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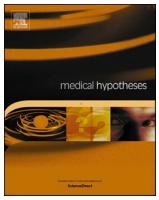

The role of carbohydrate antigen 125 in COVID-19

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ABSTRACT

Coronavirus disease 2019 (COVID-19) is an inflammatory process with complex pathophysiology and by affecting the cardiovascular system directly or indirectly that causes life threatening cardiac injuries. Therefore, clarifying the effects of this infection on the cardiovascular system is of importance in terms of the clinical course of the disease. The increases in cardiac and inflammatory biomarkers in COVID-19 have been associated with poor prognosis and mortality. However, there are no specific laboratory markers yet to assess the severity of the disease. In this context, the combination of available biomarkers is needed to better define the clinical course of this disease. Carbohydrate antigen 125 (CA-125) has become a remarkable marker in recent years as a result of the correlation of increasing levels in cardiovascular diseases with clinical, hemodynamic, echocardiographic parameters and its relation with mortality or re-hospitalization due to heart failure. These findings suggest that CA-125 might be useful biomarker to identify the damage mechanisms of COVID-19, monitoring the prognosis of the disease and the course of the treatment.

Introduction

Since one year, Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes a significant number of morbidity and mortality worldwide. Uncertainties still continue regarding the pathophysiological mechanism, prognosis and treatment of this infectious disease causing the pandemic [1]. However, clinical studies provide a consensus that increasing age and the presence of comorbidities are associated with severe form of the disease and poor outcome [2]. In particular, individuals with cardiovascular risk factors or cardiovascular disease have a higher risk of developing severe disease and death [3,4].

COVID-19 may affect the cardiovascular system directly or indirectly that causing complications. Although the pathophysiology underlying cardiac injury caused by this inflammatory disease is unknown exactly, the putative mechanisms are [5,6]: (i) SARS-CoV-2 binds to Angiotensin converting enzyme 2 (ACE2) receptor which is also found in lung alveoli cells as well as myocardial and vascular endothelial cells and may cause a direct cytotoxic effect in these cells [4,7–9]; (ii) Severe systemic inflammation and cytokine storm [4,5,8–12]; (iii) Caused by hypoxemia due to respiratory dysfunction myocardial and microvascular injuries [8]; (iv) İschemia and exacerbation of pre-existing heart disease [11,12]. Except for causing myocardial damage, all these effects may also lead to myocardial infarction (MI), myocarditis, heart failure, acute coronary syndrome, venous thromboembolism (VTE) and arrhythmia [4,13].

Laboratory findings play an essential role in assessing illness severity, determining prognosis and guiding treatment in COVID-19 [14]. Evaluation of data on electrocardiographic, echocardiographic, and cardiac specific laboratory parameters are milestones to define cardiac injury during COVID-19 [6]. However, additional data with proven clinical benefit are required to better evaluate the predicted potentials of these markers. Therefore, the use of CA-125 data may have various benefits.

The hypothesis

Carbohydrate antigen 125 (CA-125) is a high molecular weight glycoprotein that is a member of the mucin family and is synthesized by serous epithelial cells. Its half-life is approximately 7 days. As the physiological role of CA-125 is considered to protect the epithelial lumen surfaces from physical stress through the process of hydration or lubrication [15–17]. Pathophysiological mechanisms that cause serum levels to increase are expressed as activation of mesothelial cells in response to stimuli such as oxidative stress, mechanical stress (fluid overload and tissue stretching) and systematic inflammatory process (cytokine activation) [15,16,18–28].

There are many publications from the past to present suggesting that CA-125 may be a potential biomarker for heart diseases, especially heart

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failure. Elevated serum CA-125 levels together cardiac biomarkers have been reported to have prognostic effects in patients with heart failure and correlate well with clinical, hemodynamic, and echocardiographic measurements indicating the severity of the disease [18,19,22,24,26,29–31].

In line with this evidence, adding CA-125 to the COVID-19 test panel may provide prognostic data that can help identify patients at higher risk of adverse outcomes in a timely manner and monitor treatment follow-up. Moreover, it may also contribute to a better understanding of the pathophysiology of the process.

Evaluation of the hypothesis

In this hypothesis, it is evaluated what the increased CA-125 levels might mean in patients with severe COVID-19. The severe disease state associated with COVID-19 is a complex process in which various systems play a role. Hence, a collaborative biomarker based approach might help to manage the cardiac effects of this disease better.

Studies examining the interaction between COVID-19 infection and the cardiovascular system have shown that severe patients may develop cardiac injury and this too provides important information on complications and mortality associated with COVID-19. Patients with cardiac injury have higher levels of Troponin (cTnI, hs-cTnI), Creatine Kinase-MB (CK-MB), C-reactive protein (CRP or hs-CRP), natriuretic peptide (BNP or NT-proBNP) and abnormal echocardiographic or electrocardiogram (ECG) findings have been reported [4]. It has also been indicated that serum cytokine levels such as interleukin-1β (IL-1β), interleukin-2 (IL-2), interleukin-6 (IL-6), interleukin-8 (IL-8), interleukin-10 (IL-10), tumor necrosis factor-α (TNF-α) increase significantly in relation to disease severity [1,5,7,10,32–36].

In many previous studies have reported that increased CA-125 levels along with cardiac and inflammatory biomarkers are positively correlates with the degree of cardiac dysfunction and the severity of the clinical picture in patients with heart failure [18,19,21,24–27]. Heart failure condition is closely related to systemic inflammatory activity and congestion (hydrostatic pressure and serosal effusions). Congestion is a hemodynamic parameter and causes the disease to progress by integrating into the circle of inflammatory process defined in heart failure. The most important determinants of the expression of CA-125 in heart failure are factors such as serosal fluid overload, congestion and also positive correlations with various inflammatory cytokines have been detected [15,19–23,26,28,29,37]. Considering that CA-125 is a surrogate marker for both congestion and systemic inflammation that can be considered that in COVID-19 patients may have high serum levels by a multifactorial mechanism in the complications that occur.

Findings in the literature supporting this hypothesis demonstrating the clinical usefulness of CA-125 are: (I) Positive correlations were reported between serum CA- 125 levels and CRP/hs-CRP, BNP/NT-proBNP, cytokines (TNF-α, IL-1, IL-6, IL-10) [17–19,25,30,37–39]; (II) Elevated CA-125 levels were associated with the severity of diastolic and systolic dysfunctions in many studies supplemented by echocardiographic data. Positive and significant correlations also were found with left ventricular ejection fraction (LVEF), systolic pulmonary artery pressure (SPAP), right atrial pressure, pulmonary artery wedge pressure, left atrial volumes [15–18,21–27,30,31,37,39]; (III) A positive correlation was detected between CA-125 and ventricular remodeling. Thus, It was suggested that high serum CA-125 levels in coronary heart patients may help predict the risk of short-term heart failure and death [24]; (IV) It was reported that patients with increased CA-125 levels have a higher risk of developing atrial fibrillation [15,17,18,27]; (V) Elevated CA-125 levels were also observed in other cardiac pathologies such as tricuspid stenosis, mitral stenosis, mitral valve endocarditis, atrial septal defect, pulmonary hypertension, aortic stenosis, and acute coronary syndromes [25,27,37]; (VI) There is evidence that changes in serum CA-125 levels as a result of the therapy protocol used heal the clinical course [37].

Discussion

Clinical studies of COVID-19 indicate that there is cycle between this infection and cardiac dysfunction or heart failure [5,35,36,40]. There are many mechanisms that can cause cardiac hemodynamic disorders in COVID-19, and different types of cardiovascular involvement have been reported in the literatüre [4–8,10,35,41,42]. Therefore, early diagnosis and timely intervention of critical cases is very important.

Up to date, studies suggest that many laboratory biomarkers are deranged in COVID-19 infection, and some are considered predictors of poor prognosis and mortality [14,43]. Increased levels of procalcitonin, CRP, D-dimer, troponin, natriuretic peptide (NT-pro BNP, BNP) and cytokine (IL-6, IL-10, TNF-α) are associated with risk of cardiovascular complications and death. It has been indicated that all these biomarkers increase each other's prognostic values and have significant positive linear correlations [5,8,32,34,40,44].

Studies on combining risk stratification and predictive values of different biomarkers that reflecting different pathophysiological pathways and having prognostic value alone are among the current research topics [19]. CA-125 is one of the remarkable biomarkers in this context because of correlation with many parameters. Although CA-125 and natriuretic peptides have different pathophysiological mechanisms and half-lives (BNP ~ 20–30 min), significant correlations have been identified between them in the presence of heart failure. Moreover, strong associations of CA-125 with inflammatory stimuli, echocardiographic and hemodynamic parameters, mortality or re-hospitalization risk of patients during follow-up have been reported [15–23,25–28,29,31,37,39,45]. An improvement in LVEF with a marked decrease in CA 125 levels after treatment in heart failure patients, the observation of reductions in pericardial effusion, and also the ability to monitor treatments that affect cytokine levels through CA-125 levels make it a valuable marker [4,10,17,19,21,25,26,37]. CA-125 has also other strategic advantages that deserve to be highlighted: (a) the wide availability; (b) in contrast to the disadvantages of cytokines such as high temporal variability, non-standardized measurement techniques and short half-life, there is an easy, standardized and highly reproducible measurement method in a short time; (c) unlike natriuretic peptides (much lower in obese people than normal weight individuals), serum values that are not affected by factors such as kidney function, body weight and age; (d) relatively low cost [17,19–22,28,29,45]. In line with all these evidences, CA-125 has the potential to be a useful marker in COVID-19 as well.

Wei et al., have been reported positive correlations between inflammatory markers and a range of cancer biomarkers, including CA-125, in COVID-19 patients. As a result of this relation, they have suggested that acute lung injury caused by SARS CoV-2 may lead to an increase in some cancer biomarkers as an indicator of widespread and acute pathophysiological injuries [46]. However, there is no mechanism or data yet associated with increased CA-125 levels as a result of cardiac effects in COVID-19. Therefore, these theoretical possibilities will be better evaluated when clinically validated data are available.

On the other hand, there are also some uncertainties regarding the CA-125 that should be expressed. It should not be ignored that CA-125 may have increased serum levels not related to heart failure and in different types of both malignant and non-malignant diseases [28,37]. Hence, the clinical interpretation of elevated CA-125 levels should be done with caution. Such an approach would contribute to the identification of the CA-125′s major production sites and stimuli [6,15]. Accordingly, it may provide evidences as to whether the pathophysiological link between COVID-19 and CA-125 is affected by overlapping intense inflammatory stimuli that may result from underlying stimuli, stimulating environments, effusions, or associated cytokines.

In conclusion, COVID-19 is a newly emerged inflammatory process and various complications can occur even after the disease has healed. Because of the strong correlation of CA-125 with many parameters, its combination with key prognostic biomarkers in COVID-19 might make

significant contributions to the management process of this disease. Furthermore, both the problems in the supply of many laboratory biomarkers as a result of intensive health services all over the world and the inability to test some biomarkers easily in all laboratories should also encourage its use in this period.

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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