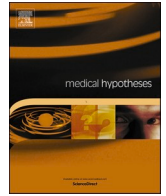




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Letter to Editors

Should we screen Eastern Mediterranean COVID-19 patients for inherited thrombophilia?



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ABSTRACT

The inflammatory component of Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) creates a pro-thrombotic state that necessitates a thromboplylactic strategy for hospitalized patients. Such strategies are difficult to be standardized because certain individuals can have pro-thrombotic conditions, such as inherited thrombophilia, which pre-dispose them to an additional coagulative risk. Whether outside the hospital or when admitted, patients with inherited thrombophilia need special anticoagulant and antiplatelet attention. Identifying such patients, especially in susceptible populations like the eastern Mediterranean (EM) region, will aid primary providers in risk stratification for choosing the optimal anticoagulation or antiplatelet plan.

To the editor. –

Background

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) targets the Angiotensin converting enzyme (ACE)-2 protein [1], which is present on the cell surface membrane of several body tissues, such as lung alveolar epithelial cells, enterocytes of the small intestine, arterial and venous endothelial cells, arterial smooth muscle cells, and epithelia of the lung and small intestine [2]. This epithelial expression, together with the presence of ACE2 in vascular endothelium [3], causing a massive release of proinflammatory cytokines, promoting a cytokine storm [4]. The inflammatory milieu abnormally activates the coagulative system manifesting as macro and micro thrombosis [5]. As a result, patients infected with SARS-CoV-2 are in need to be risk stratified accordingly in order to decide on a strategy for thromboplylaxis if needed. Many strategies and scores have been suggested, such as those by the American Society of Hematology [6] and the International Society on Thrombosis and Haemostasis [7]. However, it is difficult to apply the same guidelines to different regions of the world with different pro-thrombotic profiles. Examples of such conditions include Eastern Mediterranean (EM) patients with inherited thrombophilia, such as C677T methylenetetrahydrofolate reductase (MTHFR) gene mutation, or factor V Leiden, or prothrombin G20210A gene mutation.

Prevalence

Eastern Mediterranean countries exhibit higher prevalence of major thrombophilia genetic mutations than other worldwide regions. For example, 14.4% of apparently healthy Lebanese people, and 40% of Lebanese patients with deep vein thrombosis (DVT), are carriers of specific point mutation (G1691 to A; Arg506–Gln) in the factor V gene [8]. The prevalence of heterozygosity for factor V Leiden gene mutation among the EM countries is similar to Lebanon (Table 1).

Likewise, the prevalence of carriers of the MTHFR C677T genotypes was estimated to be in the range of 10–34% among Lebanese healthy

individuals [9], while those carrying homozygous mutation of MTHFR C677T genotype constituted 11% of the population [10]. Furthermore, prothrombin G20210A heterozygous mutation was found in 3% of healthy Lebanese individuals and 12.5% in Lebanese DVT patients [9]. One mutation in each of the three major thrombophilia genes, or triple mutation, happens in 1.1% of the population [11]. With this presumably high prevalence of major thrombophilia genetic mutations among the EM population, infection with SARS-CoV-2 predisposes such vulnerable population to higher thrombosis risk.

COVID-19

The C677T polymorphism of MTHFR had been associated with specific vulnerability to a severe course of Coronavirus disease 2019 (COVID-19) initiated by hyperhomocysteinemia [12]. Likewise, increased activity in factor V had been reported in critically ill [13], as well as non-critically ill patients [14], leading to predisposition for thrombosis. Factor II prothrombin G20210A is also associated with prothrombotic state [15], and has been linked to DVT and pulmonary embolism (PE) in COVID-19 patients [16].

Hypothesis

Despite the data supporting a higher risk for thrombosis in EM COVID-19 patients, the thromboplylactic regimens stay unclear. It is important to list all the risk factors along with the clinical presentation. Patients with previous thrombotic complications, familial history, pregnancy, estroprogestative treatment, and air travel are at higher risk [17]. In addition, the presence of a homozygous genetic mutation places the patient at higher risk of thrombosis than a heterozygous mutation patient [18]. Therefore, the risk of thrombosis should be based on the clinical symptoms and laboratory data. As a result, the anticoagulation/antiplatelet choice will depend on several factors and profiles as illustrated (Fig. 1).

However, it is still unknown whether EM COVID-19 patients with no confirmed thrombophilia should be managed similarly to thrombophilia

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Table 1
The prevalence of heterozygous mutation of factor V Leiden among some eastern Mediterranean countries.

Country	Prevalence of gene mutation
Syria [19]	13.6%
Greek Cyprus [19]	13.4%
Jordan [20]	12.3%
Turkey [21]	7.1%

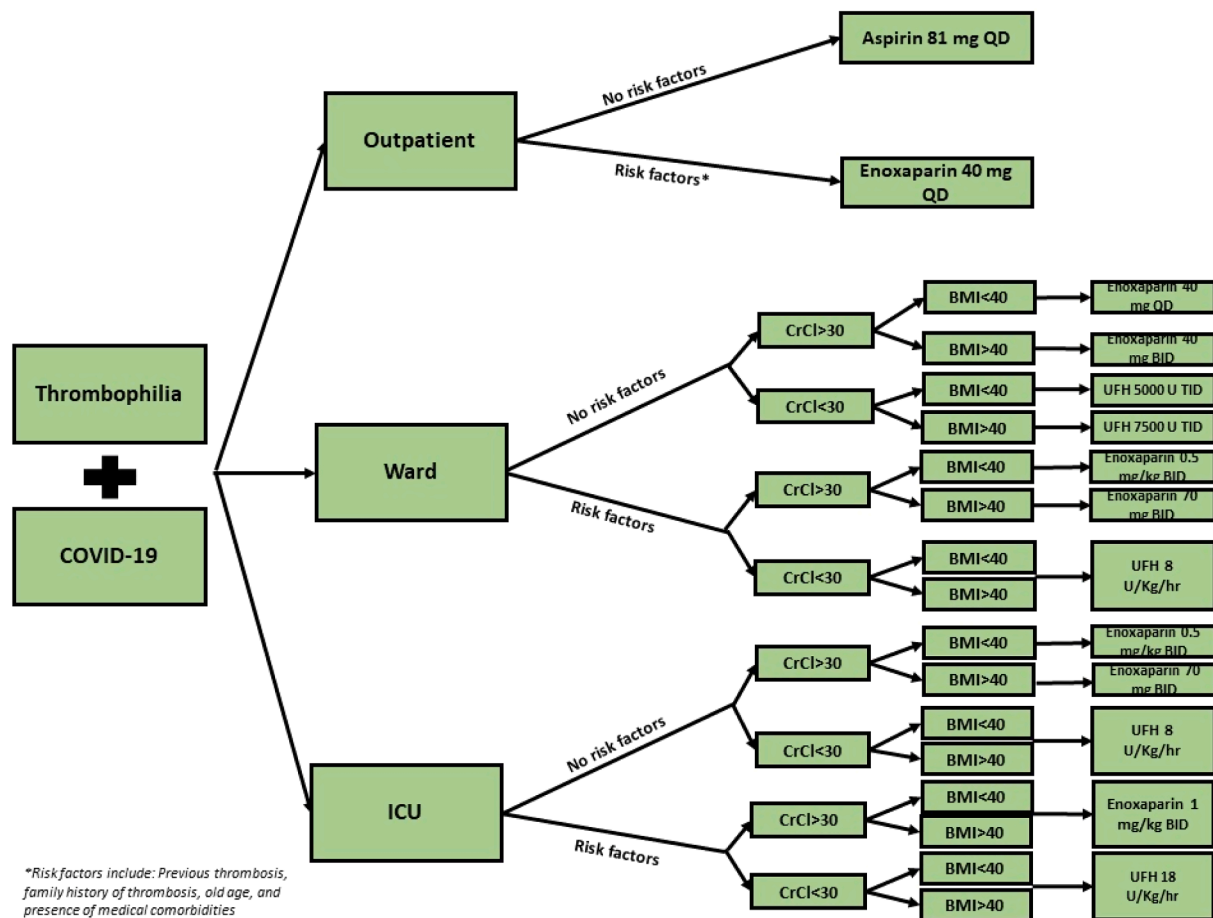


Fig. 1. A suggested guidance to physicians to anti-coagulate eastern Mediterranean COVID-19 patients with thrombophilia. ASA: Aspirin; LMWH: Low-molecular-weight heparin; UFH: Unfractionated heparin; BMI: Body mass index; BID: Twice daily; QD: Once daily; TID: Three times daily; CrCl: Creatinine clearance; ICU: Intensive care unit; mg/kg: Milligrams/kilograms; U/Kg/hr: Units/kilograms/hour.

patients. It might be impractical to screen every COVID-19 patient for thrombophilia in order to stratify the risk of thrombosis. Therefore, the choice of anticoagulation should be taken on a case-by-case basis depending on the personal and familial medical history. There are several thromboplylactic options present, and these depend on the clinical profile of each patient. A stratified risk score could benefit physicians in order to guide them in thromboplylactic regimens. Further randomized clinical trials are needed to determine anti-coagulation options for different scenarios and to study new options such as the novel oral anticoagulants.

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Consent statement/ethical approval

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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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