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VIEWPOINT

Biomarkers and Mononuclear Inflammatory Activity in COVID-19 Survivors

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Introduction

COVID-19 has globally impacted 522 million people and caused 6 million deaths, despite the administration of 12 billion vaccine doses. Beyond respiratory effects, the virus has led to complications in the cardiovascular, hematological, and nervous systems, potentially resulting in organ dysfunction and death. Individuals with pre-existing medical conditions such as hypertension, diabetes mellitus, coronary artery disease, heart failure, and chronic kidney disease are associated with worse prognoses. Increased long-term mortality risk is observed, especially in the elderly population, regardless of the acute phase severity.[1]

COVID-19 affects multiple organs beyond the lungs, including various cardiovascular diseases such as myocarditis, acute myocardial infarction, stress cardiomyopathy, arterial and venous thromboembolism, pericarditis, and arrhythmias. The pathophysiological mechanisms include systemic inflammation (cytokine storm), coagulopathy, direct viral invasion, hypoxemia, electrolyte imbalance, and fever.[2]

A previous study discussed the association between SARS-CoV-2 infection and inflammation-mediated myocardial damage. The authors suggested that the activation of the interstitial macrophage system could be the key factor in cardiac damage. This immunopathological mechanism, developing in the myocardial interstitium, can lead to myocardial dysfunction and present as heart failure with preserved ejection fraction (HFpEF).[3]

Keywords

Biomarkers; COVID-19; Cardiovascular Diseases.

Biomarkers and COVID-19

Brain natriuretic peptide (BNP), first discovered in pig brains in 1988, is mainly synthesized and released by the ventricular myocardium in response to myocyte stretch. Initially, Pro-BNP is produced as a pre-hormone, undergoing enzymatic cleavage to generate biologically active BNP and the inactive N-terminal fragment (NT-proBNP), both in equal proportions. Sabanoglu et al.[4] suggested that NT-proBNP levels could serve as a prognostic marker for the long-term clinical progression of individuals who have survived the acute phase of COVID-19.

Biomarkers elevations indicating cardiac injury are frequently observed in COVID-19 patients, with up to 36% of hospitalized individuals showing increased levels of troponin and NT-proBNP, which are independent predictors of unfavorable clinical outcomes. Echocardiographic studies have revealed an association between ventricular dysfunction and COVID-19, with right ventricular dysfunction being the most common (26.3%). Other alterations include left ventricular wall motion abnormalities (23.7%), global systolic dysfunction (18.4%), grade II or III diastolic dysfunction (13.2%), and pericardial effusion (7.2%).[5] Additionally, individuals may experience increased thromboembolic events, arrhythmias, and vascular diseases.

Acute cardiac muscle damage, evidenced by variations in serum cardiac troponin levels, is significant in hospitalized patients. A study in Brazil showed a prevalence of myocardial injury of up to 36%, which was associated with a higher in-hospital mortality rate, irrespective of the origin of the elevated biomarkers. However, there remains a gap in understanding the long-term effects of myocardial injury during SARS-CoV-2 infection.[6]

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Long COVID

Post-acute sequelae of SARS-CoV-2 infection (PASC), known as long COVID, refer to persistent symptoms lasting 30 days or more after the initial infection, presenting clinical and public health challenges. Cardiopulmonary manifestations include chest pain, shortness of breath, fatigue, postural orthostatic tachycardia syndrome, palpitations, malaise, confusion, headache, nausea, vomiting, anxiety, depression, rash, and joint pain.[7] Peripheral inflammation, characterized by increased monocyte counts and their differentiation into inflammatory/pro-fibrotic M2 macrophages, may be associated with HFpEF and an asymptomatic phase of left ventricular diastolic dysfunction.[8]

The immune system is essential in managing inflammation following organ insult or damage. The orchestration of cardiac inflammation and subsequent tissue damage involves the infiltration and activation of various immune cells in the myocardium, including neutrophils, monocytes, macrophages, eosinophils, mast cells, natural killer cells, and T and B cells.[9]

Following tissue injury, monocytes and macrophages undergo phenotypic and functional changes, regulating repair, regeneration, and fibrosis. Disturbances in macrophage functions, such as uncontrolled inflammatory cytokines production, growth factors, inefficient anti-inflammatory response, or poor communication with epithelial, endothelial, and fibroblast cells, can lead to abnormal repair, persistent injury and, ultimately, heart failure.[10]

M2 macrophages are involved in host defense, wound healing, and tissue remodeling, and also contribute to metabolic performance and endocrine signaling within the tissue.[11] Sabanoglu et al. suggested that NT-proBNP and high-sensitivity troponin could anticipate long-term outcomes in COVID-19 infection.[4]

The underlying mechanisms of long COVID's cardiovascular effects are poorly understood. The cardiovascular system may suffer both direct and indirect impacts from SARS-CoV-2 infection. Factors such as viral persistence, molecular mimicry, endothelial dysfunction, arterial stiffening, and high oxidative load are suggested to maintain cardiac and vascular dysfunction in individuals who survived acute infection. Cardiac magnetic resonance studies conducted after acute COVID-19 have reported abnormalities in up to 78% of cases, persisting up to 71 days post-infection. These abnormalities include elevated T1 values (indicating fibrosis or inflammation), T2 values (indicating edema), and late gadolinium enhancement. In a study of 52 patients with suspected long COVID cardiovascular involvement, 15% had myocardial injury, 8% had pulmonary embolisms, and 4% had both cardiovascular entities.[11] The cardiovascular symptoms of long COVID may be related to the increased disease burden observed in the 12 months following COVID-19, including myocarditis, ischemic or non-ischemic cardiomyopathy, and atrial fibrillation.[12] A retrospective analysis of 180 individuals with a previous COVID-19 diagnosis and persistent or newly developed cardiovascular symptoms (chest pain, palpitations, and arrhythmias) revealed a high prevalence of acute pericarditis. [13] Joy et al., in contrast, reported that, six months after mild COVID-19, only 4% of participants had abnormal cardiac magnetic resonance imaging, a rate similar to that of the corresponding healthy control cohort.[14] Kravchenko et al. investigated 41 patients with cardiovascular symptoms 103 days after the initial diagnosis of mild to moderate COVID-19. They found no difference in troponin levels or cardiac magnetic resonance imaging (T1 and T2 relaxation times, T2 signal intensity ratio, and late gadolinium enhancement).[15] Further studies, including molecular tissue analyses, are necessary to determine whether cardiovascular symptoms in long COVID patients are due to cardiac dysfunction. If so, it is crucial to identify the disease entities and underlying mechanisms involved.

We conclude that monitoring serum biomarker levels, such as BNP/NT-ProBNP, can help identify groups at risk for developing ventricular dysfunction over indeterminate periods. Cellular inflammatory measures, such as macrophages, also provide an opportunity to understand the mechanisms of long-term cardiac damage and help formulate therapeutic and preventive strategies.

Author Contributions

Conception and design of the research: Carvalho M; acquisition of data, analysis and interpretation of the data, writing of the manuscript and critical revision of the manuscript for intellectual content: Carvalho M, Lagoeiro A.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

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Ethics Approval and Consent to Participate

This article does not contain any studies with human participants or animals performed by any of the authors.

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