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Ethnic differences in thromboprophylaxis for COVID-19 patients: should they be considered?

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REVIEW ARTICLE

Ethnic differences in thromboprophylaxis for COVID-19 patients: should they be considered?

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Abstract

Thromboembolic events contribute to morbidity and mortality in coronavirus disease 2019 (COVID-19). As a result, thromboprophylaxis using low-molecular-weight heparin (LMWH) is universally recommended for hospitalized patients based on multiple guidelines. However, ethnic differences with respect to thrombogenicity have been reported and the incidence of thromboembolic events is considered to be lower in the Asian population. Despite the importance of thromboprophylaxis, bleeding is also a side effect that should be considered. We examine the data relating to potential ethnic differences in thrombosis and bleeding in COVID-19. Although sufficient data is not yet available, current evidence does not oppose routine anticoagulant use and thromboprophylaxis using a standard dose of LMWH for admitted patients regardless of ethnicity based on our review.

Keywords COVID-19 · Thromboembolism · Deep vein thrombus · Thromboprophylaxis · Ethnic difference

Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic has posed a significant impact on morbidity and mortality in hospitalized patients. However, the incidence of death varies among different ethnic groups, as a New York state report notes that per-population coronavirus disease 2019 (COVID-19) fatality rates were 0.03%, 0.18%, and 0.12% for Caucasian, African-American, and Hispanic populations, respectively, and 5.38-fold disparity for African-American relative to Caucasian communities was observed [1]. The cause of ethnic disparities in mortality includes presence of other disease status such as hypertension, diabetes, however, different risks for thromboembolism among populations can be involved [2]. Apart from COVID-19, a survey performed in the USA reported the prevalence of venous thromboembolism (VTE) per 100,000 population was highest in African-American, followed by Caucasian, Hispanic, and other populations (Asians/Pacific Islanders) [3]. Thus, is the incidence of death and thrombotic complications among Asian COVID-19 patients lower than the other ethnicities? Although the clinical data regarding the thrombotic complications in the Asian population is still scarce, the question of whether the standard thromboprophylaxis

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is necessary to be applied equally to all populations should be considered. In this review, we examined the data about the inter-ethnic difference of thrombosis in COVID-19 and discuss the validity of universal thromboprophylaxis.

The ethnic difference on mortality in COVID-19

The death toll of COVID-19 reached 350,000 in August 2020 and roughly half was recorded in Europe and followed by North America. The count changes depending on the timing of disease spread but it still less than 10,000 deaths in South-East Asia and Western Pacific (https://covid19.who.int accessed Aug 8, 2020). The mortality difference in COVID-19 has been reported and the National Health Service (NHS) data of the United Kingdom revealed that Black and Asian groups are at increased risk of infection and death from COVID-19. The age and region adjusted NIH data suggested a lower risk of death for White Irish and White British ethnic groups, but increased risk of death for Black African (3.24, 95% confidence interval [CI] 2.90–3.62), Indian (1.70, 95% CI 1.56–1.85), and other minor ethnic populations [4]. Another study also from the UK that utilized more than 10,000 COVID-19-related death records demonstrated that age-sex adjusted hospital death rates for Black COVID-19 patients are 2.17-times higher compared to those in White, and 1.95-times higher than Asian patients [5]. A similar but larger survey was performed in Brazil. Baqui et al. [6] performed a cross-sectional study on 11,321 patients and reported, Pardo (mixed ethnicity) and Black Brazilian ethnicity with COVID-19 had a higher risk of mortality (hazard ratio [HR] 1.45, 95% CI 1.33–1.58 for Pardo; HR 1.32, 95% CI 1.15–1.52 for Black Brazilians) compared with White Brazilians. However, the association between the Black race and increased mortality is still uncertain because the elimination of factors regarding inequity in health, health care access, and quality of care is not easy [7]. Price-Haywood [8] collected the data from 3481 COVID-19 patients from the integrated-delivery health system in Louisiana, USA and demonstrated that race, increasing age, a higher score on the comorbidity index, public insurance (Medicare or Medicaid), residence in a low-income area, and obesity were associated with increased odds of hospital admission. On the other hand, in adjusted time-to-event analyses, variables that were associated with higher in-hospital mortality were old age and elevated respiratory rate at presentation, elevated lactate levels, creatinine, or procalcitonin, or low platelet or lymphocyte counts, and Black race was not associated with higher mortality. A similar result was also reported from Ohio, USA [9]. Thus, the relationship between ethnicity and disease severity or death still remains to be clarified.

The ethnic disparities of deep vein thrombosis and thromboembolism

Even before the COVID-19 pandemic, the prevalence of VTE was high in the United States and reported to be 100 per 100,000 persons each year. Approximately one-third of patients with symptomatic VTE manifest pulmonary embolism (PE), whereas two-thirds manifest deep vein thrombosis (DVT) alone [10]. The prevalence of thromboembolism differs considerably among different ethnic and population groups, and it is significantly higher in African Americans and Caucasians compared to Hispanic and Asian-Pacific Islanders [11]. In Japanese, the incidence of VTE is reportedly approximately one-eighth of North Americans [12, 13]. Factor V Leiden mutation, deficiencies of protein C, protein S, and antithrombin are the assumed hereditary relevant factors. Hyperhomocysteinemia and elevated levels of factors I, VIII and XI, are the other possible hereditary risk factors [14]. However, the difference may not be arisen from the ethnic difference but due to the lack of well-designed studies as well as non-standardized survey designs [15]. As a matter of fact, the incidence of VTE in Asian countries has risen recently and doubled in the past 10 years [12, 13]. This could be attributed to lifestyle changes, ageing population, increasing awareness of VTE [15]. For the comparison of the inter-racial incidence, it is difficult to control lifestyle factors such as diet or exercise, and eliminate the environmental factors, but Nicole Tran et al. [16] examined more than 60,000 residents in northern California demonstrated the adjusted HR for VTE in Asian ethnic was 0.5 to the Caucasians (Chinese 0.5, Japanese 0.5, Filipino 0.6, and South Asian 0.9). In addition, a population-based study examined the risk of postpartum VTE in the US reported African American and Asian women had a greater and lower risk of VTE compared to the Caucasian women (adjusted odds ratio [OR] 1.50 and 0.67, respectively) [17]. After all, the ethnic difference in VTE incidence still remains unclear, but it could be lower in the Asian countries compared to than Western countries [18, 19].

Thrombosis in COVID-19 and ethnic differences

Thromboembolic events in COVID-19 is a major concern for clinicians. Santoliquido et al. [20] performed a systematic screening of lower limb vein by compression ultrasonography in non-ICU hospitalized COVID-19 patients and reported the incidence of DVT was 11.9%. However, the incidence considerably varies among the

reports and the prevalence of VTE ranges from 3 to 85% [21]. The wide range of this incidence probably arisen from the diversity in study design (systematic or selected screening), setting (ICU vs general wards), intervention (uniform or individual thromboprophylaxis), and timing of the examination. Therefore, inter-race differences should be examined in a similar condition. In the ICU setting, a French study examined critically ill patients using complete duplex ultrasound and reported the overall VTE rate of 69% [22]. Another study also performed in France reported a DVT rate of 65% at admission, and 79% at 48 h after ICU admission [23]. As for the Asian ethnicity, a Chinese study performed in COVID-19 ICU patients reported 46–85.4% incidence of DVT [24] (Table 1). Although the studies performed in ICU generally include only a small number of cases, the incidence of DVT in Chinese patients does not seem to be lower than that of Caucasians. However, we should be careful about translating these results since many of the ICU patients are sedated and the patients do not complain the symptom appropriately. Therefore, the routine screening is recommended in this setting.

Mechanism of thrombus formation in COVID-19

Understanding the pathophysiology of COVID-19-associated coagulopathy is important to assess the necessity of thromboprophylaxis. However, the underlying mechanisms are multifactorial [31, 32]. Recent studies emphasize the importance of the endothelial injury caused by SARS-CoV-2 infection leading to micro- and macrothrombosis in COVID-19 [33]. The relative significance of DVT/PE in the development of respiratory failure or critical illness may be decreasing based on recent reports [34]. The endotheliopathy of COVID-19 causes vascular endothelial dysfunction, loss of its anticoagulant properties, and is associated with other factors contributing to the hypercoagulability that include

Table 1 The incidence of deep vein thrombosis in ICU patients detected by ultrasonography reported from Asia and Europe

Country	Patient/setting	Number	Measure	Timing of assessment	DVT prophylaxis	Incidence of DVT
China [24]	Patients in ICU	48	Compression ultrasonography	Not assessed	Standard LMWH thromboprophylaxis	DVT; 85.4% Proximal DVT; 75% Distal DVT; 10.4%
China [25]	Critically ill patients in ICU	88	Compression ultrasonography	More than 1 week after ICU admission	Standard LMWH thromboprophylaxis	DVT; 46% Proximal DVT; 9.1% Distal DVT; 46%
China [26]	Critically ill patients managed by intensivists	143	Ultrasonography scanning	Not assessed	37.1% Received standard LMWH and others no thromboprophylaxis	DVT 46.1% Proximal DVT; 16.1% Distal DVT; 30.1%
France [22]	Patients in ICU	26	Duplex ultrasonography	Day 1–7 after admission	Standard or therapeutic dose of LMWH or unfractionated heparin	DVT; 69% Proximal DVT; 26% Distal DVT; 68%
France [23]	Patients with ARDS and treated in ICU	34	Duplex ultrasonography	48 h after admission	Standard thromboprophylaxis	DVT 79% Proximal DVT; 16.1% Distal DVT; 30.1%
Switzerland [27]	Critically ill patients in ICU	25	Ultrasonography screening	Day 5–10 after admission	Continuous intravenous infusion of heparin (15,000 IU/24 h)	DVT/VTE; 32% proximal DVT; 24% pulmonary embolism; 20%
The Netherlands [28]	Patients in ICU	75	Ultrasonography screening	Day 7–21 after admission	Standard to double dose of LMWH	DVT Day7; 26%, Day 14; 47%, Day 21; 59%
The Netherlands [29]	Patients in ICU	184	Ultrasonography screening	During ICU stay	Standard or higher dose thromboprophylaxis	Thrombosis 31% (VTE in 27%, arterial thrombosis 3.7%)
Italy [30]	Patients in ICU	61	Compression ultrasonography	During ICU stay	Standard or therapeutic dose of LMWH	Thrombosis 27.6%

DVT deep vein thrombosis, *VTE* venous thromboembolism, *LMWH* low-molecular-weight heparin

increased release of von Willebrand factor (VWF), Factor VIII, and angiopoietin 2, increased fibrinogen, presence of antiphospholipid antibodies, and dysregulated inflammation. As a result, the loss of endothelial function along with a marked systemic hypercoagulability is estimated to be the major cause of pulmonary microthrombotic injury and respiratory failure [35]. It is noteworthy that African-Americans are reported to have higher circulating levels of VWF, Factor VIII and fibrinogen [36]. The differences in endothelial function and molecular mechanisms of thrombosis risk due to genetic factors may lead to the ethnic disparities in COVID-19-associated thrombosis [37]. With respect to the comparison of endothelial dysfunction in Asians and other ethnicities, little data are available to make any conclusions. Investigations as to the levels of VWF, Factor VIII, and fibrinogen in response to infection in various races are expected to provide the data that clarify the ethnic disparity of COVID-19-associated thrombosis.

Thromboprophylaxis in COVID-19

There are two aims for thromboprophylaxis in COVID-19, suppression of microthrombus formation and prevention of macrothrombosis. The International Society on Thrombosis and Haemostasis (ISTH) released guidelines for thromboprophylaxis in COVID-19 and recommend universal standard prophylaxis using LMWH unless contraindication for all hospitalized patients [38]. Following this recommendation, other international organization such as World Health Organization (WHO) propose a similar recommendation [39]. Although thromboprophylaxis is effective, the incidence is still high with standard prophylaxis and more intensive prophylaxis is expected. However, the bleeding adverse event is a serious problem and the net effect of prophylaxis with higher dose is still unknown [40]. ISTH recommendations are conservative for a more aggressive thromboprophylaxis, and only 30% of experts agreed on the use of intermediate-dose of LMWH in hospitalized COVID-19 patients, compared to 50% of experts for intermediate-dose LMWH for the high-risk ICU patients [41]. A recent small but prospective study reported the efficacy of higher intensity regimen in critically ill patients and the application of this type of prophylaxis needs to be determined in ongoing randomized trials [42].

Anticoagulation to reverse organ dysfunction in COVID-19 may be different, although its efficacy is unknown. Russo et al. [43] analyzed the data from 192 consecutive Italian patients who underwent pre-admission antithrombotic therapy and reported that adjusted regression analyses showed no difference in ARDS on admission, or death during hospitalization between patients treated with antiplatelets or anticoagulants. This observation suggests that thromboprophylaxis does not have sufficient effects on microthrombosis prevention and protective effect in the progression of COVID-19. In contrast, another observational study from the USA revealed a better outcome in patients treated with anticoagulation compared to the patients treated without anticoagulation. The in-hospital mortality in the patients who required mechanical ventilation and treated with anticoagulation was 29.1%, while that of the patients treated without anticoagulants was 62.7% [44]. This difference may not be achieved only from VTE prevention but also from the effect of maintenance of microcirculation. With respect to the bleeding adverse events, the incidence of major bleeding was 1.9% in the patients treated without anticoagulants and 3% in those who received anticoagulants ($P=0.2$) [44]. A Chinese study also reported a better prognosis in severe cases with coagulopathy or with markedly elevated D-dimer [45]. The effects of anticoagulation on endothelial damage and microcirculation are the topics of future study.

Bleeding adverse events with pharmacologic thromboprophylaxis

Based on initial reports, the incidence of bleeding has been considered to be low in COVID-19 supporting the concept of potentially higher dose pharmacological thromboprophylaxis. However, since Asian people are estimated to be more susceptible to anticoagulation compared to the other ethnicities, the application of universal thromboprophylaxis may pose increased risk for Asian populations. Thus, comparing the bleeding incidence in COVID-19 among different populations is challenging. Currently, many of the admitted patients receive thromboprophylaxis, therefore, it is almost impossible to divide the bleeding that relates to COVID-19 itself from that relates to the anticoagulation. One previous large-scale observational study from the USA reported the incidence of 1.9% in the patients without anticoagulation and 3.0% in the patients with anticoagulation [46]. Table 2 summarized the incidence of bleeding reported from various countries, and the incidence in China does not seem to be higher than that in western countries.

The awareness of different bleeding susceptibility with anticoagulant therapy has arisen based on the experience of warfarin. Warfarin requirement is highest in Caucasians, lower in Hispanics, and lowest in Asians because of the differences in genetic background [50]. It is also known that the bleeding risk of antiplatelets is also higher in the Asian population [51]. In contrast, such differences are not seen with direct oral anticoagulants (DOACs) and the DOACs are more preferable alternatives for Asian patients [52]. As for the heparin and LMWH in COVID-19, it is too early to conclude that there is no ethnic difference in bleeding rates,

Table 2 The incidence of bleedings in COVID-19 patients

Country	Patient/setting	Number	DVT prophylaxis	Incidence of thrombotic events	Incidence of bleeding events
USA [48]	Critically ill; 144 Non-critically ill; 256	400	Standard LMWH thromboprophylaxis	9.5%	4.8% (major bleeding; 2.3%)
USA [44]	Hospitalized patients	2773	786 (28%) Received systemic anticoagulation (oral, subcutaneous, or intravenous forms)	Not assessed	Without anticoagulation; 1.9% With anticoagulation; 3.0%
Spain [46]	Patients in non-ICU	156	Standard LMWH thromboprophylaxis	14.7%	1.9%
China [49]	Hospitalized patients (critically ill 10.9%)	138	41 (30.1%) Received standard thromboprophylaxis	2.9%	4.3%
China [25]	Critically ill patients in ICU	88	Standard LMWH thromboprophylaxis	46%	6%
France [47]	Patients in ICU	92	Standard or therapeutic dose of LMWH or unfractionated heparin	40% (venous; 79%, arterial 21%)	21% (deep muscle; 23%, gastro-intestinal 14%, intracranial; 9%)
Switzerland [27]	Critically ill patients in ICU	25	Continuous intravenous infusion of heparin (15,000 IU/24 h)	DVT/VTE; 32%	Major bleeding; 0% Minor bleeding; 8%

DVT deep vein thrombosis, *VTE* venous thromboembolism, *LMWH* low-molecular-weight heparin

but the present data does not seem to support the idea that the Asians are more likely to bleed than Caucasians and other ethnics.

Recommendation of the thromboprophylaxis for COVID-19 in various patient groups

Postoperative anticoagulant therapy was proven to reduce the risk of VTE and has become routine therapy in Western countries. In contrast, postoperative thromboprophylaxis has not been done routinely in many Asian countries [53–55]. Certainly, a similar approach may not be adequate in COVID-19 because the background of the inter-ethnic risk/benefits difference of the anticoagulation is still uncertain. To reduce harm from COVID-19 associated VTE, the ISTH consequently released the guidance for VTE prevention [38, 41], and collaboratively worked with the WHO to share the knowledge for global VTE management (https://www.isth.org/news/517212/A-Systematic-Approach-for-Managing-Venous-Thromboembolism-in-Patients-with-COVID-19.htm). One of the objects of this projects is highlight the importance of a systematic approach to VTE prevention, diagnosis and treatment for patients with COVID-19 worldwide. However, ethnic differences have not been considered in these approaches.

Other than the effects on VTE prevention, anticoagulants are also expected to provide benefit for the treatment of microthrombosis. Several studies have investigated the effect of heparins, especially unfractionated heparin, in patients with bacterial sepsis-associated DIC. The reported meta-analyses, showed a trend of reduced 28-day mortality but also revealed a trend toward increased risk of bleeding. Again, no racial disparity was examined in these analyses [56–58]. The net effect of heparin on microthrombosis in COVID-19 is still unclear and further study in different ethnicities is warranted.

Summary

Important observations include the presence of microthrombosis and microangiopathy in the lung associated with hemorrhage in COVID-19. These findings significantly contributed to disease severity and death. The endothelial damage and microthrombosis contribute to the typical feature of diffuse alveolar damage, including hyaline membranes and fibrin deposition in the alveolus that are present even in patients who are not in critical condition. The development of large thrombi and embolization accelerate the respiratory insufficiency and ultimately to death. Thus, the suppression of microclot formation and prevention of thromboembolism are required as key benefits of anticoagulant therapy. Of note are the potential ethnic disparities that can exist in the thrombogenicity and bleeding risk of COVID-19. Therapeutic considerations for thromboprophylaxis should potentially be made separately based on the data constructed upon individual races although there is at present no data that support this idea. Rather the current evidence does not

oppose the same regimen to Asian populations as they are recommended to Western populations. Future protocols for thromboprophylaxis should be determined based on the balance between the benefits and the risk of bleeding in various ethnicities.

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Compliance with ethical standards

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