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Editorial

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Type 2 Myocardial Infarction: Another Hidden Cause of Mortality During the COVID-19 Pandemic

Eun Jeong Cho, MD, PhD[1,2], Kyeongmin Byeon, MD, PhD[1,2], and Young-Hoon Jeong, MD, PhD[1,2]

[1]CAU Thrombosis and Biomarker Center, Chung-Ang University Gwangmyeong Hospital, Gwangmyeong, Korea
[2]Division of Cardiology, Department of Internal Medicine, Chung-Ang University College of Medicine, Seoul, Korea

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Correspondence to
Young-Hoon Jeong, MD, PhD
CAU Thrombosis and Biomarker Center, Chung-Ang University Gwangmyeong Hospital, 110, Deokan-ro, Gwangmyeong 14353, Korea.
Email: goodoctor@naver.com
younggoodoctor@gmail.com

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ORCID iDs
Eun Jeong Cho
https://orcid.org/0000-0003-3345-2516
Kyeongmin Byeon
https://orcid.org/0000-0001-9037-381X
Young-Hoon Jeong
https://orcid.org/0000-0003-0403-3726

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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes the viral respiratory disease known as coronavirus disease 2019 (COVID-19). While its primary pathophysiology has been thought to be a respiratory infection, COVID-19 infection also leads to excessive inflammation, endothelial dysfunction, platelet activation, and hypercoagulability. These factors can predispose patients to atherothrombotic and thromboembolic events.[1)]

A recent meta-analysis (102 studies including 64,503 patients) demonstrated the high rates of venous thromboembolic event (VTE) and arterial thromboembolic event (ATE) in hospitalized patients with COVID-19.[2)] The frequency of VTE was 14.7%, in which rates of pulmonary embolism (PE) and deep vein thrombosis (DVT) were 7.8% and 11.2%, respectively. The frequency rates of overall ATE, acute coronary syndrome (ACS), stroke and other ATE were 6.4%, 3.9%, 1.6% and 0.9%, respectively. Furthermore, patients who recovered from COVID-19 infection continued to experience a long-lasting increased risk of post-acute sequelae and mortality, including cardiovascular, coagulation and hematologic, gastrointestinal, kidney, mental health, metabolic, musculoskeletal, and neurologic disorders compared with the control subjects.[3)] These observations may suggest COVID-19-induced activation of thrombo-inflammatory axis and its sustained impact on clinical prognosis.

Acute myocardial ischemia due to a sudden decrease in coronary blood flow can cause ACS phenotype, ranging from unstable angina to acute myocardial infarction (AMI).[4)] Its underlying mechanisms are heterogeneous such as reduction of myocardial perfusion (e.g., disruption of atherosclerotic plaque, coronary embolism, microvascular dysfunction, and coronary vasospasm), increased myocardial oxygen demand (e.g., severe hypertension and severe tachyarrhythmia) as well as other cardiac or systemic conditions (e.g., pulmonary embolism, acute infection, and myocarditis).[4)] Furthermore, overactivated inflammation and oxidative stress can be contributable to its occurrence. Meanwhile, myocardial infarction (MI) can be classified into various types based on pathological, clinical, and prognostic differences, along with different treatment strategies.[4)] MI caused by atherothrombotic coronary artery disease and usually precipitated by atherosclerotic plaque disruption (rupture or erosion) is designated as 'type 1 MI.' The pathophysiological mechanism leading to ischemic myocardial injury in the context of a mismatch between oxygen supply and demand has been classified as 'type 2 MI.'

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Conflict of Interest

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Data Sharing Statement

The data required to reproduce findings cannot be shared due to this paper is an editorial.

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In the COVID-19 era, hospitalized AMI cases, especially 'type 1 MI,' have been reported to decrease dramatically, particularly for non-ST-segment elevation myocardial infarction (NSTEMI) cases. In a large-scale American patients presented with NSTEMI (n=1,022,439), the odds of mortality increased by 51% (adjusted odds ratio [aOR], 1.51; 95% confidence interval [CI], 1.29–1.76; p<0.001) and the rate of revascularization decreased by 27% (aOR, 0.73; 95% CI, 0.64–0.83; p<0.001) among patients hospitalized during weeks with a high hospital COVID-19 burden (>30%) versus patients hospitalized prior to the pandemic.[5]

The linkage of COVID-19 infection with occurrence of 'type 2 MI' and its clinical prognosis have not been clearly demonstrated. In this issue of the *Korean Circulation Journal*, Thyagaturu et al.[6] presented clinical outcomes of hospitalization by 'type 2 MI' before versus during the COVID-19 pandemic (2019: n=331,180 vs. 2020: n=412,355) using the National Inpatient Sample (NIS) database. The results showed a significant increase in 'type 2 MI' hospitalizations with an increasing trend corresponding to the increase in hospitalizations due to COVID-19 in the year 2020 (6.1–21.0% between April and December) compared to 2019. The in-hospital mortality rate due to 'type 2 MI' was significantly higher in 2020 versus 2019 (11.1% vs. 8.1%: aOR, 1.19; 95% CI, 1.13–1.26; p<0.010). COVID-19 was the fourth most common diagnosis associated with mortality due to 'type 2 MI' in the year 2020.

The COVID-19 pandemic affects the prevalence and outcomes of 'type 2 MI.' Endothelial dysfunction, systemic inflammation, thrombogenic milieu, hypoxia and arrhythmia caused by COVID-19 infection lead to an imbalance in oxygen demand and supply, increasing the rate of 'type 2 MI.' The result of the current analysis suggested the close association between 'type 2 MI' and the trend of COVID-19 outbreak.[6] This pandemic also indirectly affected the outcome of 'type 2 MI,' which patients in 2020 had worse outcomes than the pre-COVID-19 era with nearly 20% increase of hospital mortality. The investigators suggested that patient-related factors (e.g., avoidance and reluctance to seek healthcare) and healthcare-related factors (e.g., resource constraints, and obscure COVID-19-related symptoms) could influence a worse outcome of 'type 2 MI' related with COVID-19 infection. Taken together, prevalence and mortality risk of overall AMI cases ('type 1 MI'+'type 2 MI') may be increased during the COVID-19 pandemic compared with prior to the pandemic.

In the pre-COVID-19 era, racial disparities in VTE risk have been widely reported.[7] In addition, African Americans show worse COVID-19-related outcomes than Caucasians and Asians.[8] This racial disparity in the outcomes of COVID-19 are naturally influenced by important social and economic factors. However, differences in thromboembolic event and combined mortality in COVID-19 may be partly explained by critical race-related disparities in intrinsic thrombogenicity. For example, The Thrombosis and Anticoagulation Therapy in Patients With COVID-19 (CLOT-COVID) registry, which included Japanese patients with COVID-19 infection, showed that only 1.87% of the total cohort had documented thrombotic events (n=54 out of 2,894) in the early phase of COVID-19 pandemic.[9] Meanwhile, a recent meta-analysis, which predominantly included hospitalized Western patients with COVID-19 infection, reported VTEs in 14.7% of cases and ATEs in 7.8% of cases, respectively.[2]

In 2012, Jeong et al.[7] first introduced the concept of the 'East Asian Paradox' to elucidate the distinctive findings in East Asian patients with atherothrombotic events, which highlights racial differences in thrombogenic traits and responses to antithrombotic therapies. The polygenic nature of inherited thrombophilia and the intricate interplay between genetic and epigenetic factors may be crucial components in explaining this interethnic disparity.

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Thrombo-inflammatory activity is closely linked to the risk of atherothrombotic phenotype, with African Americans exhibiting the highest thrombogenic state and East Asians having the lowest thrombogenic milieu.[10] Therefore, clinical factors that exacerbate this axis (e.g., infection and cancer) may further elevate the rate of ATE/VTE occurrence. Following COVID-19 infection, the lower prevalence of atherothrombotic events including 'type 2 MI' and the better clinical outcomes observed in the East Asian population may largely be attributed to this unique hemostatic characteristic. However, large-scale biomarker consortiums that encompass both East Asian and Western patients are necessary to establish the association between measured biomarkers and clinical outcomes.

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