

EDITORIAL COMMENT

Thrombosis and Anticoagulation in East Asian Patients With COVID-19

Another Phenotype of “East Asian Paradox”*



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Coronavirus disease-2019 (COVID-19) is a viral respiratory disease caused by severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), with hundreds of millions of diagnosed cases worldwide. Although the main pathophysiology of COVID-19 is considered a respiratory infection, this disease predisposes patients to thrombotic and thromboembolic events, owing to excessive inflammation, endothelial cell activation and injury, platelet activation and hypercoagulability.¹ In addition, patients who recovered from breakthrough COVID-19 infection after vaccination still showed an increased risk of death (HR: 1.75; 95% CI: 1.59-1.93) and incident post-acute sequelae (HR: 1.50; 95% CI: 1.46-1.54), including cardiovascular, coagulation and hematologic, gastrointestinal, kidney, mental health, metabolic, musculoskeletal, and neurologic disorders compared with contemporary controls at 6 months.² These findings may suggest the prolonged activation of thromboinflammatory response after COVID-19 infection and its persistent influence on the occurrence of atherothrombotic events. Accumulating evidence has supported the use of anticoagulant agents (eg, low molecular weight heparin and direct oral anticoagulant [DOAC]) for all hospitalized patients infected with COVID-19 without contraindications,

and long-term administration of anticoagulant agents after discharge in patients with high thrombotic risk.³

Numerous data have suggested a different incidence of COVID-19-associated coagulopathy. A recent meta-analysis (102 trials, $n = 64,503$) mostly including hospitalized Western patients with COVID-19, reported 14.7% venous thromboembolic events (VTEs: deep vein thrombosis and pulmonary embolism) and 7.8% arterial thromboembolic events (ATEs: stroke and myocardial infarction), respectively.⁴ In addition, the prevalence of VTE was significantly higher in intensive care units (23.2%; 95% CI: 17.5%-29.6%). However, there have been limited clinical data from East Asian populations who are considered to have low thrombogenic phenotype.⁵ In this regard, the recent surveillance studies performed in Japan demonstrated a low prevalence of VTE associated with COVID-19 infection, and Japanese expert consensus has not recommended routine prophylactic anticoagulation for these hospitalized patients.⁶ In this issue of *JACC: Asia*, Hayashi et al⁷ report the prevalence of COVID-19-associated coagulopathy and clinical effect of the prophylactic anticoagulant in Japanese patients with COVID-19 from the CLOT-COVID (Thrombosis and Anticoagulation Therapy in Patients With COVID-19) multicenter registry, in which only 1.87% of the total cohort had documented thrombotic events ($n = 54/2,894$). Pharmacological thromboprophylaxis was implemented in about 43% of patients during hospitalization. These patients had high-risk baseline characteristics such as old age, male sex, comorbidities, severe COVID-19 manifestation at admission, and worsened COVID-19 severity after admission. Interestingly, D-dimer levels at admission were lower in this registry (thromboprophylaxis yes, 1.1 vs no, 0.6 $\mu\text{g/mL}$) compared with previous reports from Western registries (2.1 to 3.8 $\mu\text{g/mL}$). In addition, patients with thromboprophylaxis showed an increased risk of bleeding without reducing ischemic

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FIGURE 1 Clinical Phenomenon Related to East Asian Paradox

EAST ASIAN PARADOX

The lowest ischemic events in East Asian population:
Precision medicine balancing efficacy and safety

Arterial
thrombosis

Venous
thrombosis

Infection
thrombosis

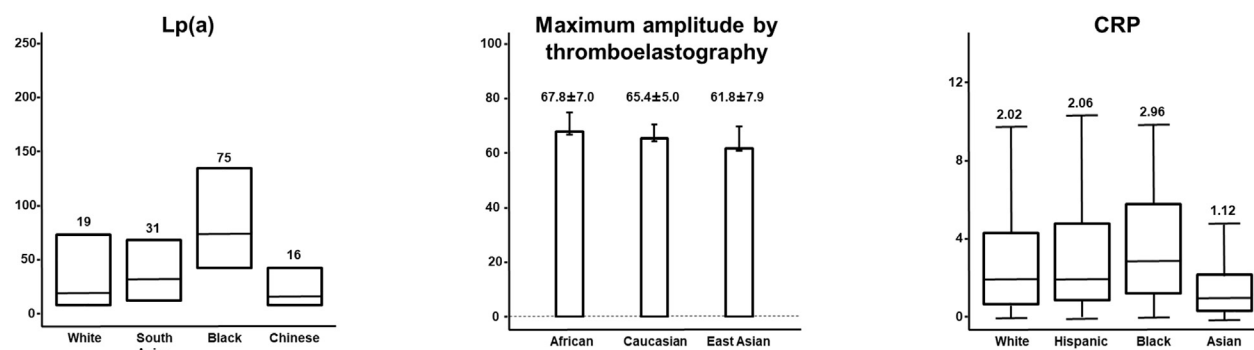
Cancer
thrombosis

Atherosclerosis-platelet-coagulation-inflammation interactions

Atherosclerosis

Platelet-fibrin clot strength

Inflammation



Clinical evidence demonstrate that East Asian population has the lowest level of lipoprotein (a) [Lp(a)],¹³ platelet-fibrin clot strength measured by thromboelastography,¹⁰ and inflammation indicated by C-reactive protein (CRP)¹⁴ compared with other races. The unique interactions between thrombogenic milieu may be related with the lowest ischemic events in the East Asian population. The East Asian population also has a different response to antithrombotic agents, which presents an unmet need to develop ethnicity-tailored precision medicine.

event rates than those without thromboprophylaxis. Taken together, hospitalized East Asian patients with COVID-19 may have a low incidence of coagulopathy-associated thromboembolic events and limited clinical benefit by anticoagulant treatment.

In 2012, Jeong et al⁸ first proposed the concept of the East Asian Paradox to explain the unique observations from East Asian patients with coronary artery disease, which pointed the racial difference in the therapeutic window of platelet reactivity. Expert consensus have suggested a unique antithrombotic strategy for East Asian populations, on the basis of different pharmacodynamic response to

antithrombotic agents (eg, P2Y₁₂ receptor inhibitor and DOAC) and a low benefit in reducing ischemic events and high risk in increasing bleeding events during antithrombotic treatment.⁵ The comparison of major biological pathways with biomarkers or surrogates may provide important clues to explain the racial difference in prevalence of prognosis in cardiovascular disease (Figure 1).⁹ The polygenic nature of inherited thrombophilia and the complex interaction between genetic and epigenetic factors are also important components to explain this interethnic disparity. Of those, a difference in hypercoagulability has been suggested as a crucial factor to account for

this phenomenon. In particular, ample evidence demonstrates the lowest levels of coagulation and inflammation in East Asians compared with other races.⁵ For example, East Asians with stable coronary artery disease showed lower platelet-fibrin clot strength (PFCS) measured by thromboelastography (61.8 ± 7.9 mm vs 65.4 ± 5.0 mm; $P < 0.001$) compared with Caucasian patients.¹⁰ In a multivariate analysis, high PFCS (≥ 68 mm) was significantly associated with the risk of 3-year atherothrombotic events (OR: 6.27; 95% CI: 2.41-16.30; $P < 0.001$), and East Asians had lower prevalence of high PFCS (OR: 0.50; 95% CI: 0.27-0.93; $P = 0.028$) than Caucasians. Baseline level of thromboinflammatory activity may be related with its peak level and the risk of ATEs/VTEs following COVID-19 infection.⁵ Racial disparities in atherothrombotic risk have been widely described in the pre-COVID-19 era. African Americans have higher VTE rates than Caucasians, whereas Caucasians have higher rates than East Asians.¹¹ Therefore, the risk of COVID-19-associated coagulopathy and its clinical outcome would be better in East Asian populations, which needs more clinical evidence.

There is a fundamental tradeoff between ischemic risk and bleeding risk that needs to be considered when deciding on the use of antithrombotic prophylaxis in patients with COVID-19 infection. Ethnicity can be related to the different balance between ischemia and bleeding risk. In addition, East Asians have shown a unique response to antithrombotic regimens,⁵ which may affect its optimal dose to maximize the net benefit of efficacy and safety. A previous report suggested that Asian patients are more susceptible to heparin, and their optimal dose is about 10 U/kg lower than for non-Asian patients.¹² Likewise, responses to various DOACs are different in

East Asian patients, and the risk-benefit ratio according to pharmacodynamic profiles seemed more vulnerable.⁵

It is common practice to follow Western guidelines, according to the results of largescale clinical trials including Caucasian patients. Extensive clinical evidence indicates racial differences in intrinsic thrombogenic phenotypes and response to antithrombotic agents.⁵ Thromboinflammatory activity is closely related to the risk of ATEs/VTEs, with African Americans achieving the most hypercoagulable state and East Asians having the lowest thrombogenic milieu. Therefore, clinical factors that promote this activity (eg, COVID-19, cancer) may further increase the risk of atherothrombotic events. The time has come to acknowledge and develop the ethnicity-tailored treatment strategy based on specific biomarkers or functional assays for thrombogenicity.⁹ Future studies should focus on establishing a particular footprint of these measurements in patients with high thrombotic profile for achieving maximum net clinical benefits.

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