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Letter to the Editor: Impact of Cardiovascular Risk Factors and Cardiovascular Diseases on Outcomes in Patients Hospitalized with COVID-19 in Daegu Metropolitan City

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OPEN ACCESS

Received: Feb 7, 2021

Accepted: Apr 12, 2021

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Disclosure

The authors have no potential conflicts of interest to disclose.

Author Contributions

Conceptualization: Siniorakis E. Writing - original draft: Siniorakis E. Writing - review & editing: Arvanitakis S, Katsianis A, Nikolopoulos I.

We read with interest the article by Park et al.¹ referring to the impact of preexisting cardiovascular diseases on outcome of patients hospitalized with coronavirus disease 2019 (COVID-19) infection. The main result of the study was that among the various pre-existing cardiac diseases, heart failure (HF) was the only independent predictor of in-hospital mortality, after adjusting for all confounding variables. However, we notice that there is a paucity of information regarding the HF phenotype upon admission, as well as during hospitalization. We believe that in order to interpret the way in which HF interfered with mortality, some further information is required, according to the following observations.

HF is a general term for a complex syndrome whose description requires characteristics which are lacking in this article. To describe the severity of HF there are clinical and imaging criteria.² The former consists of the classic stratification in stages I to IV, according to the New York Heart Association (NYHA) classification, while the latter are based on the inclusion of the left ventricular ejection fraction (EF) usually derived from a transthoracic echocardiogram (ECHO). Categories of HF thus emerge, such as HF with reduced, mid-range or preserved EF. It is expected that a patient with reduced EF and NYHA class III symptoms is in a more serious condition compared to one with preserved EF and NYHA class II symptoms. Furthermore, details comprising the nature of the therapeutic management and the observed compliance may categorize the HF into compensated or decompensated. Biomarkers such as brain natriuretic peptides are more particular in the characterization of HF.

The profile of HF in patients hospitalized for COVID-19 can be exacerbated by further cardiovascular complications related to the virus itself or to the host reactivity. Acute myocardial infarction and ischemia, stress cardiomyopathy, myocarditis, pericarditis, thromboembolism and arrhythmia-related cardiac injury are some complications that COVID-19 infection can provoke, resulting in aggravating preexisting HF.³ 'De novo' HF can also appear in the absence of previous cardiac diseases.⁴

If conservative therapeutic measures prove ineffective in treating resistant HF, patients are likely to be transferred to the intensive care unit (ICU) or even be submitted to mechanical ventilation (MV).⁵ Vasoactive drugs including vasopressors or inotropes such as dopamine or dobutamine are widely administered to such cases although their beneficial effect remains

disputable. In patients under MV, the progression of HF can be underestimated given the lack of symptoms. COVID-19 is a multi-organ syndrome with overlapping manifestations from respiratory and cardiovascular systems, leading to difficult differential diagnosis concerning the clinical expression. In this context a hemodynamic approach is inevitable.⁶ Non-invasive hemodynamics can be estimated through a transthoracic ECHO. Dimensions and contractility of cardiac chambers, diastolic function markers of both ventricles, the presence of pericardial effusions and intracardiac thrombi are some of the imaging findings without which the severity of HF in the context of ICU cannot be estimated. If a bedside ECHO is technically inconclusive, then invasive hemodynamic monitoring by insertion of a Swan-Ganz catheter is warranted.⁷ Parameters like the systemic and pulmonary vascular resistance, cardiac output and index, pulmonary artery and wedge pressure, and mixed venous blood oxygenation can be calculated. This is required for tailoring the therapeutic regimen. In particular, when the course of COVID-19 is complicated by a cytokine cascade leading to clinical manifestations mimicking the acute respiratory distress syndrome (ARDS), then the hemodynamic profile becomes indispensable. Some hemodynamic characteristics of this final stage such as a high cardiac index, normal pulmonary vascular resistance, high pulmonary wedge pressure and post-capillary pulmonary hypertension, diverge from the findings of classical ARDS, necessitating the application of a special therapeutic protocol.⁸

Patients with HF and COVID-19 are likely to express a deterioration of their myocardial function if submitted to MV. Positive expiratory pressures and widespread pulmonary vascular thrombosis frequently increase the right ventricular afterload, resulting in right ventricular dilatation and dysfunction.⁹ MV in COVID-19 patients is characterized by prolonged ventilation, difficult or failed weaning, frequent reintubations and tracheostomies.¹⁰ All of the above worsen if HF coexists.¹¹ Particularly, the weaning from MV with return to spontaneous breathing and extubation is equivalent to cardiorespiratory stress testing. Many patients do not tolerate the extubation procedure and die under MV. Shifting from MV to spontaneous breathing induces negative intrathoracic pressures, leading to increase of systemic venous return, increase of right ventricular preload and afterload, increase in pulmonary artery occlusion pressure and left ventricular filling pressure, with end result frank pulmonary edema.¹² Several therapeutic protocols have been tried in an attempt to sustain the weaning procedure in COVID-19 patients. Most of them include catecholamines such as dopamine and dobutamine, which are potentially cardiotoxic with controversial results. More promising appears to be the use of inodilators, with levosimendan as the main representative. This intracellular calcium sensitizer possesses inotropic, lusitropic and anti-inflammatory properties, and there is encouraging experience where its administration enabled weaning from MV, in cases where this appeared to be unachievable.¹³

We referred above to some significant data required to understand the conditions under which HF can influence the in-hospital mortality of COVID-19 patients. When this is missing it is unclear whether these patients die of or with HF.¹⁴ We honor the effort that Park and colleagues have contributed for the collection and elaboration of data from ten different hospitals in order to estimate the impact of HF on the outcome of COVID-19 hospitalized patients. If the authors possess information regarding the circumstances under which HF influenced the in-hospital mortality, we remain eagerly awaiting for them.

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The Author's Response: Impact of Cardiovascular Risk Factors and Cardiovascular Diseases on Outcomes in Patients Hospitalized with COVID-19 in Daegu Metropolitan City

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Received: Apr 12, 2021

Accepted: Apr 13, 2021

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Disclosure

The authors have no potential conflicts of interest to disclose.

We appreciate the opinion to our paper on 'Impact of Cardiovascular Risk Factors and Cardiovascular Diseases on Outcomes in Patients Hospitalized with COVID-19 in Daegu Metropolitan City' by Siniorakis et al. from Greece. They pointed out several aspects of heart failure (HF) and asked further information regarding 'from diagnosis to treatment of HF' in detail.

First, our study was performed based on chart review without external prospective ascertainment. The diagnosis of HF was confirmed by a medical chart review or by asking the patient about his previous medical history using a telephone. Therefore, in our study, data were not sufficient to categorize the HF into compensated or decompensated HF by the nature of the therapeutic management and the observed compliance.¹ In addition, cardiac markers such as cardiac troponin and CK-MB were obtained at the time of admission and during the follow-up. However, biomarkers such as brain natriuretic peptide (BNP) and N-terminal pro-BNP were not routinely measured in all HF patients. Therefore, there are limitations in determining the degree of HF using biomarkers.²

Second, the aim of this study was to investigate the association between underlying cardiovascular risk factors (CVRF) or cardiovascular disease (CVD) and outcome, not confined to specific disease such as HF. Severe inflammatory reactions occur in patients who require hospitalization for COVID-19. As shown in our study, such as WBC count, CRP, hs-CRP, and pro-calcitonin were greater in patients with preexisting CVRFs or CVDs at baseline and during the follow-up. In patients with preexisting HF, acute myocardial ischemia, acute pericarditis, and myocarditis caused by COVID-19 infection can lead to exacerbation of existing HF. Although HF also can be newly diagnosed during hospitalization due to the cardiac injury caused by the COVID-19 infection, 'De novo' HF was not included in this study because it is not primary outcome measure in this study.³

Third, we also agree that monitoring of hemodynamic parameters is important in patients requiring intensive care unit care (ICU). However, as you know, there were limitations in measuring hemodynamic factors in severely ill patients receiving ICU care and mechanical ventilator (MV) care during the COVID-19 pandemic. Accordingly, in-hospital mortality may increase because MV weaning is often difficult in patients with HF without intensive hemodynamic monitoring. As a result, patients with pre-existing HF might have higher mortality in the COVID-19 pandemic.⁴

Finally, we thank you for reminding us of the various reasons that may increase in-hospital mortality in patients with pre-existing HF during the COVID-19 pandemic.⁵ Since our study is multicenter and retrospective observational study, some important variables that may impact on outcome in individualized patient were not collected. Therefore, we strongly agree that there are various unmeasured factors as well as COVID-19 infection severity itself as to the cause of worsening HF during hospitalization. Further studies are required regarding HF influences on the in-hospital mortality during the COVID-19 pandemic.

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