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FORUM

Challenging the current hypothesis that thrombosis is responsible for the post-COVID-19 condition

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Abstract

People with the post-COVID-19 condition suffer symptoms that persist beyond 12 weeks following acute COVID-19 infection. Fatigue, shortness of breath, and cognitive dysfunction ("brain fog") are common. Scientists, clinicians, and patients debate the pathophysiology. One pathophysiological hypothesis is that prothrombotic changes associated with acute COVID-19 persist, causing clots that lead to symptoms. This theory, arising from a research team in South Africa and supported by a paper in Nature Medicine, has been widely disseminated on social media and entered the public narrative as a cause of the post-COVID-19 condition.

We describe the development of this theory, examine the findings of a Cochrane review that critically appraises the "microclot" beliefs, and critically appraise the influential study relating clotting biomarkers to cognitive deficits. We conclude the inferences for the hypothesis are not based on evidence, unlicensed use of antithrombotic medication is not justified, and apheresis should not be considered outside of a well-designed clinical trial.

KEYWORDS
amyloid fibrinogen, COVID-19, pathophysiology, post-acute COVID-19 syndrome, post-COVID-19 condition

1 | INTRODUCTION

People with the post-COVID-19 condition (PCC), or postacute sequelae of SARS-CoV-2 infection, suffer symptoms that persist beyond 12 weeks following acute COVID-19 infection. Fatigue, shortness of breath, and cognitive dysfunction ("brain fog") are common. Scientists, clinicians, and patients debate the pathophysiology.

One pathophysiological hypothesis is that prothrombotic changes associated with acute COVID-19 persist, causing clots that constrain oxygen to tissues, leading to symptoms. This theory, arising from a research team in South Africa, was widely promoted and disseminated [1]. The paper's Altmetric score is high at 2164, and is in the 99th percentile of attention given to an article by the news, social media, and citations compared with others of a similar age [1]. This wide influence of the article led some PCC patients to seek expensive apheresis treatment to remove these particles and for some clinicians to recommend antithrombotic drugs [2].

We initially critically appraised the research studies that had led to demand for apheresis treatment [3]. We remained interested in the persistence of this theory in the public narrative, and in April 2024, we

carried out a search in the database MEDLINE from 2019 using general search terms based on PCC and thrombosis or clotting, looking for studies linking symptoms of PCC to clots that had subsequently received wide attention and uptake (search strategy available on request to corresponding author). We identified one further study with a high Altmetric score of 2016 [4]. The lead author of this study stated in the press release that this work supported the hypothesis that "blood clots are a cause of post-COVID cognitive problems."

In this article, we describe how the hypothesis that persistent prothrombotic changes contribute to the symptoms of PCC emerged and critically appraise the 2 most influential bodies of evidence we have identified that relate symptoms of brain fog to clotting disturbances.

2 | ORIGINS OF THE PCC THROMBOTIC HYPOTHESIS

It is known that marked prothrombotic changes in severe acute COVID-19 contribute to morbidity and mortality [5]. COVID-19 pneumonia activates hemostasis, platelets, endothelium, and NETosis and causes a substantive increase in acute phase proteins (including the coagulation factors fibrinogen, factor VIII, and von Willebrand factor). We know that the risk of deep vein thrombosis and pulmonary embolism in COVID-19 is much higher than the baseline risk [6], and we recognize that thromboembolic cardiovascular risk remains raised for at least a year in people recovering from severe acute COVID-19 [7]. These findings sparked the hypothesis that the persistence of these prothrombotic changes in acute COVID-19 may underlie the symptoms seen in patients with PCC, and the pathologies became conflated in the medical and public narrative.

3 | "MICROCLOTS" THEORY

In appraising this topic, it is essential to separate the proven phenomenon of acute COVID-19 prothrombotic changes from the PCC condition. When we do this, we find there are no reliable studies in people with PCC that show an increased risk of macrovascular or microvascular thromboembolism or any other marked prothrombotic changes, in contrast to acute COVID-19.

In terms of the "microclots" theory, this literature has been thoroughly appraised and summarized in a recent Cochrane review, which some of us authored [3]. Our team appraised the clinical laboratory studies using rigorous, systematic Cochrane methodology. The team found that the phenomenon termed "microclots" were not clots but amyloid fibrin(ogen) particles; these were also found in the studies appraised in healthy individuals, in patients with acute COVID-19, and in persons with diabetes. The review concluded that the phenomena reported were not true clots, were not unique to the PCC condition, and there was no evidence linking the amyloid fibrin(ogen) particles to the pathophysiology of PCC.

4 | STUDY RELATING THEORY OF PCC PROTHROMBOSIS AND PCC SYMPTOMS

The theory that clotting and PCC are connected was re-inforced a research study in Autumn 2023published in Nature Medicine. As we outlined above, this study has been highly and widely cited as evidence of the persistent clotting hypothesis [4]. The authors of the Nature Medicine study examined the relationship between blood biomarkers and cognitive dysfunction in hospitalized patients with COVID-19 pneumonia. Using combinations of blood biomarkers, they reported that those with the highest levels of the biomarkers fibrinogen and D-dimer relative to C-reactive protein (CRP) at the time of their acute pneumonia had the highest rates of cognitive dysfunction 6 months later. They conclude that increased levels of fibrinogen and D-dimer were markers of later PCC.

There are problems with the methodology in this study. Firstly, the authors use levels of CRP relative to other biomarkers to make a large number of possible ratio traits. This use of ratio traits, in which the same denominator is used (CRP), puts the analysis at risk of collider bias [8]. The lower levels of CRP relative to fibrinogen and D-dimer may relate to other processes, such as less detection by individuals of symptoms of infection, and thus, a lower relative CRP as a denominator in their 2 measures could relate to greater or lesser detection or recognition of symptoms. Problems of using ratio traits have recently been discussed elsewhere [9].

The authors attempt to provide a mechanistic biological justification of the association and, by discussing the "mediation" of effects, suggest that there may be a causal link. However, it is more plausible that fibrinogen and D-dimer are simply markers of inflammation. The other flaw is that the authors suggest the associations between biomarker profiles and subjective cognitive deficits cannot be explained by pre-COVID-19 cognitive function. This is not epidemiologically sound, as the premorbid cognitive ability assessment was by retrospective reporting at the 6-monthly follow-up visit. Thus, there is high likelihood of recall bias.

Further, the patients in this study were acutely unwell, and thus, acute cerebral ischemic events with acute COVID-19 pneumonia would produce inflammatory changes. This is neither mentioned, nor did the authors acknowledge that most patients with PCC had mild COVID-19.

5 | EXISTING KNOWLEDGE MAY EXPLAIN PCC

There are plausible alternative hypotheses for the pathophysiology of PCC. Studies indicate that the hemostatic changes in PCC are in keeping with an inflammatory response. These studies show minor hemostatic changes, which could be mediated through endothelial cell

activation, a process known to be initiated by multiple inflammatory pathways [10]. Furthermore, there is a body of research in neuroscience, psychology, and evolution that explains the presence of PCC in those not severely unwell initially [11].

There remains no current reliable evidence to support the hypothesis of a persistent prothrombotic state underlying the symptoms of PCC.

As such, treatments aligning with this theory, such as unlicensed use of antithrombotic medication and apheresis intended for removal of amyloid fibrin(ogen) particles, are not scientifically justified, are expensive, and may not be safe. We suggest research efforts be directed toward plausible theories, practical rehabilitation, and strategies for recovery.

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AUTHOR CONTRIBUTIONS

B.H. identified the question and wrote the first draft; P.G. assembled and helped manage the author team; R.C. and T.F. conducted searches and critical appraisal of the articles; G.D.S. appraised the Taquet study; K.S. advised on statistical understanding and critique; and A.C. provided input to methods and interpretation. All authors contributed to writing the paper, finalizing the draft, and revising the manuscript. All authors approved the final version of the paper.

RELATIONSHIP DISCLOSURE

There are no competing interests to disclose.

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