# Long COVID is primarily a Spike protein Induced Thrombotic Vasculitis

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**Case Report**

**Keywords:** Long COVID, post-acute sequelae of COVID-19, microclots, platelet hyperactivation, endotheliitis, spike induced thrombotic vasculitis

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**Additional Declarations:**
RK is the patient described in this case. He consented to participation and publication.

# Long COVID is primarily a Spike protein Induced Thrombotic Vasculitis

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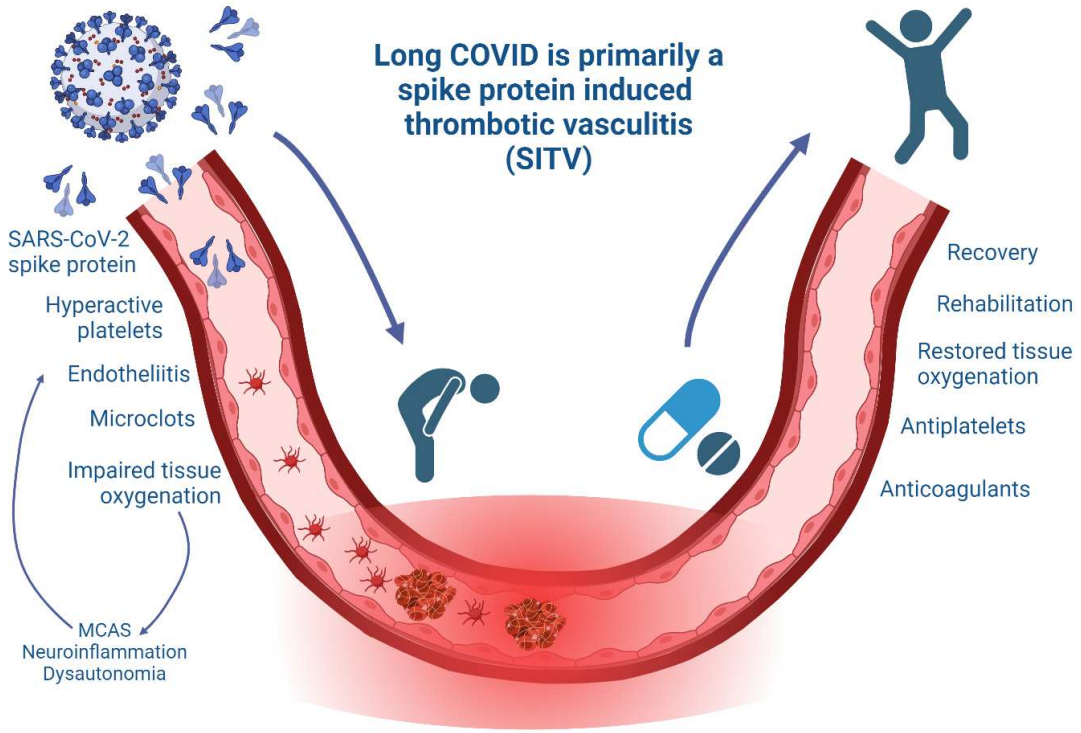
## Abstract

Long COVID describes an array of often debilitating symptoms in the aftermath of SARS-CoV-2 infection, with similar symptomatology affecting some people post-vaccination. With an estimated > 200 million Long COVID patients worldwide and cases still rising, the effects on quality of life and the economy are significant, thus warranting urgent attention to understand the pathophysiology. Herein we describe our perspective that Long COVID is a continuation of acute COVID-19 pathology, whereby coagulopathy is the main driver of disease and can cause or exacerbate other pathologies common in Long COVID, such as mast cell activation syndrome and dysautonomia. Considering the SARS-CoV-2 spike protein can independently induce fibrinaloid microclots, platelet activation, and endotheliitis, we predict that persistent spike protein will be a key mechanism driving the continued coagulopathy in Long COVID. We discuss several treatment targets to address the coagulopathy, and predict that (particularly early) treatment with combination anticoagulant and antiplatelet drugs will bring significant relief to many patients, supported by a case study. To help focus attention on such treatment targets, we propose Long COVID should be referred to as Spike protein Induced Thrombotic Vasculitis (SITV). These ideas require urgent testing, especially as the world tries to co-exist with COVID-19.


## Graphical Abstract





**Key words:** Long COVID; post-acute sequelae of COVID-19; microclots; platelet hyperactivation; endotheliitis; spike induced thrombotic vasculitis

## Background

Long COVID (or post-acute sequelae of COVID-19) is a debilitating multi-system disease causing significant disability [1]. The World Health Organization [2] defined Long COVID as those with probable/confirmed SARS-CoV-2 infection, with symptom onset within ~3 months, lasting ≥ 2 months, and no alternative diagnosis. Long COVID is estimated to affect > 200 million people globally; the majority being from those considered “mild” cases [3,4], and nearly a third from asymptomatic infection [5,6]. Long COVID-like presentations have also been described after SARS-CoV-2 vaccination [7–11]. The average Long COVID sufferer experiences 56 symptoms across nine body systems [1], with fatigue, cognitive dysfunction, dyspnoea, exercise intolerance, post-exertional symptom exacerbation (PESE), sleep disorders, and myalgia being most common [1,3,12–14]. With such an all-encompassing definition, Long COVID is likely a multi-pathology illness [10–12].

Long COVID prevalence estimates vary [3,13,18,19], but studies in Scotland have shown it affects 1.8-3.2 % of the population [20,21], comparable to cancer (2.5 %), chronic kidney disease (3.2 %), chronic obstructive pulmonary disease (2.3 %), and stroke (2.2 %) [22]. Two meta-analyses show persistent symptoms in 43-45 % of patients after acute COVID-19 [3,13]. Tracking studies suggesting that 85 % of those symptomatic at two months post-infection remain symptomatic at one year [23]. Similarly, symptom resolution after 90 days seems uncommon [24], disabling a previously economically active population [1]. Consequently, the estimated economic cost may be as high as US$25 billion in the UK alone [25].

Alongside its benefits in acute COVID-19, vaccination confers a modest reduction in the odds of developing Long COVID (13 and 9 % reduction after first- and second-dose, respectively [26]). However, other research shows that every SARS-CoV-2 reinfection increases the risk of death, hospitalisation, and/or multi-organ complications, regardless of vaccination status [27]. Thus, protections from vaccination appear far from absolute, particularly when other public health measures are being downscaled in many countries [28–30]. Resultantly, the prevalence of Long COVID continues to rise [31].

Therefore, it seems evident that: the majority of Long COVID cases are not resolving with time; prevalence continues to rise; and the economic costs of Long COVID disabling a previously productive workforce are significant. Hence, it is imperative that Long COVID pathophysiology is understood and treatments urgently implemented.

## Acute COVID-19: The foundations underpinning Long COVID

Endothelial cells have a vital role in vascular homeostasis and haemostasis, including regulating vascular tone, blood flow, fibrinolysis, and platelet aggregation [32–35]. Acute COVID-19 appears to be primarily a disease of the vascular endothelium resulting in a microcirculatory thrombotic vasculitis [33,34,36–43]. SARS-CoV-2 spike proteins allow viral attachment to target cells via to angiotensin converting enzyme 2 (ACE2) protein binding, followed by intracellular viral replication [42,44,45]. ACE2 is present in the tongue, nasal mucosa, and lungs as an initial portal of entry, as well as presenting throughout the vasculature in endothelial cells. This offers SARS-CoV-2 ample opportunity to spread easily throughout the body, including across the blood-brain barrier [33,34,37,42,46–48].

SARS-CoV-2 entry into endothelial cells downregulates ACE2 leading to a proinflammatory and prothrombotic milieu [34,49–51]. Endothelial injury can result from direct infection by SARS-CoV-2 causing endothelial cell apoptosis and endotheliitis as well as subsequent systemic inflammatory responses [33,34,37,39,49,51,52]. The spike protein alone can induce neuronal injury [53], destabilise microvascular haemostasis [54], induce thrombosis [55], (irreversibly) activate platelets [56–58] and impair endothelial function [43,59], with some effects independent of ACE2 [60] or possibly from anti-spike antibodies [61]. With endothelial dysfunction comes impaired vascular tone and a prothrombotic state [32,34,35,37,43,49].

Post-mortem examination of severe COVID-19 patients has shown widespread coagulopathy, with alveolar capillary microthrombi being nine times more prevalent than in influenza A [62]. Similarly, Pretorius *et al.* [40] found significant clot burden in acute COVID-19 patients regardless of severity, compared to those with type 2 diabetes and healthy controls. The type of blood clots found, known as microclots, were amyloid in nature, thus laying the foundation for chronic post-COVID-19 sequelae.

## Microclots

Thrombi are known to develop from inflammation, in part due to platelet hyperactivation [63]. COVID-19 is a highly inflammatory disease, with potential to cause cytokine storms [64]. Indeed, COVID-19 activates platelets and complement, causing endothelial dysfunction [43,65]. The resultant proinflammatory milieu can cause immunothrombosis, particularly affecting the microvasculature [65]. Additionally, the S1 subunit of the SARS-CoV-2 spike protein can directly interact with platelets and fibrin to cause microclots [36,56,66–68].

Specifically, the S1 subunit causes structural changes to β and γ fibrin(ogen), complement 3, and prothrombin resulting in extensive anomalous microclots [36,58,67–70]. Microclots appear to pathologically impair blood flow in systemic microcapillaries [36,71–73], including in the brain [48], heart [73–75], lungs [46,73,76], and kidneys [73]. These spike protein induced microclots are resistant to fibrinolysis creating the potential for false negative tests of clot lysis (e.g. D-dimer) [77] and for the microclots to persist into the pathogenesis of Long COVID [36,69,78].

## Long COVID as a coagulopathy

There are several proposed mechanisms offering valid explanations regarding Long COVID. For many patients, several of these pathologies may co-exist and interact. Current ideas include mast cell activation syndrome (MCAS), neuroinflammation, viral reactivation, SARS-CoV-2 and/or spike protein persistence, autoimmunity, and gut dysbiosis [9,79]. An increasingly recognised pathology is related to microclots, platelet hyperactivation, and endothelial dysfunction [36,40,43,80–82]. Herein we describe our perspective that Long COVID is primarily (though not necessarily exclusively) a thrombotic vasculitis.

Microclots in Long COVID patients were first described by Pretorius *et al.* [82] who found fibrinolysis resistant microclots to persist abundantly in the blood, accompanied by platelet hyperactivation and dysregulated haemostasis. These were macroscopically visible as a pellet in centrifuged samples of platelet poor plasma (not seen in healthy controls or those with type 2 diabetes), with comparable levels to acute COVID-19 [82].

### Capillary occlusion

Human capillaries are typically 5–10 µm in diameter, meaning red blood cells (~8 µm diameter) circulate single file aided by their (usually) flexible structure [83]. Microclots found in Long COVID patients have a diameter of 5-200 µm meaning they can occlude capillaries [82,83]. Consequently ischaemia-reperfusion injuries at a microvascular level may occur [83] offering an explanation for post-exertional symptom exacerbation (PESE) affecting 75-89 % of patients. PESE is a diagnostic criterion for myalgic encephalomyelitis, which is objectively demonstrated via cardiopulmonary exercise testing on consecutive days [1,83–87] and in subsequent prolonged recovery [88].

Microvasculature occlusion offers an explanation for several other Long COVID symptoms, such as chest pain, which may be caused by microvasculature ischaemia [89]. Evidence of capillary occlusion has been demonstrated in several studies of the microvasculature of different organs of Long COVID patients providing evidence of systemic vascular changes [89–95]. Such microvascular changes include a reduction in sublingual vascular density comparable to severe acute COVID-19 [93] and retinal vascular density [94,95], fibrin thrombi occluding capillaries in the skin [92], and muscle capillary loss [90,91]. Biomarkers of microvascular remodelling triggered by tissue hypoxia, such as vascular endothelial growth factor (VEGF), have been found in Long COVID, likely as a compensation for capillary occlusion [96–98]. However, any new vessels formed will also be susceptible to occlusion. Similar compensatory angiogenesis has been observed in multiple organs of severe acute COVID-19 patients [99]. These findings are consistent with capillary occlusion by microclots.

### Coagulopathy

Beyond “typical” Long COVID symptoms evidence of coagulopathy is found in other outcomes such as elevated risk of ischaemic heart disease and myocardial infarction following acute COVID-19 [100–102]. Risk remains elevated but reduces over time (e.g. acute myocardial infarction hazard ratio [HR] 1 week post-COVID-19: 22.10, 95 % confidence interval [CI] 21.00, 23.20, *versus* HR 27-49 weeks post-COVID-19: 1.75, 95 % CI 1.50, 2.05) [100], possibly suggesting there is ongoing coagulopathic processes in some people. Indeed, microclots have been found > 23 months after SARS-CoV-2 infection [82,103–109].

Sustained elevation of circulating thrombogenic S1 spike subunit have been observed in Long COVID patients when compared to those who recovered after COVID-19 infection [67,110–112], which may explain continued thrombosis risk post-COVID-19 in some. Analysis of COVID-19-induced microclots also showed the presence of spike protein (but not whole SARS-CoV-2) and inflammatory markers within the clots [58,66,113]. Clot lysis therefore has the potential to perpetuate further clot formation and platelet activation through release of entrapped spike protein and inflammatory proteins, causing a vicious cycle [113,114]. Entrapment of inflammatory proteins can also help explain why many Long COVID patients have "normal" test results.

**Platelet activation and endotheliitis**

Although microclots are a key pathological feature in Long COVID, they are accompanied by hyperactivated platelets and endotheliitis [43]. Markers of endothelial damage in Long COVID correlate with higher symptom burden and reduced exercise tolerance [103,105–107,109,115–121], whilst hyperactive platelets amplify and sustain endotheliitis [116] and therefore Long COVID [82,104,108,122,123]. Additionally, Long COVID patients with greatest cognitive deficits show the highest levels of cerebral hypoperfusion [124], and neuroinflammation [125], with plasma inflammatory markers consistent with endotheliitis [118,126,127]. As endothelial dysfunction is a precursor to atherosclerosis, complications of COVID-19 could be seen for decades to come [128].

**Oxygen extraction**

Microclot capillary occlusion and endotheliitis can lead to impaired systemic oxygen extraction [43,129–133]. Long COVID patients have higher mean blood lactate than healthy controls both at rest and throughout exercise, consistent with a lower anaerobic threshold [130]. The reduction in $VO_2$ max in Long COVID patients is from a peripheral rather than a central cardiac limit due to impaired capillary oxygen extraction [130–133] and not deconditioning [134]. Indeed, impaired oxygen extraction has been associated with exercise intolerance in Long COVID patients [135] along with a proteomic signature consistent with endotheliitis [133].

Radiologically this is supported with xenon 129 magnetic resonance imaging scans demonstrating impaired pulmonary gas transfer in Long COVID patients, attributed to microclots, and correlating with a reduced exercise tolerance and a greater oxygen desaturation after exertion [136,137]. Ventilation/perfusion scans and single-photon emission computed tomography (CT) are preferred post-COVID-19 for evaluating capillary thrombosis and perfusion defects, which can be underestimated with conventional CT pulmonary angiogram [138], including in paediatric cases [139,140]. These findings support the concept of microclots, and can help explain the wide-ranging symptoms of Long COVID due to multi-organ tissue hypoxia [129,131–133,136].

**Co-pathologies**

Beyond the central problem of tissue hypoxia resulting from a thrombotic vasculitis there are other consequences to persisting endothelial inflammation. Patients with Long COVID have a significantly elevated risk (HR > 80) of dysautonomia [79], with some symptoms, like postural tachycardia, being potentially partially explained by coagulopathy particularly early in disease progression [80]. The autonomic nervous system innervates blood vessels walls

to regulate vascular tone [32]. The sympathetic and parasympathetic fibres innervate the muscle layer of vessels, whereas only parasympathetic fibres innervate the endothelial layer, making parasympathetic fibres more susceptible to the consequences of endothelial inflammation [32]. Nerve ischaemia has been proposed as an aetiology [9]. Resultant dysautonomia, where sympathetic function predominates, which is found in a moderate to severe range in two thirds of Long COVID patients, is independent of initial infection severity [32,141] and is associated with exercise intolerance [142].

A major consequence of post-COVID-19 dysautonomia is postural orthostatic tachycardia syndrome (POTS) [143]. POTS aetiology is multifactorial, but endothelial disease [144], hyperactive platelets [145,146], tissue hypoxia [147], thromboinflammation [146], and enhanced sympathetic activation [144,147–149] have all been implicated. POTS causes abnormal cerebral blood flow and oxygenation [150,151] consistent with the end organ consequences of thrombotic vasculitis in Long COVID and contributes to a range of common Long COVID symptoms (e.g. fatigue, tremoring, dizziness) [152]. Predominant sympathetic activation results in symptoms which can be commonly misdiagnosed as anxiety [153–155]. Downregulation of ACE2 and tissue hypoxia can both reduce serotonin synthesis [156,157], whilst hyperactive platelets (which store serotonin) may cause serotonin depletion [113]. Thus, anxiety may be a consequence of coagulopathy and dysautonomia [158].

Increased cases of POTS have been observed after SARS-CoV-2 infection and (five times less frequently) vaccination [143,159].There is increasing recognition that Long COVID symptoms, diagnoses, and pathophysiology can also be triggered after SARS-CoV-2 vaccination in some patients [7,8,10,11] where spike protein persistence has been implicated [7–9]. With the same illnesses occurring after vaccination and infection, some have suggested spike protein (rather than whole virus) persistence can drive Long COVID and POTS pathology [7–9,11,143]. At a population level, the net benefits of vaccination against COVID-19 have been clearly established. However, as spike protein alone has been demonstrated to induce microclots in vitro [36] and a minority of those vaccinated with a spike protein based vaccine develop Long COVID-like syndrome, we believe this offers a crucial insight into Long COVID aetiology [7–9,11]. Supporting this, and in line with evidence presented above for Long COVID, several cases have been reported of post-COVID-19 vaccine retinal vascular occlusion (summarised in [160]), attributed to Susac syndrome (an autoimmune endotheliopathy) and microthrombi, with potential links to hyperviscosity syndrome.

Finally, MCAS appears to be a key Long COVID pathology, and is also implicated in POTS [161]. Mast cells are found in the vasculature and are implicated in inflammation, haemostasis, vaso-activity, vascular leakage, and endothelial cell activation [162] so their degranulation may contribute to immunological and thrombotic outcomes in COVID-19 [163,164]. Simultaneously, the vasculature facilitates mast cell activity [162], thus platelet activation and ischemia-reperfusion can contribute to mast cell degranulation [83,165]. Several mast cell mediators are directly implicated in coagulopathy: heparin has anticoagulative properties but spike protein has high binding affinity with it [55]; tryptase has a role in fibrinolysis [166]; and VEGF is stored and secreted by mast cells [162,167]. MCAS therefore may be a direct result of continued coagulopathy, even if activation was initiated via antigen exposure. Spike protein persistence may be a chronic MCAS trigger [168]. Thus, whilst MCAS appears to be a co-pathology in some Long COVID patients, mitigating the

coagulopathy could have dual benefit via reducing (inappropriate/damaging) mast cell activation whilst mitigating thrombogenesis.

Overall, current evidence suggests Long COVID is in most cases primarily a coagulopathy and a vasculopathy causing multi-system symptoms from systemic tissue hypoxia. These same features have been demonstrated in acute COVID-19, suggesting Long COVID is a continuation of thrombogenic processes occurring in acute COVID-19. That similar clinical presentations occur with other coagulopathic diseases, such as antiphospholipid syndrome, provides consilient evidence for such an idea. Long COVID is likely in many cases a Spike protein Induced Thrombotic Vasculitis (SITV) (**Figure 1**). We therefore propose the use of the term SITV as it is more descriptive of a unifying proposed mechanism and primary pathology, helps focus attention on early therapeutic interventions to avoid chronic complications, and offers a distinction for other pathologies that may predominate in some patients.

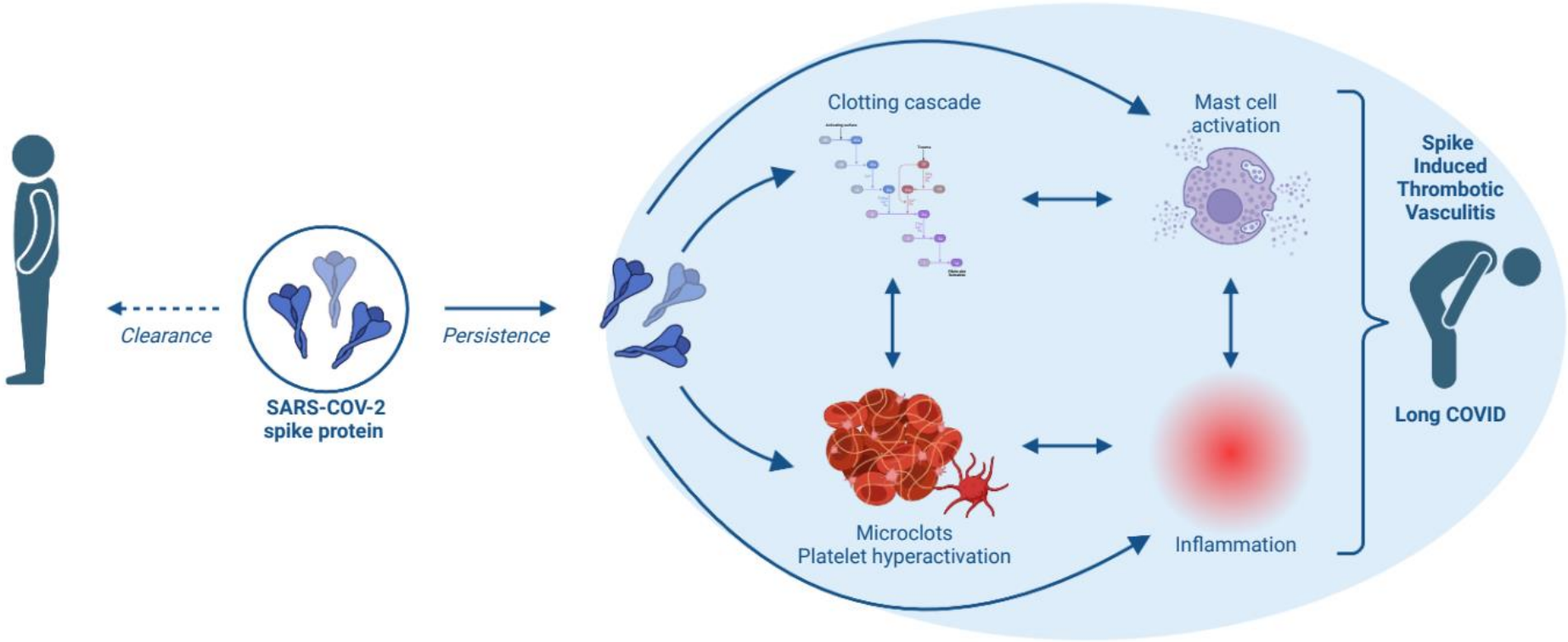



***Figure 1.*** *Schematic representation of our perspective that Long COVID is primarily a spike protein induced thrombotic vasculitis. We propose in people who recover from acute COVID, spike protein clears, whereas in those who get Long COVID, there is an inability to clear spike protein (which may include persistent SARS-CoV-2 virion). Both the spike protein and resultant inflammation induce microclots and hyperactivated platelets (as well as activating mast cells), triggering an uninhibited clotting cascade. In response, mast cells are activated which may also contribute to continued coagulopathy and inflammation. Whilst in many patients polypharmacy is needed to tackle the co-pathology(ies) (not all of which are outlined herein), targeting coagulopathy seems essential to mitigate thrombotic risks and help mitigate other immunogenic cascades.*

## Potential treatments

Therapeutic endeavours for Long COVID to date have predominantly focused on rehabilitation and psychological therapy [169], perhaps borne out of the impression that patients with Long COVID are recovering from acute COVID-19 rather than suffering ongoing pathology. Considering such pathology, these treatments can be harmful, e.g. due to PESE [1,87,170]. Indeed, rehabilitation is largely ineffective at improving Long COVID symptoms [169]. We contend that Long COVID patients (those with SITV) will not be ready to rehabilitate until the underlying illness and its complications have been effectively treated.

The treatment targets for SITV are microclots, hyperactive platelets, and endotheliitis. It has been proposed that treating this multifaceted inflammatory coagulopathy with a single drug will be insufficient and a combination of anticoagulant and antiplatelet drugs are required to achieve synergistic and superior outcomes [81,114,156], with early intervention recommended [43,114,156].

### Anticoagulants

Anticoagulants target clotting. In acute COVID-19, favourable outcomes have been hypothesised and achieved when targeting coagulopathy [38,171,172], and anticoagulants are recommended by NICE under certain circumstances [173]. In one case series of Long COVID patients, early treatment with apixaban 5 mg B.I.D. (with aspirin, clopidogrel, and a proton pump inhibitor) for ≥ 1 month resulted in symptomatic resolution in 24/24 patients [81]. Symptomatic improvement also correlated with a reduction in microclots and hyperactive platelets. Another case series (n = 91) of anticoagulation/antiplatelet treatment showed 74-87 % of patients reporting improvement in nine key symptoms and a concurrent reduction in microclots, but one gastrointestinal bleed [80].

As Long COVID microclots are resistant to fibrinolysis [36,69,78], dabigatran may be superior as it increases clot susceptibility to fibrinolysis more than other anticoagulants [174,175]. Heparin inhibits spike protein ACE2 binding meaning it has antiviral and anticoagulant properties [60,176–178]. Heparin has been utilised to effectively treat pathology such as Long COVID-related perfusion defects [139], as well as microclots in the context of pulmonary emboli [179]. Further, obstetric patients (n = 291) with Long COVID who received enoxaparin antenatally to six weeks postnatally reported ongoing Long COVID symptoms less frequently than those who did not [180].

### Antiplatelets

Treatment targets with antiplatelets are hyperactive platelets and endotheliitis. Emerging evidence suggests a unique role for $P2Y_{12}$ inhibitors (e.g. ticagrelor, clopidogrel) which attenuate platelet and endothelial cell interaction, therefore reducing platelet activation, endotheliitis, and clot formation more potently than aspirin [58,116]. In patients hospitalised with acute COVID-19, favourable outcomes (e.g. lower mortality) have been found with antiplatelet medications, with higher survival seen with dual antiplatelet treatment, without increased risk of bleeding [181,182]. Others have found improved perfusion with tirofiban, along with aspirin, clopidogrel and prophylactic dose anticoagulant [183]. In a randomised controlled trial, hospitalised patients receiving aspirin had similar rates of 28-day mortality (*versus* standard care), but a slightly shorter hospital stay, and a higher proportion discharged alive within 28-days [184]. Further, aspirin use was associated with a 0.6 % absolute risk reduction in thrombotic events, although a 0.6 % absolute risk increase in major bleeding events [184].

In terms of Long COVID, obstetric patients taking 325 mg/d aspirin were more likely to report symptomatic improvement than those who were not [180]. In a case series of 24 Long COVID patients, aspirin has been shown to reduce hyperactive platelets as a single agent but required the addition of apixaban and clopidogrel to reduce microclots [81]. Similar findings were reported in a larger case series (n = 91), showing reduced platelet activation after anticoagulation with dual antiplatelets [80]. Considering emerging evidence of Long COVID-like vaccine reactions, we note that aspirin has previously been explored as a method to reduce acute vaccine-induced endotheliitis [185] which is an area requiring further research.

**Selective Serotonin Reuptake Inhibitors**

Selective serotonin reuptake inhibitors (SSRIs) have potential in Long COVID via multiple coagulopathy-related mechanisms. SSRIs reduce (endothelial) inflammatory markers, such as interleukin-8 [186], including in COVID-19 [127], with antidepressants being associated with lower Severe Adult Respiratory Distress Syndrome and need for mechanical ventilation [126]. Sertraline binds to the S1 subunit blocking its interaction with ACE2 [187] which may be important considering growing evidence SARS-CoV-2/spike protein persistence in Long COVID [79].

SSRIs have antiplatelet [188], endothelial protective [189], and mast cell stabilising [190] properties. Such effects appear to be favourable in the context of acute COVID-19 [190], including reduced risk of clot formation [191]. Sertraline appears to have additional antiplatelet and endothelial protective properties in patients already treated with aspirin and clopidogrel (in a non-COVID-19 context) [189]. SSRIs may also directly target the neuroinflammation prominent in Long COVID [192,193] .

Overall, SSRIs have multiple mechanisms of action which seem pertinent to SITV. Studies have found an association between SSRIs and favourable outcomes in acute COVID-19 [194,195], suggesting they may positively influence underlying pathophysiology. Whilst research is warranted, since the pathophysiology is similar to acute COVID-19, we predict SSRIs may have a role in the treatment of SITV. In addition to the drugs described above, there are several other therapeutics outside the scope of this perspective that offer potential via similar and other mechanisms (e.g. fibrinolytics, statins). We encourage research on these therapeutics.

## Case study

Evidence on aggressively targeting post-COVID-19 coagulopathy is limited, with no randomised controlled trials published to our knowledge. As such, we present the case of a healthy male healthcare worker, age 36 years at the time of his first SARS-CoV-2 infection (April 2020). Baseline cardiovascular fitness was sufficient to cycle 160 km in a day. COVID-19 symptoms included cough, fever, dyspnoea, diarrhoea, rashes, anosmia, and fatigue, with desaturation (88-92 %) upon minimal exertion, including when supine.

Bloodwork was normal three weeks post-infection (**Table 1**). In the absence of recognised treatment for Long COVID, no further medical evaluation was sought for over a year. Ongoing symptoms included: dyspnoea, desaturation upon minimal exertion; myalgia consistent with claudication with most physical activities; extreme fatigue; exercise intolerance; cognitive dysfunction; sleep disturbance; and PESE. Symptoms deteriorated with each COVID-19 vaccination (all BNT162b2). POTS was diagnosed after the third vaccination.

**Table 1.** Tests conducted on our case

| | Reference range | Post-infection 1* | | | | | | | Post-infection 2* | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | April 2020 | June 2021 | July 2021 | Oct 2021 | Nov 2021 | Dec 2021 | Jan 2022 | Feb 2022 | April 2022 |
| **Haematology** | | | | | | | | | | |
| Full blood count | | Normal | Normal | - | - | Normal | - | Normal | - | - |
| D-dimer (ng/mL) | 0-230 | 63 | - | - | - | **253** | - | - | - | - |
| Blood film | | - | **Platelet clumping** | - | - | - | - | - | - | - |
| Prothrombin time (s) | 10.5-13.5 | - | - | - | - | **10.4** | - | - | - | - |
| aPPT | | - | - | - | - | Normal | - | - | - | - |
| Fibrinogen | | - | - | - | - | Normal | - | - | - | - |
| ESR (mm/h) | 0-10 | - | - | - | - | **15** | - | **15** | - | - |
| **Liver and kidney function** | | | | | | | | | | |
| Liver function tests | | Normal | Normal | - | - | - | - | - | - | - |
| Urea and electrolytes | | Normal | Normal | - | - | Normal | - | - | - | - |
| **Immunology** | | | | | | | | | | |
| C-reactive protein | | Normal | - | - | - | - | - | - | - | - |
| Coelaic serology | | - | Normal | - | - | - | - | - | - | - |
| **Endocrinology** | | | | | | | | | | |
| TSH | | - | Normal | - | - | Normal | - | - | - | - |
| Testosterone | | - | - | - | - | Normal | - | - | - | - |
| **Biochemistry** | | | | | | | | | | |
| Calcium | | - | Normal | - | - | Normal | - | - | - | - |
| Glucose | | - | Normal | - | - | Normal | - | - | - | - |
| Total protein (g/L) | 60-78 | - | - | - | - | **83** | - | - | - | - |
| **Imaging** | | | | | | | | | | |
| Chest X-ray | | Normal | - | - | - | - | - | - | - | - |
| Electrocardiogram | | Normal | - | - | - | - | - | - | - | - |
| CTPA and HRCT | | - | - | Normal[1] | - | - | - | - | - | Normal |
| **Other tests** | | | | | | | | | | |
| NASA lean test (↑HR, bpm) | < 30 | - | - | - | **> 40** | - | - | - | **> 70** | - |
| Spirometry | | - | - | - | - | - | Normal[3] | - | - | - |
| CPET (without catheterisation) | | - | - | - | - | - | Normal[4] | - | - | - |

* Infection 1: Polymerase chain reaction test positive 07/04/2020; Infection 2: Lateral flow test positive 17/02/2022; Infection 3: Lateral flow test positive 11/12/2022 (no further testing after infection 3)

SARS-CoV-2 vaccinations, all BNT162b2, were administered on 24/12/20, 09/02/21, and 02/10/21.

Abnormal results in **bold** with grey background.
[1] No filling defect within pulmonary arteries down to and including first order subsegmental level. No evidence of right heart or central pulmonary artery dilation. No focal/diffuse parenchymal/airway abnormality identified.
[2] Accompanied by pre-syncope
[3] Forced expiratory volume in 1 second (FEV1) 4.72 (107 %); Forced vital capacity (FVC) 5.85 (107 %); FEV1/FVC 0.81; total lung capacity 7.41 (101 %); residual volume 1.56 (79 %)
[4] $VO_2$ max 106 % predicted; Peak watts 114 % predicted
Abbreviations: ↑HR, heart rate increase; aPPT, activated partial thromboplastin time; CPET, cardiopulmonary exercise testing; CTPA, computerised tomography pulmonary angiogram; ESR, erythrocyte sedimentation rate; HRCT, high-resolution computerised tomography; TSH, thyroid stimulating hormone

Based on emerging evidence of inflammatory aetiology in Long COVID, treatment of prednisolone [196] tapered over two weeks was initiated 17 months post-infection (**Figure 2**). From week two, there was a notable improvement in breathing, claudication, exercise tolerance and cognition. After completion of the prednisolone course, symptoms reverted to baseline, suggesting there was an underlying vasculitis/endotheliitis that steroids temporarily compensated, but there remained a trigger to ongoing pathology (microclots and hyperactive platelets). Furthermore, if the driver to symptoms was chronic SARS-CoV-2 infection (as opposed to spike protein persistence) then a deterioration rather than a benefit would be expected with steroids.

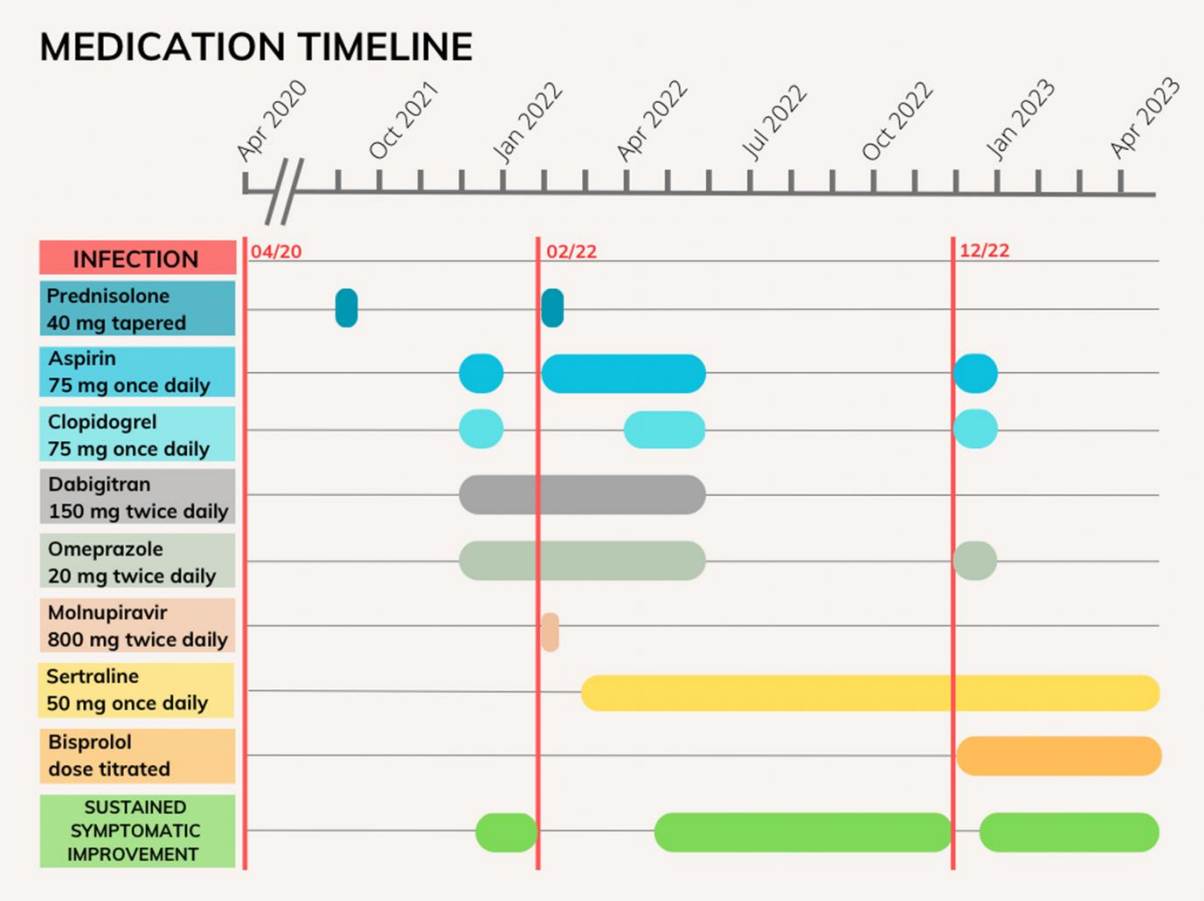



***Figure 2**. Medications initiated in our case, their respective durations, their timing relative to each SARS-CoV-2 infection, and correlation with sustained symptomatic benefit or symptom resolution. For sustained symptomatic benefit a combination of 2-3 antiplatelet drugs ± an anticoagulant were required.*

At 20 months a respiratory-physiotherapist verified ongoing desaturations with climbing stairs, which has been shown to correlate with perfusion deficits [136,197]—consistent with current understanding of microclots and further supported by 100 % of Long COVID patients tested so far in research having microclots and hyperactivated platelets [81,82]. These tests are being developed for clinical use [198]. At 21 months, aspirin, clopidogrel, dabigatran, and omeprazole were initiated (**Figure 2**). Without access to thromboelastography to monitor

coagulation status, treatment duration was one month based on published treatment approaches at the time [81], whilst continuing dabigatran alone into a second month (**Figure 2**) given the clinical picture was consistent with pulmonary microemboli. Treatment decisions conformed with UK guidance on unlicensed prescribing where the consultations took place [199]. There were no adverse bleeding events.

Symptomatic deterioration occurred in the first two weeks, which we propose was due to release of inflammatory markers within degraded microclots exacerbating endotheliitis [113] and/or widespread ischaemia-reperfusion injury [83]. From the third week there was daily incremental symptomatic improvement, which sustained beyond treatment completion.

SARS-CoV-2 reinfection occurred the following month causing the return of previously resolved (from triple anticoagulation) symptoms, plus an exacerbation of POTS. The patient received molnupiravir, prednisolone, and aspirin without symptomatic benefit. Sertraline was initiated principally for POTS and low mood with improved symptoms and tachycardia, in line with previous reports [200,201], but also for its antiplatelet and anti-inflammatory properties. With the return of dyspnoea, desaturations, and other symptoms, aspirin, clopidogrel, dabigatran, and omeprazole were recommenced, alongside sertraline acting as a third antiplatelet drug (**Figure 2**). Improvement followed a similar pattern to the initial triple anticoagulation course. Treatment was extended to eight weeks with full symptomatic resolution and return to employment and exercise. Thereafter, all treatment was stopped, except sertraline as a continued therapy for POTS.

The patient remained in good health for seven months, until their third SARS-CoV-2 infection, with the return of dyspnoea, cognitive dysfunction, and fatigue. This was the first infection where the patient was taking sertraline at the outset. Aspirin, clopidogrel, and omeprazole were restarted for one month. An exacerbation of POTS required the addition of a titrated dose of bisoprolol [201]. During this infection, there was no sustained desaturations, myalgia, claudication, or PESE. The initial symptoms were not sustained. We attribute this to early intervention targeting viral load and hyperactive platelets from the outset, but cannot rule out other factors, such as acquired immunity, as well as a less virulent and coagulopathic SARS-CoV-2 variant [202].

## Conclusion

A growing body of evidence supports that Long COVID is primarily a coagulopathic and endothelial disease. We propose the use of the term SITV as it describes the pathophysiology of post-COVID-19 and post-vaccination Long COVID presentations, and helps focus attention on early therapeutic intervention targeting microclots, hyperactive platelets, and endotheliitis. This multifaceted coagulopathy requires synergistic polypharmacy to achieve symptomatic resolution, as described in our case report. Thromboelastography can be utilised to mitigate bleeding risk. Our perspective does not negate the need to find and treat other pathologies common in Long COVID, but does highlight how coagulopathy can cause, exacerbate, and interact with other pathologies. Future research should investigate the efficacy of (particularly early) aggressive anticoagulation and antiplatelet treatment following COVID-19 infection (or similar post-vaccine sequelae) in averting or treating Long COVID.

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**Conflict of interest:** RK is the case described in the manuscript. HAC is a vaccine-induced Long COVID patient who has found significant symptomatic improvement using combined anticoagulation/antiplatelet therapy alongside treatments for co-pathologies.

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