

Tissue Factor Pathway Inhibitor and Interleukin-1 Receptor Levels in COVID-19

Diana A. Gorog^{1,2}  Brijesh Patel^{3,4}

¹Royal Brompton Campus, Faculty of Medicine, National Heart and Lung Institute, Imperial College, London, United Kingdom

²Centre for Health Services Research, Postgraduate Medical School, University of Hertfordshire, Hertfordshire, United Kingdom

³Adult Critical Care, Royal Brompton Hospital, Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom

⁴Division of Anaesthetics, Pain Medicine and Intensive Care, Department of Surgery and Cancer, Faculty of Medicine, Imperial College London, London, United Kingdom

Address for correspondence Diana A. Gorog, MD, PhD, FRCP, FESC, National Heart and Lung Institute, Imperial College, London, United Kingdom (e-mail: d.gorog@imperial.ac.uk).

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The observation that SARS-CoV-2 (severe acute respiratory syndrome coronavirus-2) predisposes patients to pulmonary immunothrombosis and venous thromboembolism (VTE), and furthermore, that the risk of VTE is directly proportional to the severity of coronavirus disease 2019 (COVID-19) disease has been recognized since early in the pandemic.¹ Guidelines recommend the use of prophylactic anticoagulation in hospitalized patients with COVID-19,^{2–4} yet despite this, trials report a VTE incidence of 6 to 10% with prophylactic and 4 to 8% with treatment-dose anticoagulation.^{5,6} Amongst critically ill patients with COVID-19, 28 to 46% of patients may experience VTE.^{7–9}

The mechanism of thrombosis in patients with COVID-19 involves an excessive inflammatory response, which is manifested through an endotheliopathy, enhanced platelet activation and coagulation, and reduced endogenous fibrinolysis.^{7,10,11}

Early on in the pandemic, it was recognized that common markers of coagulation, namely D-dimer, fibrinogen, prothrombin time, as well as platelet count, could be used to assess the severity of COVID-19 and help triage patients for admission, guide prognosis, and assess the risk of VTE.¹² Over time, other markers of thrombosis risk have emerged, which can guide prognosis and potentially guide therapy.^{7,13–16} These include, *inter alia*, interleukin (IL)-6, von Willebrand factor (vWF) antigen, or the ratio of vWF antigen to ADAMTS13, as well as markers of platelet activation, hypofibrinolysis, and neutrophil extracellular traps.

In this issue of Thrombosis and Haemostasis, Li et al provide further insight into biomarkers of thrombosis in patients with COVID-19.¹⁷ In a retrospective analysis using two-sample Mendelian randomization (MR), they evaluated the relationship between 20 biomarkers in patients with COVID-19 of varying severity, including nonhospitalized, hospitalized, and critically ill patients. Data from genome-wide association studies (GWAS) were analyzed from 38,984 patients from 37 studies with COVID-19 and from a GWAS meta-analysis of 9,986 hospitalized COVID-19 patients from 22 cohorts and from 5,101 and 4,792 critically ill COVID-19 patients from 15 and 14 studies, respectively. The main finding was that patients with COVID-19 had lower levels of tissue factor pathway inhibitor (TFPI) and lower levels of IL-1 receptor type 1 (IL-1R1). Additionally, patients with COVID-19 exhibited a trend toward lower levels of multiple coagulation factor deficiency protein 2 and increased C–C motif chemokine 3. Furthermore, patients hospitalized with COVID-19 had lower levels of plasminogen activator, tissue type plasminogen activator, and P-selectin glycoprotein ligand 1. Finally, the authors confirmed earlier findings that critically ill patients had higher mean platelet volume and lower platelet count.

The authors provide information from a very large dataset that appears to yield new insight into the mechanism of thrombosis and inflammation in patients with COVID-19.

TFPI is the key inhibitor of the tissue factor-induced coagulation pathway. Findings in animal models indicate a role of TFPI in attenuating arterial thrombus formation,¹⁸

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and TFPI has also been implicated VTE including in patients with cancer.^{18,19} In animal models of sepsis, coagulation in the lung was associated with decreased TFPI in the lung endothelium.²⁰ However, prior studies evaluating TFPI in COVID-19 patients have shown conflicting results. Some small studies showed significantly elevated TFPI levels in patients with COVID-19,²¹ which did not relate to disease severity, while others found reduced TFPI in patients with moderate to severe disease.²² Other studies have found increased TFPI associated with the severity of COVID-19.^{23,24} Likewise, TFPI has been directly correlated with D-dimer levels, which were associated with high mortality,²¹ while others showed an inverse correlation of TFPI with D-dimer levels.²⁵

The finding of lower TFPI levels in COVID-19 patients by Li et al supports the possible contribution of TF pathway activation to COVID-19 coagulopathy.²² Although approximately 10% of circulating TFPI is stored in platelets, the largest pool of TFPI exists bound to endothelial surfaces. Therefore, in light of the endotheliopathy associated with COVID-19, one would expect an increase in TFPI levels in those with severe disease. In addition, heparin infusion has been shown to displace endothelial TFPI resulting in a two- to fourfold increase in circulating TFPI levels,²⁶ and may explain the increased plasma TFPI reported in some studies in COVID-19 patients.^{21,24} However, the reduced TFPI shown in the present study indicates that a procoagulant pheno-

type, without endotheliopathy, is prevalent in the majority of patients with COVID-19 patients.

It is recognized that a subgroup of patients with severe COVID-19 show hyperinflammatory features, with increased circulating levels of cytokines, including IL-1 and IL-6, which are significantly upregulated in patients with severe disease and associated with adverse outcomes.²⁷⁻²⁹ IL-1 is a highly potent proinflammatory mediator, composed of cytokines IL-1 α and IL-1 β , whose biological effects are predominantly mediated by binding to IL-1R1. Pharmacological blockade of IL-1R signaling, for example with anakinra, would be expected to lead to reduced inflammation, but the observed low levels of IL-1R shown in the study by Li et al in patients with COVID-19 could explain the observed lack of significant benefit of anakinra in many COVID-19 studies.³⁰ The antagonism of P-selectin glycoprotein ligand-1 (PSGL-1) by COVID-19 requires further investigation given the key role of PSGL-1 in platelet-leukocyte interactions and hence, the regulation of immunothrombosis at a cellular level.

However, there are important caveats when interpreting the findings of the current paper. First, the timing of blood sampling was not standardized, and could have occurred at any stage of the disease. Second, treatment with prophylactic or treatment dose anticoagulation of hospitalized COVID-19 patients may have impacted on the results. Further, several

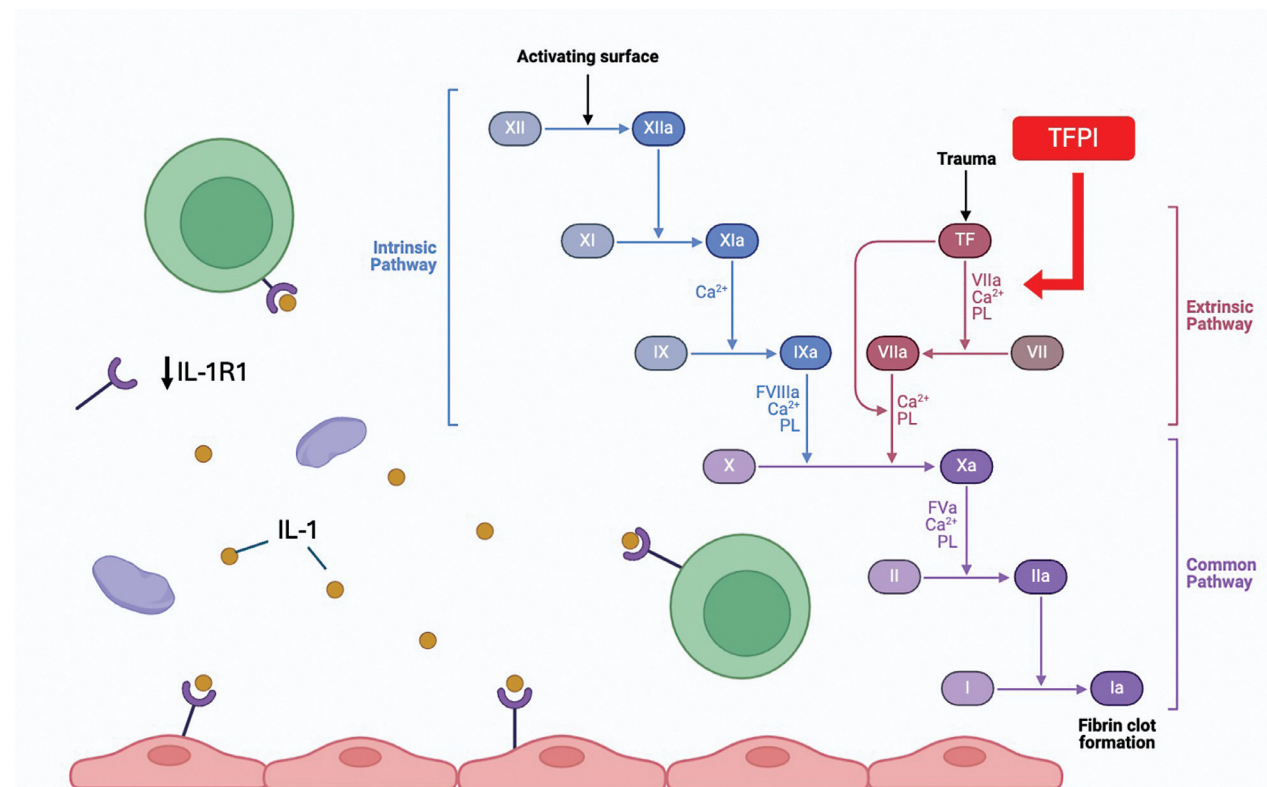


Fig. 1 Patients with COVID-19 had lower levels of tissue factor pathway inhibitor (TFPI) indicating a pro-coagulant phenotype. Additionally, high levels of inflammatory markers, including interleukin 1 (IL1) levels are a recognised feature in severe COVID-19, but the lower levels of IL 1 receptor type 1 (IL-1R1) may explain why treatment with interleukin receptor inhibitors in some clinical trials of COVID-19 did not lead to improved clinical outcomes.

patients were taking part in clinical trial interventions for COVID-19 with subsequent impact on the biomarkers measured. Finally, while the authors examine how genetic variants affect the outcome of interest, i.e., thrombotic markers, and suggest minimal horizontal pleiotropy, it is likely that there may still be undetermined associations. In particular, MR analyses provide estimates of associations over a lifetime and hence, how these markers relate to age-related changes in biomarkers of thrombosis is unknown. Indeed, whether they provide additive value, or could guide response to treatment, requires further assessment.

Whether the observed low levels of TFPI and IL-1R1 are causally involved in the mechanism of disease in COVID-19, are simply bystanders, or represent a physiological response to overwhelming inflammation and procoagulant phenotype remains unclear. However, given now the reduced impact of COVID-19, the findings should stimulate further research to evaluate these markers in other immunothrombotic conditions. This is important given the concerns of hypercoagulability after COVID-19 vaccination,^{31,32} changes in anticoagulation control post-vaccination,³³ and in long COVID. Indeed, potential biomarkers and even therapeutic targets could guide treatment options and monitor response to therapy in preparation for future pandemics (→ Fig. 1).

Conflict of Interest

None declared.

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