). The risk of mortality increased with an increase in Il-6 levels (95% CI1.09-1.24; P < 0.001).

Also in the study Constantinos Ergatoudes, it is noted that the risk of developing HF increased with an increase in the level of C-reactive protein (CRP)[25]. In a cohort of 798 participants, CRP levels in people with heart failure were >3 mg/L (95% CI 1.59–4.29, p=0.0002) [26]. CRP levels of > 2 mg/L are known to be associated with worse survival (p = 0.008). As well as the combination of sST2 and CRP in people with CVS diseases is a predictor of mortality (CI 2.8–35.1, p <0.001).[27]

According to these studies, the inflammatory process plays a key role in the pathogenesis of heart failure. Dunley et al. in the Olmsted County study concluded that the level of (TNF)-α in patients with HF with a preserved ejection fraction was higher and directly correlated with mortality in this group of patients [28].

(прошлая версия): Pro-inflammatory cytokines tumor necrosis factor (TNF)-α, interleukin (IL)-1 and IL-6 play an important role in the pathogenesis of heart failure. Inflammatory cytokines cause an inflammatory reaction in the myocardium, followed by a decrease in the contractile function of cardiomyocytes. (Hanna A, Frangogiannis NG. Inflammatory Cytokines and Chemokines as Therapeutic Targets in Heart Failure. Cardiovasc Drugs Ther. 2020 Dec;34(6):849-863. doi: 10.1007/s10557-020-07071-0. Epub 2020 Sep 9. PMID: 32902739; PMCID: PMC7479403.).

TNF-α has a negative inotropic effect in cardiomyocytes, which leads to a decrease in intracellular calcium content and a decrease in contractile function (https://pubmed.ncbi.nlm.nih.gov/8227345/). It has also been empirically established that this cytokine calls for cardiomyocyte apoptosis (https://pubmed.ncbi.nlm.nih.gov/17694177/). The association between TNFα and CHF was first discovered in a study by Levine et al, which noted that serum TNFα levels were significantly higher with CHF compared to healthy control groups. Subsequent studies also showed that TNFα levels correlated with the development of HF in healthy people. The risk of developing CHF increased by 46% with an increase in plasma TNF-α (https://pubmed.ncbi.nlm.nih.gov/12654604/)

IL-1 plays a large role in the development and progression of heart failure. IL-1, like TNF-α inhibits the systolic function of cardiomyocytes, a decrease in intracellular calcium, has an apoptotic effect (https://link.springer.com/article/10.1007/s10557-020-07071-0#Sec3). Also , IL-1 causes activation and mobilization of leukocytes, which subsequently leads to inflammatory reactions in the myocardium (https://pubmed.ncbi.nlm.nih.gov/24078695/). It causes hypertrophy of the heart due to the proliferation of fibrous tissue (https://insight.jci.org/articles/view/125074#SEC3)

IL-6. It acts through the gp130 / STAT3 pathway providing a negative inotropic effect, which leads to the development of cardiomyocyte hypertrophy (https://pubmed.ncbi.nlm.nih.gov/7518362/). In experiments on rats, interleukin 6 has been shown to cause concentric hypertrophy, fibrosis and diastolic myocardial dysfunction (https://pubmed.ncbi.nlm.nih.gov/20606113/). There was a close relationship between the risk of developing CHF and the level of serum IL-6. Mean IL-6 levels were 1.76 +/- 1.73 in stable patients and 4.62 +/- 7.98 pg/mL in patients who developed exacerbation of heart failure (https://pubmed.ncbi.nlm.nih.gov/15261178/) Rice development of CHF increased by 36% with an increase in IL-6 levels (https://pubmed.ncbi.nlm.nih.gov/12654604/). Studies have also been conducted that have shown that IL-6 is an independent predictor of mortality in patients with chronic HF (https://pubmed.ncbi.nlm.nih.gov/11079662/).

Studies have also been conducted that showed that plasmaconcentrations of tumor necrosis factor (TNF)-α, interleukin (IL)-1 and IL-6 in plasma in patients with severe COVID-19 infection in the intensive care unit (ICU) were higher than in patients not admitted to ICU(p=0.030) (https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)30183-5/fulltext#sec1)

Thus, the cytokines described above can be considered as biomarkers reflecting the severity of the disease.

CRP is an acute pro-inflammatory cytokine produced by hepatocytes in response to an interleukin-6 (IL-6) (https://pubmed.ncbi.nlm.nih.gov/1699862/) signal. The change in CRP levels showed that in people who had severe COVID-19, the level of CRP was higher relative to other patients in the mild form (57.9 mg / l vs. 33.2 mg / l, P < 0.001)

Empirically, it has been proven that there is a relationship between the level of CRP and the development of heart failure. There was an increased concentration of CRP levels in 30 out of 40 patients with HF (https://pubmed.ncbi.nlm.nih.gov/13302128/). CRP became a potential predictor of the risk of adverse outcomes in patients with HF (https://link.springer.com/article/10.1007/s11897-019-00450-1)
There were also studies that proved that regardless of the level of CRP, it is associated with a twofold increase in cardiovascular mortality (https://pubmed.ncbi.nlm.nih.gov/16129801/

CONCLUSION

Thus, higher values of cardiovascular biomarkers in patients who have undergone SARS-CoV-2 are predictors of a higher risk of complications, a worsening prognosis of the course of the disease in patients and mortality. Further research on the effect of COVID-19 on long-term outcomes in patients suffering from heart failure is clearly needed.

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