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Characterising COVID-19 as a Viral Clotting Fever: A Mixed Methods Scoping Review

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Abstract

The COVID-19 pandemic has claimed over 1 million lives globally and results from the SARS-CoV-2 virus. COVID-19 is associated with a coagulopathy. In this mixed-methods PRISMA-compliant scoping review, we set out to determine if ARDS, sepsis and DIC could account for the coagulopathy and if there were any other features of the coagulopathy we could determine so as to inform future research. Methods: We used a search strategy to identify papers with clinically relevant thromboembolic events in COVID-19. We then developed a technique referred to as an Abridged Thematic Analysis (ATA) to quickly identify themes in the papers so as to increase the yield of clinically relevant information. We further developed Validated Abridged Thematic Analysis (VATA) to validate the resulting taxonomy of themes. Finally we developed a number of methods that can be used by other researchers to take forwards this work. Results: We identified 56 studies with 10,523 patients, 456 patients with COVID-19 and Thromboembolic Events (TBE's) and 586 thrombembolic events. There was an average of 1.3 TBE's per patient. There were five main arterial territories with corresponding clinical sequelae: Acute limb ischaemia, myocardial infarcts, strokes, mesenteric ischaemia and pulmonary embolism. We also identified DVT's. There were two further groups: medical-device-related coagulopathy and dermal lesions. In a subgroup of 119 patients we found mortality ranged from 26% in DVT to 79% in acute limb ischaemia although there was evidence of selection bias in the latter group. All patients were hospitalised and the average age of survivors was 63 versus 73 for those who died. 91/150 patients with TE's had fever. From the ATA, we identified 16 characteristics of the clotting pathology in COVID-19. From the VATA, we identified 34 mechanisms leading to coagulopathy and grouped them according to Virchow's triad of vascular damage, stasis and hypercoagulability. Coagulopathy occurred with and without each of ARDS, Sepsis and DIC. We conclude that COVID-19 leads to the syndrome of a viral clotting fever in a subgroup of patients and that the presentation of coagulopathy and fever should raise the possibility of COVID-19 as a differential. We make recommendations for future research studies.

Keywords: COVID-19 • Coagulopathy • Clotting fever • Abridged Thematic Analysis (ATA)

Introduction

On December 1st 2019, the first patient with Pneumonia of unknown origin was reported in Wuhan, China followed by several cases associated with the Huanan seafood market reported by the Health Commission of Hubei province on December 31st 2019 [1-3]. The illness was associated with a novel Coronavirus, SARS-CoV-2 which was isolated and characterized [4]. The resulting infection has been termed COVID-19.

Epidemiological characteristics of COVID-19 have been characterized and facilitated using SARS-CoV-2 genome sequencing [5-8]. Verity, et al. estimated the overall infection fatality rate in China at 0.66% (95% CI 0.39-1.66) [9]. The case fatality ratio varies according to age with 0.32% (0.27-0.38) in those aged less than 60 years and 13.4% (11.2-15.9) in those aged 80 years or older. A number of risk factors were identified for more severe illness including chronic cardiac disease, diabetes and obesity [10,11]. Factors affecting the transmission dynamics of SARS-CoV-2 have been identified and informed public health measures [12-14].

Asymptomatic presentation has been well described and is essential in understanding transmission dynamics but fever is recognized as a prominent clinical feature occurring in 98.6% of 138 symptomatic patients in an early study [15,16]. Other studies have confirmed the significance of fever which has been reported in 83-98% of symptomatic cases [17-21]. Further studies have characterized the longer-term consequences of COVID-19 which has been termed 'Long COVID' [22]. Whilst the classical presentation of COVID-19 is described as bilateral pneumonia with acute respiratory distress syndrome in more severe cases, extrapulmonary manifestations have been described including neurological, renal, dermatological, cardiac and gastrointestinal symptoms [23-25]. Silent hypoxia has been described in COVID-19 and can present a clinical challenge in routine practice [26].

An abnormal coagulation state is an important finding in COVID-19 with similarities to other coronavirus infections including MERS and SARS [27-31]. D-Dimer levels were found to be elevated in a study of 1099 patients with COVID-19 and other coagulation abnormalities have been identified [20,32].

In this scoping review we focus on the COVID-19-related coagulopathy. We firstly provide an overview of SARS-CoV-2 and the pathological findings identified in COVID-19. We then outline the typical host response to a viral infection as well as the clotting cascade and then Virchow's triad which underlies our analytical framework. We consider three important pathologies in COVID-19 which have featured in the early discussions around the COVID-19-related coagulopathy-ARDS, DIC and septicaemia. These pathologies inform our initial analysis of the literature.

SARS-CoV-2

Coronaviruses are single-stranded RNA viruses and are positive sense which means they can be read as mRNA by the ribosomes in the host cell and then translated into proteins [33]. Taxonomically SARS-CoV-2 is a member of the suborder Coronoavirineae and the genus Betacoronaviridae which specifically infect mammals [33]. Although viruses are not classified as living organisms, the sequence of events leading to replication is described as a life cycle. Ryu outlines six steps in the virus life cycle: Attachment, penetration, uncoating, gene expression and genome replication, assembly and release [34].

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During attachment, the virus attaches to the surface of the host cell followed by entry into the cytoplasm (penetration) and shedding of the viral capsid (uncoating). The viral RNA is then read (gene expression and genome replication) and then the gene products are assembled into a virion (assembly) and released from the cell (release).

Turning to coronaviruses there are four main structural proteins-spike, envelope, membrane and nucleocapsid [33] (see also Figure 1). The SARS-CoV-2 spike protein is divided into two functional components: S1 binds the receptor on the host cell and S2 facilitates the fusion of the virus with the host cell membrane. Like SARS, SARS-CoV-2 binds the ACE-2 receptor on the host cell. The ACE-2 receptor is found in tissues throughout the body [35]. SARS-CoV-2 also requires the priming action of Trans-Membrane Serine Protease 2 (TMPRSS2) which activates the SARS-CoV-2 spike protein so that the virus can fuse with the cell membrane [36-37].

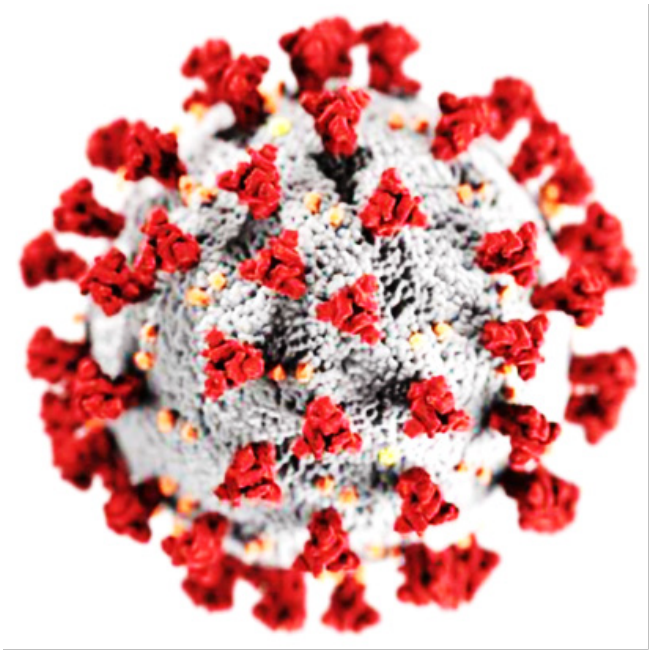

Figure 1. Illustration of SARS-CoV-2 virus: Authors CDC/ alissa eckert, MSMI; dan Higgins, image in public domain.

The degree of glycosylation of the S-protein is thought to interfere with the adaptive immune response by reducing the likelihood of antibody formation [33]. The open reading frames coding for the structural proteins are contained within one third of the genome and the genome also codes for accessory proteins [33]. The virus then appropriates the cell machinery to generate replication organelles including double-membrane vesicles. Viral RNA is transferred into the organelles which offer protection against the host cell's cytosol-based RNA-sensing immune mechanisms [33]. SARS-CoV-2 has 79-86% sequence homology with SARS-CoV or SARS-CoV-like viruses [38].

A further consideration is the effect of the virus on the host and this is inferred from a range of studies. Cardot-Leccia et al, found evidence of reduced pericytes in alveolar capillaries together with thinning of the walls of the alveolar capillaries and venules [39]. Bouhaddou et al, present the results of a phosphoproteomics survey in SARS-CoV-2 infected cells and found evidence of induction of cell cycle arrest and p38 MAPK activation amongst other findings [40].

Bösmüller, et al. in a post-mortem series (n=4) found evidence of progression of pulmonary pathology with findings typical of ARDS in the more severe cases of pathology [41]. In milder pathology they found evidence of increased mRNA expression of IL-1 beta and IL-6 as well as capillaritis with the presence of neutrophils and also microthromboses in the capillaries. Tabary, et al. review the pathological findings in COVID-19 and summarise the findings in the lungs, gastrointestinal tract, liver, kidney, skin, heart blood, spleen and lymph nodes, brain, blood vessels and placenta [42]. Hepatocyte degeneration is noted in the liver as well as an altered vascular structure. Diffuse alveolar damage and lymphocyte infiltration is found in the lungs. Intramural non-occlusive thrombi and fibrin deposition are found in the placenta. Necrosis of the keratinocytes and Langerhans cell nests are found in the skin. Inflammatory cell infiltrates and endotheliitis are found in the blood vessels. Sinus fibrosis and white pulp atrophy are found in the spleen. Axonal injuries and leukocyte infiltration are found in the CNS. Proximal acute tubule injury, tubular necrosis and interstitial fibrosis are found in the kidneys. The post-mortem findings will represent the more severe end of COVID-19 depending on the cause of death which may limit generalisation.

The host response to viral infections

The human immune system is broadly divided into the adaptive and innate immune response and what follows is a simplified account of their function so as to contextualise subsequent material in this paper. The innate immune system responds to novel microbes in the early phase of an infection in contrast with the adaptive immune system which predominantly recognizes and responds to a previously encountered microbe. The innate immune system includes physical barriers in the body together with a range of cells including phagocytes (neutrophils and macrophages), mast cells, natural killer cells and the complement cascade [43]. The adaptive immune system consists mainly of B and T-lymphocytes. The T-lymphocytes recognize antigens on microbes, referred to as epitopes upon which the T-cell will clone itself to increase the number of circulating T-cells capable of recognizing the antigen [43]. In this case the T-cell has not previously encountered the microbe and is thus referred to as a naieve T-cell although any subsequent encounters will result in a more effective initial adaptive immune response. T-cells are further divided into helper T-cells which activate B-cells to respond to antigens and cytotoxic T-cells which are capable of killing other cells. T-cells and B-cells have antigen-receptors on their cell surface but B-cells are also capable of secreting antibodies that mirror their cell-surface antigen-receptor [43]. Antibody secretion results in binding of the antibody to the antigen in a process referred to as opsonisation. Opsonisation causes the affected antigen-containing body (e.g. cell) to be targeted by phagocytes which proceed to kill target cells.

The clotting cascade

Coagulation is the process by which a liquid changes to a solid or semi-solid state. Coagulation of blood is essential in haemostasis, the process which prevents blood leaking from damaged blood vessels. The haemostatic system is a balance between procoagulant and anticoagulant mechanisms [44]. On the one hand the platelets adhere to damaged surfaces and aggregate whilst fibrin forms a clot. Fibrin has complex physical properties and the conditions in which fibrin clots are formed determine the structure of the clot which in turn influences the fibrinolytic susceptibility.

There are a number of anticoagulant mechanisms that provide a counterbalance. There are four main antithrombotic systems-the fibrinolytic system and the systems involving protein C and S, Tissue Factor Pathway Inhibitor (TFPI) and antithrombin. The fibrinolytic system degrades fibrin clots in a complex interplay which features the activation of plasminogen to plasmin which then acts on fibrin. Tissue plasminogen activator activates plasminogen [45].

The clotting cascade is the mechanism by which clotting is initiated and amplified in response to triggers. The clotting cascade can in the simplest form be divided into the intrinsic pathway, the extrinsic pathway and the common pathway. The clotting cascade consists of a number of clotting factors. Historically the clotting factors received many names with one factor receiving 14 different names [46]. The nomenclature of the clotting factors was rationalized in a series of meetings of the International Committee for the Nomenclature of Blood Clotting Factors between 1955 and 1958 and resulted in the use of Roman numerals. A selection of clotting factors with Roman numeral equivalents is shown in Table 1 and note that the first four factors are referred to by the clotting factor names rather than the Roman numerals (Table 1) [47].

Table 1. Clotting factors names with equivalent Roman numerals.

Roman numeral	Clotting factor name
I	Fibrinogen
II	Prothrombin
III	Tissue Factor
V	Proacclerin
VII	Proconvertin
VIII	Antithaemophilic Factor
IX	Christmas Factor
X	Stuart- Prower Factor
XI	Plasma thromboplastin antecedent
XII	Hageman Factor

The extrinsic pathway is initiated with the exposure of Factor VII to Tissue Factor. Tissue Factor is expressed on circulating particles released by monocytes and platelets and components of the vascular subendothelium including smooth muscle cells and fibroblasts [44]. Expression of Tissue Factor results from damage to the blood vessel walls. The exposure of Factor VII to Tissue Factor leads to activation of Factor VII (Factor VIIa). Factor VIIa then activates Factor X in the common pathway (Figure 2).

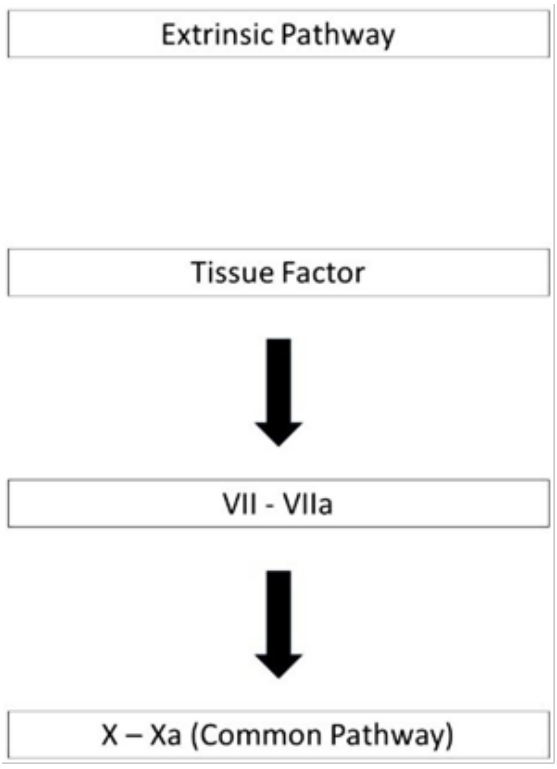

Figure 2. The extrinsic pathway.

The intrinsic pathway is also known as the contact pathway [48]. The intrinsic pathway is initiated in vivo by the inflammatory response. The intrinsic pathway in vitro can be initiated when the blood comes into contact with glass and other artificial surfaces. In the intrinsic pathway, Factor XII is activated to Factor XIIa. Factor XIIa then activates Factor XI to Factor XIa which in turn activates Factor IX to Factor IXa. Factor IXa then activates Factor VIII to Factor VIIIa (Figure 3).

The intrinsic and extrinsic pathways both act on the common pathway via activation of Factor X to Factor Xa. Factor Xa then activates Factor V to Factor Va. Finally Factor Va activates Prothrombin (formerly known as Factor II) (Figure 4).

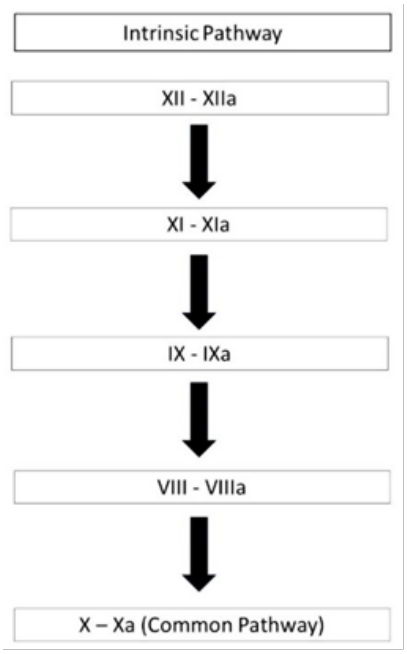

Figure 3. The intrinsic pathway.

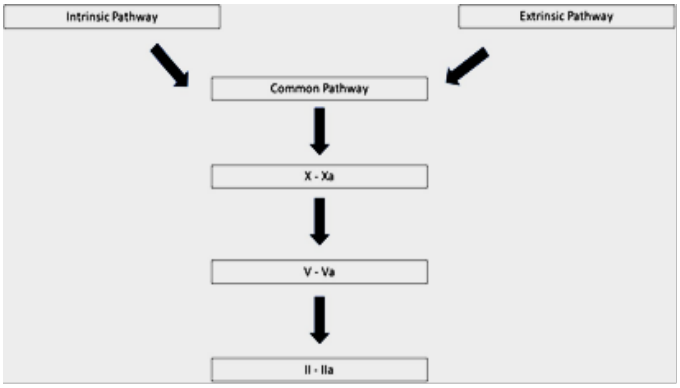

Figure 4. The common pathway.

There is evidence to suggest that the intrinsic pathway's role is to amplify the extrinsic pathway [47].

Virchow's triad

Virchow's triad is a well-established model of coagulation and provides a central framework for the interpretation of the data in this paper. Virchow's triad is named after the 19th century physician Dr Rudolph Virchow. Prior to Virchow there were different explanations for coagulation. Hippocrates advocated the model of the four humors which was further refined by Galen and remained dominant for 1300 years [49,50]. This model described pathology as resulting from an imbalance in the four humors. Organs had special functions (e.g. the spleen was believed to remove black bile) and deep vein thrombosis was believed to result from retention of humor [51,52]. This model was eventually displaced.

Dr Richard Wiseman, royal physician to King Charles II, identified stasis and the characteristics of the blood as causes of thrombosis in a paper published in 1676 thus identifying two of the components of Virchow's triad [53]. In the late nineteenth century, Jean Cruvielhier, a French pathologist promoted an inflammatory theory of thrombosis. Virchow reacted against this theory and following experimental work, published his seminal work on thrombosis and emboli in 1856.

Virchow focused on pulmonary emboli and viewed them as originating in the deep veins. Rather than accounting for the process of thrombogenesis, Virchow identified a triad of effects resulting from the thrombus as well as

explaining the propagation of the thrombus [53]. Over the next one hundred and sixty-five years, the meaning of Virchow's triad has been reworked and this interpretation is supported by accumulating evidence.

Virchow's triad as it is now understood refers to three factors that predispose towards coagulation: Stasis of the blood, vessel wall damage and hypercoagulability. Whilst individual components of the triad are more easily investigated, the simultaneous in vivo characterization of all three components is technically more challenging. Wolberg et al, differentiate arterial thrombi arising from ruptured atherosclerotic plaques and venous thrombi resulting from a combination of immobility, inflammation and hypercoagulability [612]. There are numerous factors that lead to hypercoagulability and describe a central role for Tissue Factor.

Blood flow is another key feature of Virchow's triad. Laminar flow describes a streamlined flow which contrasts with turbulent flow in which some parts of a liquid will travel at a different velocity resulting in different characteristics of the overall flow. Atherosclerotic plaques create stenosis and can produce turbulent flow with high shear rates contrasting with low shear rates downstream of a plaque. The downstream area with low shear rates can predispose to thrombogenesis.

In areas of low shear (post-stenotic), viscosity increases and many factors predispose to thrombosis [54]. The white platelet-rich head of the arterial thrombi in the highshear region is contrasted with the red tail of the thrombus in the low-shear region which is rich in red-cells.

In summary, Virchow's triad involves a complex interplay between three factors that can each predispose to coagulation but together form a potent combination.

Investigating COVID-19 related coagulopathies

Three possible aetiologies for a hypercoagulable state in COVID-19 are listed in Table 2 and were used in the initial examination of the literature in this paper (Table 2).

Table 2. Pathologies relevant to COVID-19 related coagulopathy.

Related coagulopathy
Sepsis
ARDS
Disseminated Intravascular Coagulation

Sepsis

Sepsis is an important differential for COVID-19-related coagulopathy. The sepsis definition was revised in 2016 by a taskforce of the European Society of Intensive Care Medicine and the Society of Critical Care Medicine and the resulting definition was termed sepsis-3 [55]. Sepsis-3 defines sepsis as a combination of infection with a dysregulated immune response and organ dysfunction. The construct of severe sepsis was removed in this definition and more severe pathology is described with the construct of septic shock which includes circulatory involvement (vasopressors are required to achieve a MAP ≥ 65 mmHg) and cellular and metabolic abnormalities (with serum lactate levels >2 mmol/l). Previously the construct of the Systemic Inflammatory Response Syndrome (SIRS) was used in the definition of sepsis. In SIRS there is a normal immune response occurring with or without an infective aetiology [43]. The taskforce determined that SIRS did not have construct validity for sepsis.

Organ dysfunction in sepsis has been assessed using the SOFA score and in the sepsis-3 definition an increase of at least 2 points is used as a threshold for organ failure. The SOFA score has been specifically developed for the evaluation of organ failure in severe sepsis [56]. A number of practical drawbacks with the use of the SOFA score led to the development of the qSOFA score which is simpler to use in clinical practice and also referenced in the sepsis-3 definition [55]. Giesen and Singer suggest that organ dysfunction is functional rather than structural and may reflect an adaptive hibernation-like mechanism [57].

Sepsis commonly leads to coagulation with elevated D-Dimers, fibrinolysis and turnover of thrombin markers [58]. Clinically significant haemostatic changes have been identified in up to 70% of patients with sepsis [59]. Levi describes a central role for cytokines in sepsis-related coagulopathy with IL-1, IL-6 and Tumour Necrosis Factor having a prominent role [59]. Levi also notes that fibrinolysis may be downregulated and there is a reduction in the levels of Protein C/S, TFPI and antithrombin all of which may contribute to a coagulopathy. And also notes the important balance between inflammation and sepsis-related coagulopathy [59]. Iba, et al. published their findings from the development of the sepsis-induced coagulopathy scoring system which has been widely used [60].

The importance of sepsis in COVID-19 has been recognised with the development of consensus guidelines for the management of sepsis in a critical care setting [61]. Dumitrascu et al provide an example of COVID-19-related coagulopathy with sepsis in case where ophthalmic artery occlusion developed despite thromboprophylaxis [62].

ARDS

Acute Respiratory Distress Syndrome (ARDS) is a syndrome of respiratory failure that is predominantly diagnosed and managed in an ICU setting. ARDS was first described in 1967 and the definition has changed in response to practical and prognostic challenges [63,64]. The Berlin definition were published in 2012 (ARDS Definition Task Force) and include a threshold value for PaO2/FiO2, bilateral chest infiltrates evident on chest imaging, an absence of atrial hypertension or a threshold value for the pulmonary arterial pressure and an acute onset. ARDS was graded into mild, moderate and severe and requirements were made for PEEP or CPAP thresholds.

A number of treatment approaches have been developed for ARDS including prone positioning, mechanical ventilation, fluid therapy, cell-based therapy and surfactant therapy although some are experimental [65-69]. The consensus guidelines for treatment of sepsis in a critical care setting include the management of ARDS [61].

Mitchell reviews the relationship of thromboinflammation to acute lung injury in COVID-19. There is noted to be damage to the endothelium and thrombosis in the perialveolar capillaries [70]. Mitchell notes the antithrombotic and anti-inflammatory mechanisms of the vascular endothelium and that in COVID-19 there is loss of the contact with the basement membrane, exposing procoagulant factors. Mitchell also notes the influx of neutrophils and macrophages seen in COVID-19 in response to acute lung injury and their role in promoting thrombosis and inhibiting fibrinolysis [70]. The Berlin definition does not include the construct of Acute Lung Injury (ALI) due to inconsistencies in the use of the terminology although this is referenced in the older literature and refers to a milder form of lung injury [71].

Wheeler and Rice outline a number of relationships that are relevant to the question of COVID-19-related coagulopathy [72]. They note that up to 50% of cases of acute lung injury result from sepsis but also patients with acute lung injury may be more likely to develop sepsis. Wheeler and Rice also note that there is increased tissue factor expression, fibrin generation and impaired fibrinolysis sharing similarities to the pathology seen in sepsis. They note that in more severe cases of sepsis, the lung is usually involved and they suggest that this may be related to the extensive capillary network with exposure to the endothelial cells [72]. The relationship between sepsis and ARDS is important not just in terms of coagulation but also for the risk of sepsis with prolonged ventilation [73].

ARDS has been identified in COVID-19 but the utility of the syndrome has been questioned [74]. COVID-19-related ARDS may arise in multiple non-specialist settings which together with the silent hypoxia associated with COVID-19 has potential implications for the early recognition of ARDS in COVID-19. The association of ARDS with coagulopathy means that this is an important consideration in the aetiology of COVID-19-related coagulopathy.

Disseminated intravascular coagulation

Disseminated Intravascular Coagulation (DIC) is an excessive activation of coagulation that can lead to significant mortality and morbidity. The 2001 definition by the International Society on Thrombosis and Haemostasis (ISTH) describes DIC as an acquired and generalised intravascular activation of coagulation [75]. DIC is associated with many diseases and conditions (Table 3).

Table 3. Aetiology of disseminated intravascular coagulation adapted from McKay, De Gopegui, et al. and Venugopal.

Aetiology of disseminated intravascular coagulation
A. Intravascular haemolysis
Haemolytic transfusion reactions
Haemolytic anaemia
B. Tissue injury
Massive tissue injury
Massive transfusion
Massive inflammation
Surgical procedures
Heat stroke
Severe trauma
Crush injuries
Massive burns
Severe hypo/hyperthermia
Severe pancreatitis
C. Infections
Bacterial infections
Gram negative (endotoxin)
Gram positive (bacterial coat mucopolysaccharide)
Viraemia (e.g. HIV, dengue)
Parasitic infections (e.g. malaria)
Fungal infection (e.g. invasive pulmonary Aspergillosis)
Protozoal infection
D. Obstetric complications
Fatty liver disease of pregnancy
Amniotic fluid embolism
Abruptio placentae
Pre-eclampsia
Retained products of placenta
E. Venoms/Toxins
Snake bite
Bee/insect sting
F. Malignancy
G. Miscellaneous
Diabetes mellitus
Vascular disorders - aortic aneurysms, giant
haemangiomas (Kasabach-Merritt syndrome)
Anoxia
Graft versus host disease
Endothelial damage
Release of tissue thromboplastin
Proteolytic enzymes
Particulate or colloidal matter
Ingestion of certain lipid substances

Activation of coagulation is recognised as a part of the host response to infection in sepsis [76]. In DIC, the coagulation response is pathological and can result from the host response to infection. Semeraro et al, describe the mechanisms of sepsis-related coagulopathy including disseminated intravascular coagulation [77]. One of the mediators of the relationship between the host response to infection and coagulopathy is complement and Kurosawa et al, review the complex relationship between complement and coagulation [78].

Iba, et al. distinguishes between the microthrombosis that occurs predominantly in capillary venules in DIC and in arterioles in thrombotic microangiopathy [79]. The distinction between thrombotic microangiopathy and DIC is also covered by [80]. Toh et al, note the importance of the multidisciplinary team in decision making with DIC as well as the nuances of interpretation of the haematological parameters [81]. Wada et al, distinguish four types of DIC according to their characteristics and recommend stratifying DIC according to these types when undertaking diagnosis and treatment [82]. Papageorgiou et al, review the treatments approaches for DIC [83].

There is an emerging evidence base for DIC in COVID-19. In a position statement by the Italian Haematology Society, DIC was suggested as a cause of the hypercoagulable state in COVID-19 [84]. Levi argues that COVID-19-related coagulopathy is distinct from DIC and notes that the thrombocytopenia is not as profound as expected in DIC, that most patients with COVID-19 would not reach the criteria for overt DIC and that there isn't evidence for excessive thrombin production [85]. Lillicrap on the other hand cites the evidence that the criteria for overt DIC are more likely in non-survivors of COVID-19 [86].

Joob and Wiwanitkit describe a case of COVID-19 with petechial rashes and low platelet count, initially diagnosed as Dengue fever [87]. Dengue fever is also associated with DIC which in turn can result in petechial rashes. This case highlights the diagnostic challenges in COVID-19.

Aim

The primary aim of this study was to determine if clotting pathology in COVID-19 occurs in the presence or absence of sepsis, disseminated intravascular coagulopathy and ARDS.

The secondary aims of this study were to use an iterative approach within the scoping review to:

1. Characterize the clotting pathology in COVID-19 with reference to the literature
2. To utilise the identified characteristics to develop a testable model
3. To identify knowledge gaps
4. To make recommendations on research methodology based on the findings
5. To generate testable hypotheses in addition to those in the model

Methodology

The PRISMA extension for scoping reviews checklist was used for this paper and was a key framework for this paper [88]. Additionally we developed a number of the methods used in this scoping review which we outline below.

Overall structure of study

To test the hypothesis that there was a clotting mechanism independent of ARDS, sepsis and DIC we used a simple search strategy to identify the main papers. We described the quantitative findings and also applied a thematic analysis to identify themes both for the clinical findings in relation to the coagulopathy as well as the suggested explanatory mechanisms. We then utilized an iterative semi-structured search strategy to identify further papers relevant to the results of the thematic analysis for explanatory mechanisms [89]. These papers were utilized in the development of a theoretical framework for the characterization of the COVID-19-related coagulopathy.

Protocol and registration

There was no protocol due to the exploratory and iterative nature of the scoping review and no registration given the need to avoid a delay due to the COVID-19 pandemic.

Rationale for using a mixed methods scoping review

Whilst there is evidence to suggest that COVID-19 is associated with a coagulopathy, there are diverse views on this coagulopathy and a number of potential mediators as above. COVID-19 has only recently been described and the evidence base is developing. Given the above, a scoping review was selected in favour of a meta-analysis or systematic review where the research questions are clearer and the research evidence base may be well-developed. A mixed methods approach was used to maximize the yield from the identified studies.

Literature search for papers with evidence of clotting

As this is a scoping review, broad search terms were used to identify evidence of clinically significant clotting disorders. The search terms used in the Pubmed database are shown in Table 4.

Table 4. PubMed search terms.

PubMed data
mesenteric and COVID-19
COVID-19 and skin
COVID-19 and limb
COVID-19 and stroke
COVID-19 and myocardial
COVID-19 and pulmonary embo*
COVID-19 and DVT
Note: * Signifies for COVID-19 and pulmonary embo

The inclusion and exclusion criteria are shown in Table 5. The COVID-19 initiative has made COVID-19 related papers available during the pandemic [90]. We therefore included only papers that were freely available including through the COVID-19 initiative as this review did not receive any external funding (Table 5).

Table 5. Inclusion and exclusion criteria.

Criteria
Inclusion Criteria
Paper contains original clinical data on patients with COVID-19 with evidence of clotting/ischaemia
English language
Paper freely available including under COVID-19 publishers' agreement
Exclusion Criteria
All clinical data for patients with COVID-19 and evidence of clotting/ischaemia aggregated with data for other groups

The abstracts were evaluated and after exclusions, the remaining papers were examined in detail and further exclusions took place. We excluded papers that did not present any of the data for patients with COVID-19 separately from patients without COVID-19 as this was needed for the analysis.

Analysis of Main Papers

Software:

We used Microsoft Excel® for Windows 365 to store and analyze the data.

We used Microsoft PowerPoint for the Diagram Mapping.

Data analysis: A template was created using an Excel spreadsheet and the data was filled on analyzing the papers. Several columns were used to describe the pathology where more than one pathology existed in the same patient. We utilized reports of pathology, descriptions of imaging findings, operative findings, and autopsy and biopsy evidence. In cases where there was clear evidence of end-organ ischaemia, we counted this as a thromboembolic event and grouped this together with clotting episodes where thromboembolism was identified or inferred from the evidence (e.g. loss of patency of a blood vessel on imaging).

For each of the studies we collected information on the number of cases, individual thromboembolic complications, sex, mortality, number of non-COVID-19 or non-thromboembolic cases and whether information was recorded on D-Dimers, fibrinogen, platelet count, prothrombin time, PaO2/FiO2, bilateral chest infiltrates evident on chest imaging, an absence of atrial hypertension or a threshold value for the pulmonary arterial pressure, acuteness of onset, confirmation of ARDS, sepsis, DIC, antithrombin, Protein C, whether respiratory rate or blood pressure were recorded, whether qSofa or SOFA score were recorded, mental status, main country of authors. We looked for evidence of randomisation or blinding as well as a power analysis.

Whilst the analysis was underway we identified a further potential mediator of the COVID-19-related coagulopathy - activation of the alternative complement pathway and added this to the analysis of the 56 papers [91]. Where clarification was needed, we contacted the authors of the papers.

A subset of 34 papers was identified in which individual patient data was available including sex, age and pathology. This enabled us to look at sex as a biological variable. The data was aggregated and analyzed, further separated according to outcome and sex and comparisons between groups based was undertaken. We utilized a two proportion Z-test to determine the statistical significance of the difference in proportions between various sample proportions.

We used the Benjamini and Hochberg procedure to correct for multiple comparisons using a false discovery rate of 0.25 [92,93].

Abridged thematic analysis and Validated abridged thematic analysis: A qualitative analysis was undertaken, using what we refer to as an Abridged Thematic Analysis (ATA) which we extended this with a Validated Abridged Thematic Analysis (VATA) (Figure 5). The 56 main papers are classed as a secondary source for the purposes of thematic analysis (Figure 5) [94].

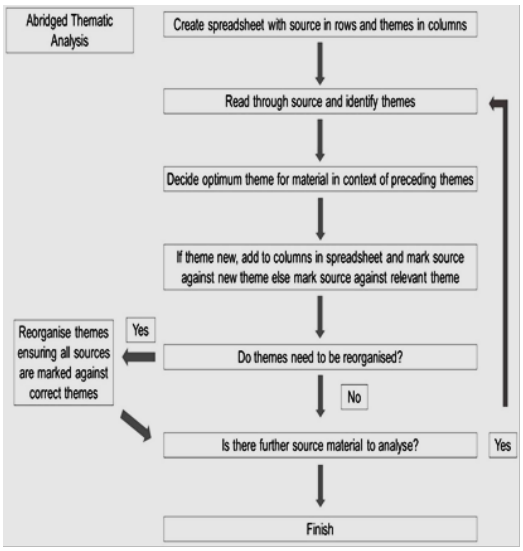

Figure 5. Outline of abridged thematic analysis procedure.

We abridged the thematic analysis by removing the coding process and working out the themes as we moved through the papers. We have outlined the process in figure 6 to enable this to be reproduced (Figure 6).

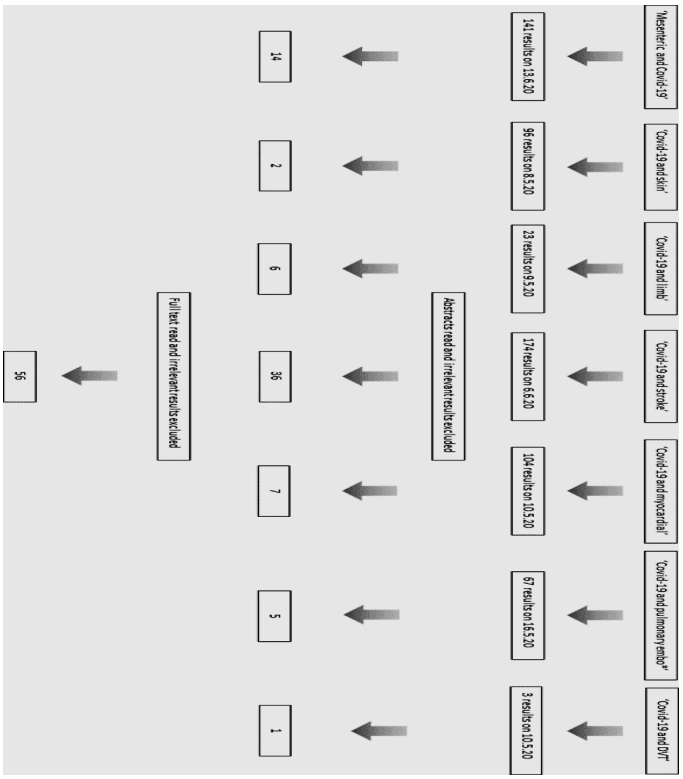

Figure 6. Illustrating the process of selection of papers for final analysis.

The application of the abridged thematic analysis was two-fold:

1. Firstly we looked for any characterization of the coagulopathy. We identified any distinct characteristics reported by the authors based on their clinical findings and determined if they qualified as a theme and if so which theme. When we had identified all of the themes, we then quantified the frequency of the theme in the papers.

2. Secondly we looked for explanatory mechanisms for the COVID-19-related coagulopathy. Again we identified the themes and organized them into an initial structure. We then validated the themes with an exploratory literature search. We then restructured the taxonomy. We refer to this as Validated Abridged Thematic Analysis (VATA).

Exploratory literature search: The exploratory literature search involved using specified search terms in Pubmed and selecting English language articles that were freely available including under the COVID-19 agreement and which were predominantly meta-analyses or systematic reviews in order to gain a rapid overview of the subject. We used these together with case studies or case series. We also used 'forward searching' from within the citations index of identified papers as well as personal knowledge of papers we were already familiar with [95,96]. For more selective questions we used additional resources including MedRxiv (RRID:SCR_018222), bioRxiv (RRID:SCR_003933), DOAJ - Directory of Open Access Journals (RRID:SCR_004521) and AMEDEO: The Medical Literature Guide (RRID:SCR_002284). We thus used a combination of primary, secondary and tertiary literature (Grewal et al, 2020). We have included search terms used in the exploratory literature search as part of the VATA as open data in the supplemental data.

Indexing the results from the validated abridged thematic analysis: After validating the identified themes against the clinical literature, we then reorganized the themes and documented a justification for the final taxonomy of themes. We used alphanumeric identifiers to label the themes. We also utilized the resulting taxonomy to generate a narrative summary which is presented at the end of the paper.

Diagram mapping:

We mapped the final taxonomy of themes onto corresponding diagrams using the alphanumeric identifiers and a set of rules which we outline below.

1. Each diagram is labelled with an alphanumeric identifier which maps onto the taxonomy

2. Concepts/constructs/phenomenon are represented by boxes with text descriptions

3. The relationships between concepts/constructs/phenomenon are identified by arrows

4. The arrows are colour coded according to the strength of evidence for the relationship and whether the evidence exists in the COVID-19 literature or in the general (i.e. non-COVID-19) literature.

5. The arrows encompass a broad range of logical relationships resulting from deductive, inductive and abductive reasoning based upon the evidence.

6. The relationships encompass multiple ontological levels

Results

Results of main literature search

The initial results of the literature search are shown in Figure 6 and include the dates of the searches. The searches identified a total of 608 papers which were reduced to 71 papers after a review of the abstracts and finally 56 papers after inspection of the full text and application of the inclusion/exclusion criteria. A number of the papers reported on mixed clotting/ischaemic pathologies (e.g. stroke and lower limb deep vein thrombosis) and so the final 56 papers are pooled. The final papers are listed in Table 6.

Table 6. Summary of identified studies.

Authors	Type of study	Number of patients with COVID- 19 and thromboembolic events
(Escalard et al, 2020)	Case Series	10
(Fara et al,2020)	Case Series	3
(Zayet et al,2020)	Case Series	2

(Wang et al, 2020)	Case Series	5
(Benussi et al, 2020)	Retrospective Cohort Study	40
(Gunasekharan et al,2020)	Case Study	1
(Rudilosso et al, 2020)	Randomised Control Trial	1
(Morassi et al, 2020)	Case Series	6
(Yaghi et al, 2020)	Retrospective Cohort Study	32
(Jain et al, 2020)	Retrospective Cohort Study	26
(Meza et al, 2020)	Observational Study	6
(Deliwala et al, 2020)	Case Study	1
(Valderrama et al,2020)	Case Study	1
(Barrios Lopez et al, 2020)	Case Series	4
(Co et al,2020)	Case Study	1
(Tunc et al, 2020)	Case Series	4
(Viguier et al,2020)	Case Study	1
(Gonzalez- Pinto,2020)	Case Study	1
(Lodigiani et al, 2020)	Retrospective Cohort Study	28
(Oxley et al, 2020)	Case Series	5
(Moshayedi et al, 2020)	Case Study	1
(Hughes et al,2020)	Case Study	1
(Siddam reddy et al, 2020)	Case Study	1
(Ueki et al, 2020)	Case Study	1
(Stefanini et al, 2020)	Retrospective Cohort Study	28
(Xiao et al, 2020)	Case Series	3
(Cai et al,2020)	Case Study	1
(Lacour et al, 2020)	Case Study	1
(Middledorp et al,2020)	Retrospective Cohort Study	39
(Le Berre et al, 2020)	Case Study	1
(Poggioali et al, 2020)	Case Series	2
(Harsch et al, 2020)	Case Study	1
(Klok et al, 2020)	Observational Study	73
(Azouz et al, 2020)	Case Study	1
(Beccara et al, 2020)	Case Study	1
(Vulliamy et al, 2020)	Case Series	2
(de Berry et al, 2020)	Case Study	1
(Zhou et al,2020)	Case Study	
(Cui et al, 2020)	Retrospective Cohort Study	20
(Valdivia et al, 2020)	Case Series	4
(Bellosta et al, 2020)	Observational Cohort Study	20
(Giacomelli et al,2020)	Case Study	1
(Qian et al, 2020)	Case Study	1
(Bozzani et al, 2020)	Case Series	3
(Casas et al, 2020)	Prospective Cohort Study	21
(Bouaziz et al, 202)	Retrospective Observational Study	2
(Kaafarani et al,2020)	Case Series	5
(Ignat et al, 2020)	Case Series	3
(Helms et al,2020)	Prospective Cohort Study	27
(Farina et al, 2020)	Case Study	1
(La Mura et al, 2020)	Case Study	1
(Varga et al, 2020)	Case Series	3
(Norse et al, 2020)	Case Study	1
(Bianco et al, 2020)	Case Study	1
(Diago Gomez, 2020)	Case Series	4
(Chan et al, 2020)	Case Study	1

Country of publication of included papers

The countries of publication are shown in Figure 7. There were no authors based in Africa, Oceania or South America. The authors of 84% of the papers included in the analysis were based in five countries (Italy, USA, France, Spain and China) (Figure 7).

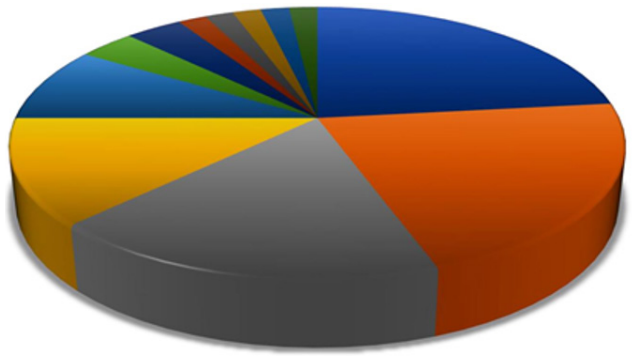

Figure 7. Country of publication. **Note:** ( ) Italy; ( ) USA; ( ) France; ( ) Spain; ( ) China; ( ) Switzerland; ( ) Holland; ( ) Germany; ( ) England ;( ) Philippines; ( ) Wales; ( ) Turkey

Thromboembolic/Ischaemic events in 56 papers

The descriptive statistics for thromboembolic/ischaemic events in the 56 papers are shown in Table 7.

Table 7. Descriptive statistics for thromboembolic/ischaemic events in the 56 papers.

Statistics	Number of papers
Total Number of Patients in All Studies	10523
Total Number of Patients with COVID-19 and Thromboembolic/Is- chaemic Events	456
Total Number of Thromboembolic/Ischaemic Events	586
Average Number of Thromboembolic/Ischaemic Events Per Patient	1.3 (1 d.p.)

The analysis shows that just over 4% of the total number of patients in all the studies had a combination of COVID-19 and thromboembolic/ischaemic events. Furthermore the average number of thromboembolic/ischaemic events was above 1.

The distribution of the average number of ischaemic/clotting events per patient is illustrated in Figure 8. The spread of the data was not normally

distributed but instead was skewed towards the mode which was one thromboembolic/ischaemic event per patient (Figure 8).

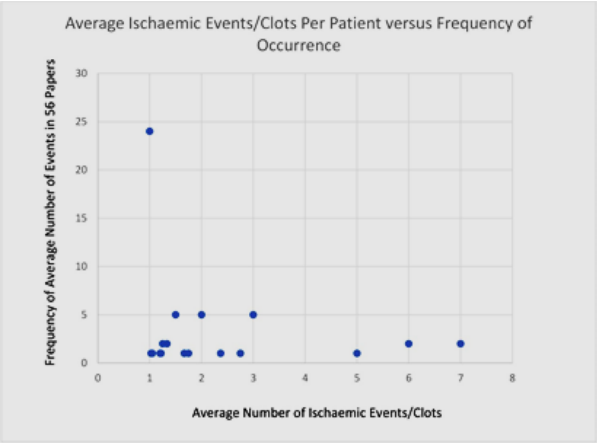

Figure 8. Average number of clots/ischaemic events per patient v frequency of occurrence.

The number of thromboembolic/ischaemic events is categorised in Table 8. Strokes are differentiated according to the description. Where the occluded artery/arteries are not identified, the pathology has been identified through the infarcted regions. Several infarcted regions may result from the occlusion of a single artery but the location is not predictable due to anatomical variants and collateral circulation and therefore in these cases the distinct regions are counted. Skin livedo and necrosis are counted as thromboembolic/ischaemic events although data was not available in these cases on the potentially relevant arterial patency (e.g. acute limb ischaemia). Upper limb DVT was differentiated according to the absence or presence of a catheter with the latter group being included with medical device-associated clotting (Table 8).

Table 8. Thromboembolic/ischaemic/clotting events in 56 main papers.

Clotting events	Number of papers
Stroke (Infarcted Regions)	126
Stroke (Excluding Carotids)	65
Transient Ischaemic Attacks	5
Carotid Arteries Thrombosis	16
Cerebral Venous Thrombosis	2
Aortic Thrombus	13
Cardiac Thrombi	2
Coronary Artery Ischaemic Event	34
Inferior Vena Cava Thrombosis	2
Subclavian and Jugular DVT	2
Pulmonary Emboli	130
Splanchnic Artery Ischaemia	24
Superior Mesenteric Vein Thrombus	1
Portal Vein Thrombosis	4
Acute Limb Ischaemia	34
Lower Limb DVT	62
Upper Extremity DVT	5
Skin livedo, necrosis	23
Clotting in ECMO Centrifuge	3
Clotting in Dialysis Machine	28
Catheter-Related Upper Limb DVT	3
Systemic Arterial Embolisms	2
Total	586

Table 9 shows the number and percentage of papers reporting a range of syndromes, diagnoses and blood test results relevant to COVID-19-related coagulopathy. The D-Dimers and platelet count were the two most frequently reported parameters in the 56 papers (Table 9).

Table 9. Number (%) of papers reporting clinical variables/diagnoses/syndromes for 56 main Pa-pers.

	Number of papers	% of Total papers (2 s.f.)
Platelet	22	39
PT Prolongation	18	32
Fibrinogen	15	27
D-Dimer	35	63
Antithrombin	4	7
Protein C	3	5
DIC confirmation	4	7
ARDS confirmation	7	13
Sepsis confirmation	3	5.4
AH50	0	0

ARDS

Out of the fifty-six main papers, seven studies provided evidence of ARDS with a total of 159 patients with COVID-19 and ARDS. With the exception of these were all case studies or case series and are shown in Table 10 [97]. Helms et al, reported 150 patients with 64 thrombotic complications and without evidence of disseminated intravascular coagulation [97]. The authors also compared the patients with COVID-19 and ARDS to a group with ARDS but without COVID-19. They reported a significantly increased likelihood of thrombotic events in the patients with COVID-19 (Odds Ratio 2.6 [1.1-6.1], p=0.035). The SOFA scores did not differ between the two groups (Table 10).

Table 10. Papers with ARDS confirmation.

Authors	Study
(Deliwala et al, 2020)	Single case with stroke
(Siddamreddy et al, 2020)	Single case with inferior wall STEMI
(Ueki et al, 2020)	Single case with inferoposterior STEMI
(Bellosta et al, 2020)	4 fatal cases with limb ischaemia
(Qian et al, 2020)	Single case with upper and lower limb ischaemia
(Ignat et al, 2020)	Single case of bowel ischaemia with ARDS
(Helms et al, 2020)	150 patients with ARDS with 64 thrombotic events

Sepsis

In the 56 main papers, two of the papers provide evidence of sepsis and are shown in Table 11. Norse, et al. report the case of a 62-year-old man who developed mesenteric ischaemia requiring bowel surgery and later died of septic shock [98]. In another paper the sepsis results from an E.Coli infection comorbid with COVID-19 and there is mesenteric ischaemia (Table 11) [99].

Table 11. Papers confirming sepsis.

Authors	Sepsis
(La Mura et al, 2020)	E.Coli sepsis with mesenteric ischaemia
(Norse et al, 2020)	Case study with mesenteric ischaemia

There are other papers where sepsis is discussed but the confirmation

is less clear. Barrios Lopez, et al. report on 4 cases of ischaemic stroke with COVID-19 and suggest septic shock as a cause [100].

Other papers mention the use of the SOFA or qSOFA score which are intended for use in sepsis although they have been used for critically ill patients more generally and are shown in Table 12.

Table 12. Papers with SOFA/qSOFA/SIC score.

Authors	Study
(Benussi et al, 2020)	35 patients with ischaemic stroke, higher qSOFA on
(Kaafarani et al, 2020)	141 patients with COVID-19, SOFA score aggregated, subset of patients with mesenteric ischaemia
(Helms et al, 2020)	150 patients with COVID-19 and 64 thrombotic complications, SOFA scores aggregated
(La Mura et al, 2020)	E.Coli sepsis with mesenteric ischaemia
(Poggiali et al, 2020)	Case study with elevated SIC score and DVT

La Mura et al, mentions both the diagnosis and the SOFA score [99]. Poggiali et al, present two cases of COVID-19 who present with venous thromboembolism [101]. They present their findings with the Sepsis-Induced Coagulopathy (SIC) score as evidence for this pathology. The main focus of Helms, et al. is on ARDS although they exclude DIC (depending on the scoring system) and have included aggregated SOFA scores [97].

Disseminated intravascular coagulation

DIC was specifically confirmed or excluded in four papers which are shown in Table 13.

Table 13. Papers confirming or excluding DIC.

Authors	Confirming or excluding DIC
(Klok et al, 2020b)	DIC excluded in all cases
(Lodigiani et al, 2020)	8 patients with overt DIC, 2 (25%) with thromboembolic events, 7 (88%) died
(Validivia et al, 2020)	1 case of acute limb ischaemia with DIC and death
(Helms et al, 2020)	0-6 patients with DIC depending on scoring system

Helms, et al. have used different scoring systems to assess DIC in patients and identified between 0 and 6 patients with DIC depending on the scoring system [97].

Klok, et al. excluded DIC in all cases while identified eight patients with overt DIC [102,103]. Klok, et al. excluded DIC in all cases [102]. Lodigiani, et al. identified 8 patients with DIC, with 25% of patients manifesting thromboembolic events and 88% of patients dying underlining the important consequences of DIC [103]. Valdivia, et al. report a single case of acute limb ischaemia with DIC and death [104]. Helms, et al. investigated DIC as a secondary outcome and used various scoring methods to ascertain caseness [97]. No patients were identified with DIC using the ISTH "overt" score, 6 cases of DIC were identified using the JAAM-DIC score and 22 patients were identified using the SIC score indicating those at risk of DIC. Thus there was evidence of thromboembolic complications in patients with COVID-19 and where DIC had both been confirmed and excluded.

A subset of 34 studies with demographic data

We identified a subset of 34 studies which contained individual information on the age and gender of the patient as well as the corresponding pathology, enabling a more detailed characterisation of the pathology. The 34 studies are listed in Table 14.

Table 14. 34 papers with individual clinical information on pathology, gender and mortality.

Authors		
(Fara et al, 2020)	(Deliwala et al, 2020)	(Valderrama et al, 2020)
(Barrios Lopez et al, 2020)	(Co et al, 2020)	(Viguier et al, 2020)
(Gonzalez-Pinto, 2020)	(Lodigiani et al, 2020)	(Oxley et al, 2020)
(Hughes et al, 2020)	(Siddamreddy et al, 2020)	(Ueki et al, 2020)
(Stefanini et al, 2020)	(Xiao et al, 2020)	(Cai et al, 2020)
(Lacour et al, 2020)	(Le Berre et al, 2020)	(Poggiali et al, 2020)
(Harsch et al, 2020)	(Beccara et al, 2020)	(Vulliamy et al, 2020)
(de Barry et al, 2020)	(Zhou et al, 2020)	(Cui et al, 2020)
(Bellosta et al, 2020)	(Giacomelli et al, 2020)	(Ignat et al, 2020)
(Farina et al, 2020)	(La Mura et al, 2020)	(Varga et al, 2020)
(Norse et al, 2020)	(Bianco et al, 2020)	(Diago Gomez, 2020)
(Diago Gomez, 2020)	-	-

In the 34 studies, the distribution of thromboembolic/ischaemic events per patient was similar to Figure 7, being skewed towards the mode value of 1 thromboembolic/ischaemic event per patient with a range of 1-8. The results are shown in Tables 8-12. In the limb ischaemia group, eight of the patients had been reported from one study where the data had been published selectively for patients that had died (i.e. individual data was not available for patients that had not died).

The 34 papers included 119 patients with COVID-19 and thromboembolic/ischaemic events and the overall results are shown in Table 15. All of the studies are based in a hospital setting. There are a number of patients with multiple thromboembolic/ischaemic events but the numbers are counted for each type of event and the sum is therefore greater than the number of patients. 38% of the patients in this group died. The percentage of deaths varied from just under 8% in those with stroke-related thromboembolic events to just under 77% in those with acute limb ischaemia (Table 15).

Table 15. Results from analysis of cases from 34 papers with individual data.

Events analysis	Number of papers
Number of Patients	119
Average Age of Patients	67(2.s.f)
Number of male patients	82
Number of male patients	45(38%(2.s.f))
Number of Thromboembolic/ Ischaemic Events	205
Average Number of Events Per Patients	1.72(2 d.p.))
Range of Number of Events Per Patients	(1-8)
Mode of Number of Events Per Patients	1
Number of Patients with Aortic Thromboembolic Events%	9(7.6(1.d.p))
Death in Patients with Aortic Thromboembolic Events%	3(33%)
Number of Patients with Stroke related Events Including Carotid Arteries (%)	3(27.7% (1.d.p.))
Death in Patients with Stroke related Events (%)	9 (7.6% (1d.p.))
Number of Patients with Cardiac Thromboembolic/ Ischaemic Events (%)	42 (35%)

Death in Patients with Cardiac Thromboembolic/ Ischaemic Events (%)	15 (36% (2 s.f))
Number of Patients with Pulmonary Emboli (%)	16 (13% (2 s.f))
Death in Patients with Pulmonary Emboli (%)	4 (25%)
Number of Patients with Venous Thromboembolic Events Excluding PE (%)	19 (16% (2 s.f))
Death in Patients with Venous Thromboembolic Events Excluding PE (%)	5 (26% (2 s.f))
Number of Patients with Thromboembolic Events in Splanchnic Arteries (%)	15 (12.6% (1 d.p))
Death in Patients with Thromboembolic Events in Splanchnic Arteries (%)	59(60%)
Number of Patients with Acute Limb Ischaemic Events (%)	14 (12% (2 s.f))
Death in Patients with Acute Limb Ischaemic (%)	15 (78.6% (1 d.p))

The results from the analysis of the female cases in the 34 papers are shown in Table 16. 32% of the patients in this group died. The deaths associated with each type of thromboembolic/ischaemic event ranged from 21% with cardiac thromboembolic/ischaemic events to 100% with acute limb ischaemia. The results from the analysis of the male cases in the 34 papers are shown in Table 17. There were just over twice as many males as females in the 34 papers and 40% of the patients in this group died. There were eight deaths reported in one of the studies where the data was not available for those who survived. The deaths associated with each type of thromboembolic/ischaemic event ranged from 18% with pulmonary emboli to 75% with acute limb ischaemia (Tables 16 and 17).

Table 16. Analysis of female cases in 34 papers with individual data.

Analysis of female cases	Number of papers
Number of Patients	37
Average Age of Patients	66
Number of Deaths (%)	12 (32% 2 s.f.)
Number of Thromboembolic/Ischaemic Events	55
Average Number of Events Per Patient	1.48 (2 d.p.)
Range of Number of Events Per Patient	(1-6)
Mode of Number of Events Per Patient	1
Number of Patients with Aortic Thromboembolic Events (%)	2 (5.4% (1 d.p.))
Deaths in Patients with Aortic Thromboembolic Event (%)	1 (50%)
Number of Patients with Stroke Related Events Including Carotid Arteries (%)	12 (32%)
Deaths in Patients with Stroke Related Events (%)	4 (33%)
Number of Patients with Cardiac Thromboembolic/ Ischaemic Events (%)	14 (38% 2 s.f.)
Deaths in Patients with Cardiac Thromboembolic/ Ischaemic Events (%)	3 (21% (2 s.f.))
Number of Patients with Pulmonary Emboli (%)	5 (14% 2 s.f.)
Deaths in Patients with Pulmonary Emboli (%)	2 (40)%
Number of Patients with Venous Thromboembolic Events Excluding PE (%)	7 (19% 2 s.f.)
Deaths in Patients with Venous Thromboembolic Events (%)	2 (28.6% (1 d.p.))
Number of Patients with Thromboembolic Events in Splanchnic Arteries (%)	3 (8% 1 s.f.)
Deaths in Patients with Thromboembolic Events in Splanchnic Arteries (%)	2 (67% 2 s.f.)
Number of Patients with Acute Limb Ischaemic Events (%)	2 (3.6% (1 d.p.)
Deaths in Patients with Acute Limb Ischaemia (%)	2 (100%)

Table 17. Analysis of male cases in 34 papers with individual data.

Analysis of male cases	Number of papers
Average Age of Patients	67
Number of Deaths (%)	33 (40% 2 s.f.)
Number of Thromboembolic/Ischaemic Events	150
Average Number of Events Per Patient	1.83 (2 d.p.)
Range of Number of Events Per Patient	(1-8)
Mode of Number of Events Per Patient	1
Number of Patients with Aortic Thromboembolic Events (%)	7 (8.54% 2 d.p)
Deaths in Patients with Aortic Thromboembolic Event (%)	2 (28.6% (1 d.p.))
Number of Patients with Stroke Related Events Including Carotid Arteries (%)	21 (25.6%(1dp))
Deaths in Patients with Stroke Related Events (%)	5 (23.8% (1 d.p.))
Number of Patients with Cardiac Thromboembolic/ Ischaemic Events (%)	28 (34% (2 s.f.))
Deaths in Patients with Cardiac Thromboembolic/ Ischaemic Events (%)	12 (42.9% 1 d.p.)
Number of Patients with Pulmonary Emboli (%)	11 (13%(2 s.f.))
Deaths in Patients with Pulmonary Emboli (%)	2 (18% (2 s.f.))
Number of Patients with Venous Thromboembolic Events Excluding PE (%)	12 (14.6%(1 d.p.))
Deaths in Patients with Venous Thromboembolic Events (%)	3 (25%)
Number of Patients with Thromboembolic Events in Splanchnic Arteries (%)	12 (14.6%(1 d.p.))
Deaths in Patients with Thromboembolic Events in Splanchnic Arteries (%)	7 (58% (2 s.f.))
Acute Limb Ischaemic Events (%)	12 (14.6%(1 d.p.))
Deaths in Patients with Acute Limb Ischaemia (%)	9 (75%)

We also compared the results in the 34 papers for those who died and those who survived. The results for the cases of those who died are shown in Table 18 where the average age is 73. The four main types of thromboembolic/ischaemic events in this group in increasing percentages were thromboembolic/ischaemic events in the splanchnic arteries (20%), stroke-related events including the carotid arteries (24%), acute limb ischaemia (24%) and cardiac thromboembolic/ischaemic events (33%) (Table 18).

Table 18. Calculating difference between proportions using Z-test: F-Female, M -Male, FP-Female Proportion of sample, MP- Male Proportion of sample, F PC-Female Proportion of Cases, M PC-Male Proportion of Cases, D-Difference between proportions (smaller value subtracted from larger), SP- Sample Proportion for test statistic calculation, SE-Standard Error, TS-Test Statistic, p- P-value.

	F	M	F P	M P	F PC	M PC	D	SP	SE	TS	p
Number of Deaths	12	33	0.3243	0.4024	-	-	0.078115	0.378151	0.096038	0.813377	0.20897
Number of cases of aortic thromboembolism	2	7	0.0541	0.0854	-	-	0.031312	0.07563	0.052364	0.597958	0.2776
Number of deaths with cases of aortic thromboembolism	1	2	-	-	0.5	0.2857	0.2143	0.02521	0.031046	6.902618	0.00003
Number of cases of stroke	12	21	0.3243	0.2561	-	-	0.06823	0.277311	0.088659	0.769574	0.07353
Number of deaths with cases of stroke	4	5			0.3333	0.2381	0.095205	0.07563	0.052364	1.818124	0.03515
Number of cases of cardiac thromboembolism	14	28	0.3784	0.3415	-	-	0.036915	0.352941	0.094643	0.390044	0.34827
Number of deaths with cardiac thromboembolic events	3	12	-	-	0.2143	0.4286	0.214284	0.12605	0.065733	3.259938	0.00058
Number of cases with pulmonary emboli	5	11	0.1351	0.1341	-	-	0.000989	0.134454	0.067561	0.01464	0.49601
Number of deaths with pulmonary emboli	2	2	-	-	0.4	0.1818	0.218182	0.033613	0.035694	6.112534	0.00003
Number of cases with DVT	7	12	0.1892	0.1463	-	-	0.042848	0.159664	0.072543	0.59065	0.2776
Number of deaths with DVT	2	3	-	-	0.2857	0.25	0.035714	0.042017	0.039733	0.898845	0.18673
Number of cases with splanchnic arterial thromboembolism	3	12	0.0811	0.1463	-	-	0.06526	0.12605	0.065733	0.99281	0.16109
Number of deaths with splanchnic arterial thromboembolism	2	7	-	-	0.6667	0.5833	0.083336	0.07563	0.052364	1.591462	0.00592
Number of cases with acute limb ischaemia	2	12	0.0541	0.1463	-	-	0.092291	0.117647	0.063808	1.446386	0.07493
Number of deaths with acute limb ischaemia	2	9	-	-	1	0.75	0.25	0.092437	0.057362	4.358259	0.00003

The results of the analysis of the patients that survived in the 34 papers are shown in Table 20. The average age in this group was 74 and there were twice as many men as women in this group. The four main types of thromboembolic/ischaemic events in this group in increasing percentages were pulmonary emboli (16%), venous thromboembolic events not including pulmonary emboli (19%), cardiac thromboembolic/ischaemic events (26%) and stroke-related events including the carotid arteries (32%) (Table 19 and 20).

Table 19. Analysis of cases where patients died in 34 papers with individual data.

Analysis died patients	Number of papers
Number of Patients	45
Average Age of Patients	73 (2 s.f.)
Number of Male Patients	33
Number of Female Patients	12
Number of Thromboembolic/Ischaemic Events	84
Average Number of Events Per Patient	1.87 (2 d.p.)
Range of Number of Events Per Patient	(1-8)
Mode of Number of Events Per Patient	1
Number of Patients with Aortic Thromboembolic Events (%)	3 (6.7% (1 d.p.))
Number of Patients with Stroke Related Events Including Carotid Arteries (%)	11 (24% (2 s.f.))
Number of Patients with Cardiac Thromboembolic/ Ischaemic Events (%)	15 (33% (2 s.f.))
Number of Patients with Pulmonary Emboli (%)	4 (8.8% (1 d.p.))
Number of Patients with Venous Thromboembolic Events (not including Pulmonary Emboli) (%)	5 (11% (2 s.f.))
Number of Patients with Thromboembolic Events in Splanchnic Arteries (%)	9 (20%)
Number of Patients with Acute Limb Ischaemic Events (%)	11 (24.4% (1 d.p.))

Table 20. Analysis of cases where patients survived in 34 papers with individual data.

Analysis of survived patients	Number of papers
Number of Patients	74
Average Age of Patients	62.8 (1 d.p.)
Number of Male Patients	49

Number of Female Patients	25
Number of Thromboembolic/Ischaemic Events	121
Average Number of Events Per Patient	1.635 (3 d.p.)
Range of Number of Events Per Patient	(1-7)
Mode of Number of Events Per Patient	1
Number of Patients with Aortic Thromboembolic Events (%)	6 (8.1% (1 d.p.))
Number of Patients with Stroke Related Events Including Carotid Arteries (%)	24 (32% (2 s.f))
Number of Patients with Cardiac Thromboembolic/ Ischaemic Events (%)	32 (26% (2 s.f.))
Number of Patients with Pulmonary Emboli (%)	12 (16% (2 s.f.))
Number of Patients with Venous Thromboembolic Events Not Including	14 (19% (2 s.f.))
Pulmonary Emboli (%)	
Number of Patients with Thromboembolic Events in Splanchnic Arteries (%)	6 (8% (1 s.f.))
Number of Patients with Acute Limb Ischaemic Events (%)	3 (4% (1 s.f.))

D-Dimers

One paper reported the units (Fibrinogen equivalent units or D-Dimer units) and there were 27 values which cited a laboratory reference range for interpretation of the results. The other values in the studies did not include the units or reference range and so our analysis was limited to the 27 values which cited the reference range. We therefore expressed the results as multiples of the reference range and the results of the analysis are shown in Tables 21 and 22.

Table 21. D -number who died, S- number who survived, DP-proportion of sample who died, SP- proportion of sample who survived, D-difference between proportions with smaller value subtracted from larger value, SaP -sample proportion for test statistic calculation, SE-standard error, TS-test statistic, p- p-value.

	D	S	D P	S P	D	SaP	SE	TS	p
Number of Male Case	33	49	0.73333	0.65333	0.08	0.689076	0.087501	0.91427	0.18141
Number of Female Cases	12	25	0.26667	0.33783	0.071164	0.310924	0.087501	0.813292	0.20897
Number of Cases with Aortic Thromboembolic Events	3	6	0.06667	0.08108	0.014415	0.07563	0.049983	0.288397	0.38974
Number of Cases with Strokes	11	24	0.24444	0.32432	0.07988	0.294118	0.086135	0.927381	0.17879
Number of Cases with Cardiac Thromboembolic Events	15	32	0.33333	0.43243	0.099099	0.394958	0.09241	1.072378	0.14231
Number of Cases with Pulmonary Emboli	4	12	0.08889	0.16216	0.073272	0.134454	0.064489	1.136196	0.12924
Number of Cases with Deep Vein Thromboses	5	14	0.11111	0.18919	0.078078	0.159664	0.069244	1.127576	0.13136
Number of Cases with Splanchnic Thromboembolic Events	9	6	0.2	0.08108	0.118919	0.12605	0.062743	1.89532	0.02938
Number of Cases with Acute Limb Ischaemia	11	3	0.24444	0.04054	0.203904	0.117647	0.060907	3.347804	0.00042

Table 22. Analysis of D-Dimer results expressed as multiples of upper limit of laboratory reference range.

D-Dimers as multiples of upper limit of reference range	Value
Number of values	27
Mean	21.6 (1 d.p.)
Standard Deviation	41.5 (1 d.p.)
Standard Error of Mean	7.98
95% Confidence Interval	21.6 ± 15.6 (1 d.p.)

Benjamini–Hochberg procedure applied to values in Tables 18 and 21 with exception of deaths in cases of acute limb ischaemia. F-Female, M-Male, D-Deaths, S-Survival, p-p-value, (i/m) Q rank/number of values x false discovery rate (0.25)

Fever

The papers in which the confirmation or exclusion of fever were reported are shown in Table 26. From these papers we identified 150 patients and these are summarized (Tables 23-26).

Table 23. Analysis of fibrinogen results expressed as multiples of upper limit of laboratory reference range.

Ratio of fibrinogen level to upper limit of reference range	Value
Number of values	13
Mean	1.29 (2 d.p.)
Standard deviation	0.277 (3 d.p.)
Standard error of mean	0.077 (3 d.p.)
95% Confidence Interval	1.286 +- 0.15

Table 24. Clinical correlates of 10 highest (D-Dimer/Reference range) values.

Case	Paper	D-Dimer as multiple of reference range	Clinical presentation
1	(La Mura et al, 2020)	202	72y/o male. Parkinson's disease, vascular dementia, E. Coli sepsis with hypotension as well as COVID-19 acute Portal vein thrombosis, total occlusion of left portal venous system and branches of right portal vein
2	(La Berre et al ,2020)	69	71y/ o male, previously healthy, free – floating aortic thrombus. Thrombosis of right posterior tibial vein, pulmonary embolism
3	(harsch et al, 2020)	64.79	66y/o female bilateral pulmonary emboli. Atrial fibrillation – unclear if this was in onset, discharged
4	(Poggiali et al, 2020)	48	82y/o female, right common femoral vein DVT, acute renal failure, improved
5	(Vulliamy et al, 2020)	47	60y/o male, bilateral acute lower limbs ischaemia with no stenosis and minimal calcification, thromboembolectomy with improvement
6	(Zayet et al, 2020)	38	84y/o Male, Ischaemic stroke in multiple vascular areas, history of diabetes, hypertension, peripheral, arterial disease , atrial fibrillation, patient died
7	(Oxley et al, 2020)	27.6	44y/o male, undiagnosed diabetics, left middle artery stroke, admitted to stroke unit
8	(Morassi et al,2020)	15.5	64y/o male, acute myocardial infarct, acute renal failure, multi organ failure, mechanical ventilation , Multiple Cortical and splenic infarcts, pulmonary embolism
4	(Poggiali et al, 2020)	14	Case 4 at 3 days of heparin infusion
1	(la Mura et al, 2020)	8	Case 1 at time of portal nein thrombosis diagnosis

Table 25. Patients with fever.

Exclude and confirmed patients	Number
Number of patients where fever is excluded	59
Number of patients where fever is confirmed	91

Table 26. Studies in which the exclusion or confirmation of fever is reported.

Authors
(Fara et al, 2020)
(Zayet et al, 2020)
(Gunasakeren et al, 2020)
(Escalard et al, 2020)
(Wang et al, 2020)
(Benussi et al, 2020)
(Morassi et al, 2020)
(Yaghi et al, 2020)
(Deliwala et al, 2020)
(Valderrama et al, 2020)
(Barrios Lopez et al, 2020)
(Co et al, 2020)
(Tunc et al, 2020)
(Viguier et al, 2020)
(Oxley et al, 2020)
(Hughes et al, 2020)
(Xiao et al, 2020)
(Cai et al, 2020)
(Lacour et al, 2020)
(La Berre et al, 2020)
(Poggiali et al, 2020)
(Harsch et al, 2020)
(Beccara et al, 2020)
(Vulliamy et al, 2020)
(de Barry et al, 2020)
(Zhou et al, 2020)
(Giacomelli et al, 2020)
(Qian et al, 2020)
(Bozzani et al, 2020)
(Bouaziz et al, 2020)
(Farina et al, 2020)
(La Mura et al, 2020)
(Varga et al, 2020)
(Bianco et al, 2020)
(Chan et al, 2020)

The results show that there were 1.5 times as many patients with COVID-19 and thrombo-embolic events that were reported to have fever compared to those without fever.

Reported characteristics of thromboembolic events in COVID-19

The 56 identified papers were analyzed and a thematic analysis was undertaken relating to the clinical thromboembolic/ischaemic features reported in patients with COVID-19. The themes are summarised in Table 27.

Table 27. Percentage of papers containing comments on specified clinical features of Covid-19.

Reported clotting characteristic of Covid19	Percentage of papers reporting characteristics
No known risk factors	19.60%
Thromboembolic event despite anticoagulation/antiplatelet therapy	17.90%
High in-hospital mortality	16%
Asymptomatic prior to thromboembolic event	12.50%
Cryptogenic/Without any source of Thromboembolism	10.70%
Multiterritory stroke	7%
Rethrombosis	5.40%
Mild symptoms prior to presentation	3.60%
Minimal or no improvement after revascularisation for stroke	3.60%
No recanalisation after one pass for Stroke	3.60%
Clot fragmentation with embolisation with intervention	1.80%
Unusual location of clots	1.80%
Non-detachable residual clots	1.80%
Desert Foot	1.80%
Low rate of successful revascularisation for ALI	1.80%
Thrombosis of a graft	1.80%
Clotting of medical devices	1.80%

No known risk factors: This was the most commonly reported characteristic of thromboembolic events in COVID-19 in the papers. Escalard, et al. report on two patients under the age of 50 with developed stroke without risk factors [105]. Fara, et al. report one previously healthy 33-year old lady who developed a thrombus in the common carotid artery extending to the internal carotid artery and associated with a middle cerebral artery thrombus [106]. Wang, et al. report on two patients with stroke and no underlying medical risk factors including a patient in their 40's [107]. Gunasakeren, et al. report on a 40-year old lady without prior medical history with a large right middle cerebral artery stroke [108]. Yaghi, et al. report on several patients who developed stroke with no significant medical history including two patients in their 40's who died [109]. Barrios-Lopez, e al. found no aetiology for stroke in two of their patients apart from hypercoagulation and systemic inflammation which were assumed to be COVID-19 related [100]. Vigueir, et al. report on a 73-year old man with common carotid artery thrombosis with ischaemic stroke but no medical history or vascular risk factors [110].

Stefanini, et al. present a case series of STEMI which includes four patients between the ages of 45 and 67 with no medical risk factors [111]. Xiao, et al. present a 62-year old man with inferior wall MI but without medical risk factors [112]. Poggiali, et al. report on a 64-year old man without significant medical history who presented with a combination of deep vein thrombosis and subsegmental pulmonary embolism [101]. Diago-Gomez, et al. present a previously healthy 50-year old who developed aortic thrombosis with acute limb ischaemia, DVT and stroke and a 69-year old male with no significant medical history who developed aortic thrombosis and pulmonary embolism [113].

High in-hospital mortality: Escalard, et al. report 60% mortality in their series of ten patients with large vessel stroke [105]. Wang, et al. presents a series of five patients with stroke with an average age of 52.8 years and a mortality of 60% [107]. Benussi, et al. reports high in-hospital mortality in a COVID-19 cohort although not distinguishing between those with stroke and without [114]. Morassi, et al. report 83% mortality in their case series of six patients with stroke [115]. Yaghi, et al. compared their series of thirty two patients with COVID-19 and stroke with a control group and found an increased mortality in the COVID-19 group after adjusting for age and NIHSS score with an odds ratio of 64.87 (95% CI 4.44-987.28) [109]. Middledorp, et al. presented their findings in 199 patients with COVID-19 who were admitted to hospital [116]. They found that venous thromboembolism was associated with high mortality and calculated a hazards ratio of 2.7 (95% confidence interval 1.3-5.8).

Cui, et al. report 40% mortality in twenty patients with COVID-19 and lower limb deep vein thrombosis [117]. Bellosta, et al. report 40% mortality in their series of twenty patients with acute limb ischaemia [118]. Kaafarani, et al. report on 141 critically ill patients with COVID-19 of which there were four cases of mesenteric ischaemia and one case of hepatic necrosiss [119]. Although they do not distinguish between the ischaemia and non-ischaemic pathology in the mortality, overall they report a mortality of 40% in those requiring surgery.

Thromboembolic events despite anticoagulant or antiplatelet treatment: Escalard, et al. report in their case series that four out of ten patients with large vessel stroke were prescribed anticoagulant or antiplatelet treatment and one patient was on a combination of anticoagulant and dual antiplatelet treatment prior to the stroke [105]. Zayet, et al. report on a patient who was being treated with apixaban for atrial fibrillation and subsequently developed ischaemic stroke in multiple areas [120]. Morassi, et al. in their case series describe a patient with a previous myocardial infarct who was being treated with dual antiplatelet therapy and developed multiple ischaemic strokes and pulmonary embolism [115]. They also report a man in his 80's who was on aspirin but developed multiple ischaemic strokes and in hospital whilst receiving treatment with aspirin, clopidogrel and enoxaparin he developed another stroke. They further report on a lady in her 70's who despite treatment with aspirin and warfarin develops multiple ischaemic strokes. They report on a man in his late fifties who despite treatment with Enoxaparin develops a dural sinus thrombosis but also a cerebral haemmorhage. Barrios Lopez, et al. report on a patient who develops ischaemic stroke whilst on bemiparin (a low weight molecular heparin) and another patient with known atrial fibrillation taking acenocoumarol prior to an ischaemic stroke [100].

Lodigiani, et al. draws attention to the high rate of arterial and venous thromboembolic events in patients with COVID-19 in their study (8%) despite anticoagulant prophylaxis and they believe that the figure may be higher due to undetected cases [103]. Lacour, et al. report on a patient in his late 60's with an anterior STEMI who is started on dual antiplatelet therapy and a bolus of heparin [121]. Despite this he experienced another thrombus in the left anterior descending artery and after several interventions including IV unfractionated heparin experiences another thrombosis in the left anterior descending artery and dies. Middledorp, et al. in their cohort study reported on the development of venous thromboembolism in twenty-five patients (13% of the cohort) despite thromboprophylaxis [116].

Klok, et al. report the case of a lady in her 80's who was started on low molecular weight heparin and who went on to develop a deep vein thrombosis [122]. Giacomelli, et al. report on a 67-year old man with an aortic graft and aspirin prophylaxis who was commenced on Enoxaparin prophylaxis after admission [123]. Despite this the graft occluded and he

later died.

Asymptomatic prior to thromboembolic event: Escalard, et al. report two patients (20% of their sample) who were asymptomatic prior to large vessel stroke [105]. Wang, et al. presents a case series of five patients all of whom were normal two-and-a-half hours prior to presentation with stroke [107]. Yaghi, et al. present five patients with ischaemic stroke who were asymptomatic prior to presentation [109]. Oxley, et al. report two patients with no COVID-19 symptoms prior to presentation with large vessel stroke [124]. Stefanini, et al. presents twenty-four patients who presented with STEMI as the first clinical feature of COVID-19 [111]. Xiao, et al. report on two patients who present with sudden chest pain in the absence of other symptoms and confirmed acute myocardial infarct [112]. Lacour, et al. presents the case of a man in his sixties who is asymptomatic apart from chest pain with confirmation of myocardial infarct and is similarly asymptomatic prior to re-presenting with stent thrombosis [121].

Cryptogenic/Without any source of thromboembolism: Fara, et al. report two cases of patients without obvious sources of thromboembolism including unremarkable echocardiography and no patent foramen ovale [106]. Yaghi, et al. report cryptogenic strokes in most of their patients (21/32 (65.6%)) [109]. Valderrema, et al. report on a case of middle cerebral artery stroke with internal carotid artery thrombosis in the absence of patent foramen ovale or a cardiac embolus [125]. Barrios-Lopez, et al. could not identify any source of emboli in two patients with ischaemic stroke and determined that this was secondary to a COVID-19-induced hypercoagulable state [100]. Stefanini, et al. report in their case series that 11 (39.3%) patients did not have evidence of obstructive coronary artery disease [111]. Diago-Gomez, et al. report on four cases of aortic thrombosis without atrial fibrillation or previous pro-thrombotic disease and attributed this to a COVID-19-induced hypercoagulable state [113].

Multi-territory stroke: In their case series Escalard, et al. report that fifty-percent of the patients with COVID-19 and stroke had multi-territory stroke involving the middle cerebral artery plus posterior or anterior cerebral artery involvement [105]. Zayet, et al. describe two cases with ischaemic strokes affecting multiple vascular territories [120]. Wang, et al. report one case with both anterior and posterior circulation ischaemic stroke [107]. Morassi, et al. report multiple bilateral ischaemic strokes and suggest an embolic aetiology [115].

Rethrombosis: Escalard, et al. report four patients (40%) with reocclusion within twenty-four hours in their case series of ischaemic stroke [105]. Wang, et al. describes their experience with mechanical thrombectomy in ischaemic stroke patients with COVID-19 [107]. They report two cases in which recanalisation with a stent retriever was followed by reocclusion within minutes and which they attributed to a hypercoagulable state. Bellosta, et al. report twenty cases of acute limb ischaemia with revascularization. They identify a high rate of technical and clinical failure and attribute this to a hypercoagulable state [118].

Mild symptoms prior to initial presentation: Escalard, et al. report fifty percent of patients in their case series as presenting with mild symptoms at stroke onset [105]. Fara, et al. present one case of a lady who was coughing prior to stroke but otherwise had no symptoms [106].

Minimal or no improvement after revascularisation for stroke: Escalard, et al. reports no significant neurological improvement in any of their patients 24 hours after mechanical thrombectomy for stroke [105]. Benussi, et al. reported worse neurological outcome for COVID-19 patients with stroke compared to a control group without COVID-19 [114].

No recanalisation after one pass for stroke: The ability to recanalise an occluded blood vessel at first pass is associated with better outcome. Escalard, et al. reported an absence of first-pass effect for recanalisation in their series of ten patients with COVID-19 and ischaemic stroke [105]. Wang, et al. report an average of just under three passes with the stent-retriever to achieve recanalization [107].

Clot fragmentation with embolisation with intervention: Wang, et al. report on the fragmentation of clots with intervention in a case series of patients with ischaemic strokes [107]. They report on the intervention in one patient where aspiration was used initially with resulting embolisation from the carotid bulb thrombus distally. After using a stent-aspiration approach there was further embolisation of the thrombus into the middle cerebral artery. They report another case involving stent-aspiration of a thrombus in the internal carotid artery which embolised to the anterior cerebral artery. They report on another patient where a thrombus in the basilar artery was treated with a combination of balloon-guide catheter and aspiration resulting in embolisation to the posterior cerebral arteries. In another case they describe embolisation of fragments of a thrombus from the middle cerebral artery following stent-aspiration.The authors confirmed distant emboli in 100% of their cases. They also confirm embolisation into a different vascular territory in 40% of their cases which they contrast with a rate of 4.5% in a study involving patients without COVID-19 [126].

Unusual location of clots: Vigueir, et al. report a case of a floating thrombus in the common carotid artery [110]. They note that this is an unusual location for strokes resulting from occlusion within the cervicocephalic arteries and particularly in the absence of atheroma or dissection. They cite evidence that this location occurs in less than 1% of strokes involving the cervico-cephalic arteries [127].

Non-detachable residual clots: Bellosta, et al. describes the need for an additional surgical procedure in the treatment of acute limb ischaemia due to the occurrence of residual non-detachable clots [118].

Desert foot: Desert foot refers to the occlusion of all of the main arteries of the foot. Bellosta, et al. refers to several cases of desert foot in their case series of 20 patients with acute limb ischaemia [118].

Low rate of successful revascularisation of acute limb ischaemia: Bellosta, et al. reports a low rate of successful revascularisation in their case series of acute limb ischaemia [118]. They note that patients receiving intravenous heparin did not undergo reintervention and low oxygen saturation was significantly associated with unsuccessful revascularisation.

Thrombosis of a graft: Giacomelli, et al. report on a case of a man in his late sixties with an abdominal aortic aneurysm that had been repaired with an aortic graft six years previously [123]. At admission to hospital, the graft was patent. His overall condition deteriorated and nine days after admission, the graft was completed occluded with a thrombus and the patient died before revascularisation was possible.

Clotting of medical devices: Helms, et al. report on 150 patients with COVID-19 who were admitted to four intensive care units in France [128]. They report circuit clotting with the use of renal replacement therapy. They also report the thrombotic occlusion of the centrifugal pumps in patients receiving Extracorporeal Membrane Oxygenation (ECMO). The centrifugal pump needed replacing after between 4 and 7 days. They also report that the average lifespan of the renal replacement therapy circuit was reduced by 50%. The authors hypothesized that the occlusion of the centrifugal pumps was due to a combination of ultrafiltration and high fibrinogen levels.

Results of exploratory literature search

We screened over 12,000 references from the clinical and scientific literature as well as references from prior and successive searches. The search strategy was determined from the specified aetiology unless there was sufficient evidence from the existing material.

COVID-19 related coagulopathy aetiologies suggested in the 56 main papers

We identified 50 COVID-19 coagulopathy-related mechanisms suggested in the 56 main papers and have listed them in Table 28. Some of the mechanisms were mentioned by single authors whilst others such as a hypercoagulable state were mentioned by most of the authors (Table 28).

Table 28. Coagulopathy-related aetiologies in COVID-19 suggested in 56 main papers.

Papers related coagulopathy aetiologies in COVID-19
Coagulopathy Reacted Aetiologies Suggested in 56 Main papers
A, Hypercoagulable State
Hypercoagulability/ thrombophilia state
B. Receptor Mediated
ACE-2 Mediated pathway via Lung and binding
C. Immune mediated
1.Hyperinflammatory State
2. SIRS Mediated by IL-6
3.ARDS
4. Secondary to septic Shock
5. Sepsis- associated Disseminated Intravascular Coagulopathy
6. Cytokine storm/ Cytokine
7. Immune-mediated hyperviscosity
8. Neutrophil extracellular traps
9. Sepsis induced coagulopathy
10. Immunothrombosis Hypothesis
11. Thromboinflammation/thrombogenesis
12. Systemic Inflammation with plaque disruption
13. Lymphopenia
D. SARS-Like Mechanism
E. Direct Invasion of Tissue
1. Central Nervous System
a. Direct Virus nervous system injury
2. Cardiovascular
a. Cardio embolism 2nd to cardiac injury
b. Secondary to cardiogenic shock
c. Cardiovascular compromise
d. Myocarditis due to direct infection
3. Gastrointestinal
a. Viral enteroneuropathy
4. Respiratory
a. Respiratory pathology
b. Respiratory failure leading to myocardial mismatch perfusion
5. Endothelial
a. Microangiopathy leading to ischaemia
b. Endotheliatis
c. Endothelial Dysfunction
d. Vasculitis or Vasculitis- like mechanisms
e. SARS-CoV-2-induced small-vessel thrombosis
E. Iatrogenic
1. Pharmacological Adverse events
2. Mechanical Ventilation
F. Immune-mediated syndromes
1. Antiphospholipid syndrome
2. Type-1 interferonopathy
G. general Factor
1. Critical illness-related encephalopathy
2. Hypertension
3. Hypertension
4. Lymphokenia
5. Atrial Fibrillation
6. Immobilisation / bed rest
7. Hypoxia/ hypoxia with vasoconstriction
8. Stress cardiomyopathy
9. Dehydration due to fever, diarrhoea
10. Metabolic/ Electrolyte Distribution
11. Low platelet count
12. Plaques unstable due to mononuclear infiltrates, hypoxia
H. Secondary Infection
1. Septic embolization with bacterial superinfection
2. Secondary bacterial and fungal infection
3. Stroke risk with infection
I. Autopsy/ Biopsy Finding related Mechanisms
1. Pyrotosis
2. Apoptosis

Hypercoagulable/Thrombophilic state: In most of the main papers, the authors suggest that the coagulopathy results from a hypercoagulable state. Also termed a thrombophilic state, the hypercoagulable state is one which there is an increased likelihood of clotting or else a severe clotting response [129]. In this section we treat this primarily as resulting from a change in the components of the blood although more general properties such as viscosity are considered in other sections.

Many studies have reported on the haematological, biochemical and immune parameters in COVID-19. Henry, et al. in their meta-analysis examined 21 studies (n=3377), identifying 27 altered laboratory values in severe or fatal COVID-19 [130]. These included elevated prothrombin time, elevated D-Dimer, elevated CRP, IL-6 and myoglobin, cardiac troponin I and decreased platelet count. In a meta-analysis of coagulation dysfunction in COVID-19 (Jin et al, 2020) analyzed 22 studies (n=4889) and found higher D-Dimer levels and prolonged prothrombin time in patients with more severe COVID-19. Non-survivors were more likely to have higher D-Dimer levels, decreased platelet count and increased prothrombin time compared to survivors.

Di Minno, et al. completed a meta-analysis looking at sixty subjects with 5487 patients with severe COVID-19 and 9670 patients with mild COVID-19 [131]. They also found evidence of higher D-Dimer levels in non-survivors compared to survivors while non-survivors had lower platelet levels. In another meta-analysis of patients with COVID19, 34 studies were included (n=6492) [132]. They found that patients with severe COVID-19 had lower platelet count, higher D-Dimer levels, higher fibrinogen, longer prothrombin time and shorter activated partial thromboplastin time. Again non-survivors were more likely to have higher D-Dimer levels. Ibañez, et al. found evidence of elevated D-Dimers and hypofibrinolysis in a prospective cohort study with COVID-19 in an ICU setting and suggest that the lungs are the source of the elevated D-Dimers [133].

Receptor-Mediated-ACE-2 receptor-mediated pathways: Siddamreddy, et al. suggests that SARS-CoV-2 can cause myocardial injury via the ACE-2 receptor [134]. Ciaglia, et al. suggests that a reduced expression of ACE-2 receptors in older adults may increase susceptibility to more severe COVID-19 [135].

The Renin-Angiotensin System (RAS) plays a central role in fluid homeostasis. There are a number of molecules, receptors and enzymes involved in the RAS (Figure 9). One of the key functions is the tonic

control of blood pressure which can be contrasted with the actions of the baroreceptors which drive changes more rapidly. Aldosterone release is an end-result of the action of Angiotensin II on the AT1 receptor which causes the retention of sodium in exchange for potassium. In hyperaldosteronism there is elevated blood pressure with hypokalaemia (Figure 9).

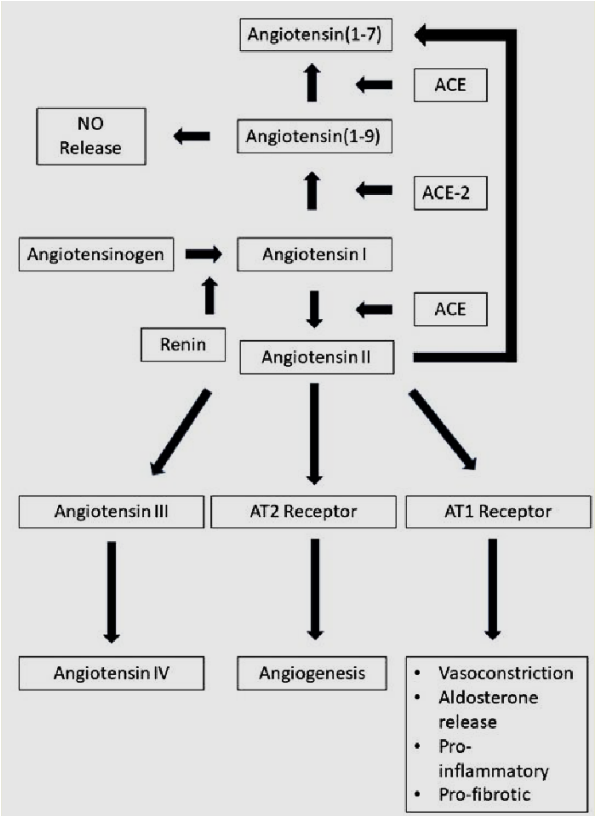

Figure 9. Overview of Renin-Angiotensin-Aldosterone System (RAAS). **Note:** (▬) Vasoconstriction; (▬) Aldosterone release; (▬) Pro-inflammatory; (▬) Pro-fibrotic.

Miesbach describes a reduction in ACE-2 receptors with SARS-CoV-2 infection and cites evidence of increased Angiotensin II levels in patients with COVID-19 [136]. Further outlines the mechanisms by which an increase in Angiotensin II levels could predispose to coagulation. Draws attention to the role of Angiotensin II in promoting smooth muscle cell proliferation which can contribute to atherosclerotic plaques, that Angiotensin II promotes the expression of Tissue Factor which in turn initiates coagulation and also promotes the expression and release of Plasminogen Activator Inhibitor-1 (PAI-1) which in turn inhibits fibrinolysis and promotes thrombus formation [136]. Senchenkova, et al. provides evidence of a role for IL-6 and T-Cells in Angiotensin II-induced thrombo-inflammation [137]. Spillert, et al. demonstrated an in-vitro procoagulant effect of Angiotensin II using a modified recalcification time test [138]. Lamas-Barreiro, et al. note that the relationship between ACE-2 receptor activity and angiotensin II levels varies between organs [139]. Bryson, et al. has in a model shown a protective effect from Angiotensin II-induced hypertension through antagonism of a prostaglandin receptor [140]. Prostaglandins can inhibit platelet aggregation and it has been suggested that Eicosanoids such as prostaglandins may play a key role in COVID-19 [141,142].

Nguyen, et al. Suggest that Angiotensin II's actions may be mediated in part through reactive oxygen species (ROS) signaling [143]. The evidence for a more ubiquitous presence of RAS is outlined by [144]. Veras, et al. found evidence of ACE-2 receptor and serine protease involvement in activation of NET's [145]. Fang and Schmaier review the role of the MAS receptor and the relationship between kallikrein/kinin and the RAA system in thrombosis [146].

In terms of ACE-2 receptors, a NICE review found no evidence to suggest that ACE-inhibitors or Angiotensin Receptor Blockers either increased the risk of contracting COVID-19 or else lead to a more severe manifestation of COVID-19 [147].

In their case study, Wang et al. report their findings in a man with COVID-19, ARDS and septic shock who experienced a marked response to the administration of angiotensin II [148]. The authors discuss these findings whilst noting that a similar response has been found in non-COVID-19-related sepsis. Liu, et al. found elevated plasma angiotensin II levels in patients with severe COVID-19 compared to a control group with COVID-19 [149].

Garvin, et al. analyzed gene expression data from bronchial lavage specimens in patients with COVID-19 and used the Summit supercomputer to analyze the results [150]. Their findings support the role of a bradykinin storm, an amplifying circuit of bradykinin production in response to the infection and mediated by RAS. They also found that the levels of hyaluronic acid were elevated and note that hyaluronic acid is associated with thrombosis. They suggest that the hyaluronic acid produces a gel in the lungs which interferes with the oxygenation of blood and thereby predisposes to hypoxaemia. Garvin, et al. looked at mRNA levels and found a reduction in ACE mRNA expression as well as an upregulation in ACE2 mRNA expression which may be expected to reduce the production of Angiotensin II [150]. The mRNA levels do not necessarily correlate strongly with protein levels. The correlation between mRNA expression and protein levels (R2) was 0.4 across species in one study [151]. This would suggest that the protein levels should be measured in preference to the mRNA or else in conjunction with this as de Sousa, et al. suggest that as much as 70% of the variance between mRNA and protein levels is accounted for by a combination of measurement accuracy and post-translation factors such as protein degradation [151].

Kusadasi, et al. also note the inter-relationship of the Renin-Aldosterone-Angiotensin system, complement system, Kinin-Kallekrein system and coagulation system as well as the relationship to ACE-2 while Urwyler, et al. report their initial findings with the use of Conestat Alfa In COVID-19, which targets the Kallikrein-Kinin system [152,153]. Curran, et al. provides a model of pathology in COVID-19 involving a number of systems including the RAAS system and suggests that COVID-19 disrupts regulatory networks [154]. Wiese, et al. hypothesise that pathology in COVID-19 arises from an upregulation of the classical arm of the RAS pathway and a downregulation of the 'protective arm' of the RAS pathway [155]. Czick, et al. suggests a role for RAS imbalance in multiple aspects of COVID-19 [156].

Akoumianakis, et al. note the relationship between obesity and dysregulation of the RAAS axis as well as myocardial and lung injury and suggest that this relationship may be relevant in COVID-19 [157]. In the Dyhor-19 Study Villard, et al. demonstrates a correlation between CRP and Aldosterone levels and COVID-19 severity [158]. Dudoignon, et al. found that half of patients with COVID-19 and ARDS had acute kidney injury and this was significantly associated with activation of the RAAS with patients having high levels or renin and aldosterone on admission [159].

Santamarina, et al. provide evidence of ventilation/perfusion (V/Q) mismatch in the lungs and draw attention to two findings-well perfused areas of damaged lung and poorly perfused areas of healthy lung [160]. They suggest this may explain the benefit of the proning position in patients with COVID-19 and ARDS. To partially explain this they suggest that Angiotensin II in COVID-19 results in vasoconstriction in the lungs and disrupts the ventilation/perfusion matching resulting in areas of healthy lung that are well perfused. Lang, et al. found evidence of pulmonary perfusion abnormalities in COVID-19 which supports the notion of disrupted perfusion/ventilation matching in COVID-19 secondary to RAA system disruption [161].

Sepsis related

SIRS via IL-6: Valderrema, et al. suggest the septic inflammatory response syndrome (SIRS) mediated by IL-6 as one of the mechanisms that predisposes to ischaemic stroke in COVID-19 [125]. Barrios Lopez, et al. cites evidence that severe inflammation occurs during the acute phase of COVID-19 [100]. The difference between sepsis and SIRS is one of organ

dysfunction and a dysregulated immune response in sepsis in contrast with SIRS. If we consider a thromboembolic event then organ dysfunction is a function of the location of the event. The key question is whether there is a dysregulated immune response and in asking this question it can be argued that SIRS cannot lead to a clotting event as this cannot be considered a healthy response. The new sepsis consensus definition has removed the construct of SIRS, although there is an argument for the utility of SIRS [162]. We will not consider this further although we will add a section for IL-6 separately below. Also we consider septic shock on the continuum with sepsis and refer back to the introduction for discussion of the procoagulant mechanisms including DIC.

IL-6: The suggestion of a key role for IL-6 in COVID-19 pathology is a basis for the recommendation for trialling IL-6-related therapies in COVID-19 [163]. Kuppalli and Rasmussen suggest a potentially important role for IL-6 in the host response to SARS-CoV-2 and cite evidence for a reduced type-1 helper T-cell (Th1) antiviral response [164]. However Leisman, et al. as well as Sinha, et al. outline the evidence against a central role for IL-6 in COVID-19 [165,166].

Liu, et al. found a correlation between IL-6 levels and disease severity [167]. Luo, et al. found a correlation between both IL-6 levels and CD8+ T cell counts and mortality [168]. Zhao, et al. found IL-6 to be elevated in the later stages of severe COVID-19 but found that RANTES, a chemokine, was elevated earlier in the course of illness [169]. Mansouri, et al. present a case of COVID-19 in which IL-6 and other parameters normalised after treatment with Colchicine and this was accompanied by a rapid improvement in presentation [170].

In a prospective comparative study compared the immune responses of patients with COVID-19, influenza or bacterial sepsis [171]. They found that in COVID-19 there was a more marked deterioration and they attributed this to immune dysregulation. This immune dysregulation was characterised by a disruption in antigen-presentation combined with lymphopenia but with monocytes producing IL-6 and TNF-α. IL-6 was elevated in patients with immune dysregulation. Immune dysregulation was characterised by a number of factors including absolute numbers of molecules of human leukocyte antigen on CD14 monocytes.

Varhana and Wolchok review the evidence for the immune response in COVID-19 and identify an accentuated innate immune response which results in elevated IL-6 levels [172]. They suggest that a cytokine response syndrome could mediate pathology in COVID-19 while distinguishing the typical description of the cytokine response syndrome and the features of COVID-19. They also identify a reduced adaptive response with T-cell exhaustion.

Gubernatorova, et al. suggest a key role for IL-6 in COVID-19 and provide a detailed review of the evidence [173]. They note that IL-6 has properties which both promote and counter viral infections. Chatterjee, et al. 2020 suggest that elevated IL-6 and hypoxia in COVID-19 could both lead to a reduction in Protein S and subsequent coagulopathy [174]. In the non-COVID-19 literature demonstrated an association between IL-6 levels and size of infarcts in ischaemic strokes [175].

Cytokine storm: Many of the authors in the 56 main papers have suggested that a COVID-19-related cytokine storm mediates the COVID-19-related coagulopathy. Yaghi, et al. 2020 cite evidence of cytokine storm association with COVID-19 [109,176]. Jain, et al. 2020 suggests that a subset of patients with COVID-19 may have a cytokine storm [100]. Barrios-Lopez, et al. again suggests that a small subset of patients with COVID-19 may experience a cytokine storm and cite evidence that this is associated with high mortality [177,178].

The cytokine storm is a dysregulated elevation of cytokines that results in pathology. Tisoncik, et al. outlines the three main types of resulting pathology-endothelial dysfunction, pulmonary fibrosis and inflammatory responses and note that the lung injury can progress to ARDS [179]. They also note a number of viruses associated with a cytokine storm in a number of the early descriptions (Table 29).

Table 29. Infectious agents associated with cytokine storm response adapted from (Tisoncik et al).

Cytokine storm
Cytomegalovirus
Epstein-Barr virus-associated hemophagocytic lymphohistiocytosis
Group A streptococcus
Influenza virus
Variola virus
SARS-CoV

Shimizu outlines the features of the cytokine storm syndromes including those resulting from IFN-γ, TNF, IL-6, IL-1β and IL-18 and note the features of cytokine storm syndrome including fever, hepatomegaly and splenomegaly [180]. Van der Poll, et al. notes the procoagulant effects of IL-1, IL-2, IL-6, IL-12 and TNF [181].

Barnes, et al. provides an overview of the elevated cytokines in COVID-19 with reference to the literature (see Table 30 but also the earlier section on IL-6) [182]. Coperchini, et al. provides an overview of the cytokine storm in COVID-19. They suggest that ARDS in COVID-19 results from a cytokine storm [183]. Manjili, et al. makes a case for COVID-19 as an acute inflammatory disease and provide evidence of an association between elevated cytokine levels and more severe illness (Table 30) [184].

Table 30. Elevated cytokines in COVID-19 (Barnes et al).

Elevated cytokines
IL-1 Beta
IL-2
IL-6
IL-7
IL-8
IL-10
IFN-Gamma
IFN-inducible protein 10
Monocyte Chemoattractant protein 1
G-CSF
Macrophage inflammatory protein 1- alpha
TNF-alpha

Immune-mediated hyperviscosity: Valderrema, et al. suggests the IL-6 immune mediated response as mediating hyper-viscosity and cite evidence for this [125,176]. Hyperviscosity in turn can increase the risk of stroke. Waldenström macroglobulinemia represents an example of an immune-mediated plasma hyperviscosity resulting from elevated levels of IgM although there is evidence for a role for IL-6 [185,186]. Maier, et al. found evidence of hyperviscosity in COVID-19 but were not clear on what caused this although suggesting fibrinogen [187].

Immunothrombosis hypothesis/thromboinflammation/hyperinflammation: Valderrema, et al. suggests an immune-mediated thrombogenic mechanism as do who in turn cite [105,125,188]. Klok, et al. suggests thromboinflammation as a mediator of coagulopathy and in turn cite who review the evidence for this [102,189]. Connors and Levy cite evidence for a strong correlation between IL-6 and fibrinogen in COVID-19 [189].

The immunothrombosis hypothesis is at the simplest level a restatement of the inflammatory theory of thrombosis promoted by Cruvielhier. Schattner, et al. note the origin of the term thromboinflammation in 1994 to describe arterial stent restenosis-related platetet-neutrophil interactions [190]. In a key paper in the modern restatement of the immunothrombosis hypothesis Nieswandt et al. postulate a thrombotic cascade leading to ischaemic

stroke. They suggest the thrombotic cascade begins when the platelet Gp1 receptor binds to von Willebrand factor released from granules in the endothelium after vessel wall injury. This binding is transient and slows down the platelets so that Gp6 can bind with collagen at the site of the vessel wall injury. Following this there is upregulation of integrin receptors which facilitate platetet aggregation. The Gp6 also activates Factor XII leading both to the coagulation cascade and also the activation of the kallikreinkinin system leading to inflammation and to the end-product bradykinin. There is evidence that the Gp1-VWF-Gp6 pathway is not involved in acute ischaemic stroke injury however and instead it has been suggested that this is mediated by interactions with a damaged vessel wall [192].

Mitchell discusses the role of thrombin in thromboinflammation, driving the coagulation cascade and the immune system and activating leucocytes and other cells to release cytokines [70]. Bray, et al. discuss a potential role for thromboinflammation in microvascular thrombosis [193]. They note a vast increase in shear stress in the arterioles compared to the venules sufficient to impact on the dynamics of blood flow as well as endothelial cell morphology.

Platelets interact with a number of immune cells including neutrophils, leucocytes, monocytes and macrophages in a diverse range of immune-related functions [194]. Platelets contain α-granules with a variety of over 300 proteins, lysosomes containing proteolytic enzymes and dense granules containing molecules including serotonin, calcium and magnesium which mediate platelet activation [195]. Guo and Rondina distinguish between immunohemostasis (trapping pathogens with a combination of coagulation and inflammation and involving blood vessel injury without pathology) and thromboinflammation (vasculature-based pathological responses in response to infectious and immune triggers) [196]. Guo and Rondina associate thromboinflammation with DIC, viraemia, stroke, DVT and myocardial infarct [196]. There are a number of diseases where thromboinflammation has been suggested to play a significant role including Behçet's syndrome and delayed ischaemia after cerebral haemmorhage [197,198].

Thromboinflammation has been suggested as a mechanism which mediates the effects of snake venoms [199]. The relationship between platelets and complement are outlined [200]. The role of platelets in mediating thromboinflammation in myeloproliferative disorders is examined [201]. Senchenkova, et al. provide evidence that IL-6 mediates angiotensin-II mediated thrombosis and that IL-6 potentiates platelets to activate Gp6 receptors [137]. There has been a suggestion that the von Willebrand Factor/ADAMTS13 axis plays a pivotal role in thromboinflammation and has been a focus for exploring therapeutic interventions [202]. There is evidence that endothelial cell-derived von Willebrand factor plays a role in post-ischaemic stroke related thrombinflammation [203]. The lectin pathway has also been suggested to play a role in thromboinflammation [204]. Jayarangaiah, et al. presents a thromboinflammatory model of COVID-19-related coagulopathy [205].

We note however that Webb, et al. have proposed and validated criteria for a COVID-19-related hyperinflammatory syndrome which we consider as a broader category including thromboinflammation [206]. Lima, et al. report a case of hemophagocytic syndrome in which there was a hyperinflammatory response with macrophage activation [207]. Cole, et al. suggests that low grade inflammation with diabetes and adipose tissue dysfunction in obesity is vulnerability in people who develop COVID-19 [208]. Giamerellos, et al. found evidence of two types of hyperinflammatory response in COVID-19 with severe respiratory failure-immune dysregulation and macrophage activation syndrome [171]. They found that IL-6 results in immune dysregulation with monocytes producing excessive inflammatory cytokines and also resulting in CD4 lymphopenia and B-cell lymphopenia. They also found that IL-6 elevation was associated with a reduction in CD14 monocyte HLA-DR expression and that the HLA-DR expression increased in convalescence. They also found that IL-1α levels increased and resulted in macrophage activation syndrome.

Systemic inflammation with plaque disruption: Morassi, et al. discusses the association between sepsis and rupture of plaques [115]. In the pre-pandemic literature Maillet, et al. present a case of infective aortitis [209]. The case is characterised by a bacterial infection of the aortic intima which is an unusual location. The authors suggest that the atherosclerotic plaques may have resulted in a vulnerability to aortic infection enabling direct seeding or alternatively that the bacteria infiltrated via the vasa vasorum. The case demonstrates a possible relationship between arterial pathology and susceptibility to infection of the vessel wall which is relevant to the question of SARS-CoV-2 and vascular pathology. However we would group this under both secondary infection and vulnerabilities in COVID-19.

Neutrophil extracellular traps: Escalard, et al. suggest Neutrophil Extracellular Traps (NETs) as one possible explanation for the absence of reperfusion with recanalisation in their case series of thrombectomy for ischaemic stroke [105]. They reference Barnes, et al. and Varga, et al in relation to the combination of NETs and endothelial involvement [182,188]. Varga, et al. identified widespread endothelial involvement together with neutrophil as well as mononuclear infiltration of a large arterial vessel in COVID-19 [188]. Barnes, et al. presents the case for NETs as a driver of the pathology in COVID-19 [182]. NETs are a mechanism by which neutrophils eject intracellular material including DNA and enzymes such as neutrophil elastase which form an extracellular web which can destroy pathogens but can also cause collateral damage to other cells.

Barnes, et al. cite evidence for more severe disease with both neutrophilia and a high neutrophil-to-lymphocyte ratio and suggest that neutrophilia may be relevant to the role of NETs [182]. They cite evidence of the relationship between NETs and ARDS, the regulation of neutrophils by cytokines and the relevance to the cytokine storm, NET-mediated thrombosis and a similarity between the mucous production in the airways in both COVID-19 and Cystic Fibrosis for which they cite evidence of NET involvement in the latter.

Zuo, et al. found evidence of NETosis in patients with COVID-19 in a hospital setting while Cicco, et al. suggest NETs and Damage-Associated Molecular Patterns (DAMPs) as potential treatment targets [210,211]. Radermecker, et al. found evidence of NETs in the airways, interstitium and vascular spaces in the lungs in COVID-19 postmortems cases (n=4) [212]. Middleton, et al. provide evidence of NETs triggering thromboinflammation in COVID-19 in a prospective cohort study while Beswick, et al. find a role for NETs in ARDS-associated thromboinflammation in COVID-19 [211,213]. Wang, et al. identified a correlation between neutrophil activation in 55 patients with COVID-19 and 17 NET-associated genes [212]. Leppkes, et al. found evidence of pulmonary microvessel occlusion with NETs [214]. Tomar, et al. suggests NETs as a source of necroinflammation leading to endothelial cell death and promoting thrombosis [215].

Liu, et al. found that Neutrophil-to-Lymphocyte Ratio (NLR) was prognostic for critical illness in COVID-19 in their prospective cohort study (n=61) [216]. Using a cut-off of NLR of 3.13 they found that 50% of patients aged over 50 with an NLR>3.13 developed critical illness. Lian, et al. demonstrated prognostic significance of the neutrophil-to-lymphocyte ratio [217]. Moutchia, et al. found four predictors of a more severe course of COVID-19: high markers of innate immunity (e.g neutrophils, neutrophil-to-lymphocyte ratio), low markers of adaptive immunity (e.g. lymphocytes), high markers of tissue and organ damage (e.g. LDH and markers of renal function) [218].

SARS like mechanisms: Deliwala, et al. note a similarity between infections with SARS and SARS-CoV-2 [219]. They note a common association with stroke and that the SARS viral load plays a role in the SARS-related coagulopathy and endothelial dysfunction. SARS is a useful model for COVID-19 as it is similar to SARS-CoV-2, the clinical features of SARS infection have an overlap with COVID-19 and there is a body of research on SARS. The number of papers on COVID-19 including pre-prints however exceeds that of SARS. Additionally a number of clinical features in SARS are less clear as the overall number of cases was smaller than in COVID-19.

Both ACE-2 and TMPRSS2 are required for the entry of both SARS and SARS-CoV-2 [220]. Franks and Galvin review the evidence on SARS and note that watery diarrhoea occurs in 70% of cases and fibrin thrombi may also be present [213]. Cleri, et al. provides an overview of the clinical presentation of SARS [222]. Singh, et al. describe a case of SARS without the typical findings and reference evidence that SARS presentations range from asymptomatic to severe and fatal [223]. Wan, et al. found evidence of a correlation between radiographic lung lesions and clinical presentation [224].

Zarhariadis, et al. demonstrated coinfection in SARS [225]. Ng, et al. report a case of pulmonary artery thrombosis and cite the evidence for both pulmonary emboli and deep vein thrombosis in SARS [226]. Chen, et al. found evidence of a history of stroke, hypertension and diabetes in patients who developed ARDS in SARS [227]. Wei, et al. found evidence of thyroid involvement in SARS [224]. Vijayanand, et al. review the evidence of SARS and identify a number of factors associated with worse prognosis including older age, lymphopenia, high peak LDH and comorbid conditions [228].

Ding, et al. report on an autopsy series in SARS and find localised fibrinoid necrosis and small vein thrombosis [229]. Mazzulli, et al. found evidence of SARS-CoV in lung tissue in post-mortem and also found a relationship between viral load and duration of illness [230]. Farcas, et al. reported on the autopsy findings in people with SARS finding a distribution of virus in the lungs in 100% of cases, in the bowel in 73% of cases, the liver in 41% of cases and the kidneys in 38% of cases with the highest viral loads being in the lungs and bowel respectively [231]. Hwang, et al. reported on an autopsy series of 20 patients with SARS and found evidence of damage to the vascular endothelium of small and medium pulmonary vessels as well as vascular fibrin thrombi with pulmonary infarcts [232]. Gu and Korteweg review the pathology and pathogenesis of SARS [233].

Frieman and Baric review the mechanisms of severe acute respiratory syndrome pathogenesis and innate immunomodulation [234]. Gralinski, et al. suggests SARS pathogenesis as predominantly immune-mediated in their review of the role of the complement pathway [235]. Chen et al. identified the course of the haematological parameters in SARS [227]. McBride and Fielding provide an overview of the role of the accessory proteins in SARS pathogenesis [236]. Venkataraman and Frieman review the evidence for the role of epidermal growth factor receptor signaling in pulmonary fibrosis in SARS [237].

The mechanisms of evasion of the immune system are outlined [238]. Jones, et al. identified prolonged dysregulation of the cytokine response in patients who had experienced SARS [239]. Tan, et al. outline the evidence for apoptosis and necrosis induced by SARS and also identifies three of the accessory proteins which lead to apoptosis [240]. Lau and Peiris suggest a lack of a type-1 interferon response in SARS and note that lymphopenia with a decrease in both CD4+ and CD8+ T-cells is a common occurrence [241]. Nicholls, et al. suggested similarities between SARS and H5N1 with haemophagocytosis possibly related to cytokine dysregulation and lymphopenia together with white-pulp atrophy of the spleen [242]. van den Brand, et al. review the pathogenesis of SARS in this paper and comment on the role of immunosenescence to account for the vulnerability of the older adult population [243]. Totura and Baric review the role of the innate immune system in response to SARS COV pathogenesis [244]. Thiel and Weber review the interferon and cytokine responses to SARS-coronavirus infection [245].

Direct invasion of tissues

Central nervous system:

Direct virus nervous system injury: In the 56 main papers Morassi, et al. note encephalopathy preceding stroke and could not exclude direct CNS invasion as a possibility [115]. Valderrama, et al. also suggest the possibility of direct CNS invasion in relation to neurological involvement in COVID-19 [125].

Kishfy, et al. report on a case of Posterior Reversible Encephalopathy Syndrome and suggest direct endothelial involvement [246]. Agagholi, et al. cites evidence of encephalitis, meningoencphelitis and detection of SARS-CoV-2 in the CSF [247]. In their review of the literature Ellul, et al. report evidence of encephalopathy, encephalitis, meningoencephalitis and disseminated encephalomyelitis in COVID-19 [248]. They also discuss the possibility of a trans-olfactory route into the central nervous system. Ashraf, et al. report two cases of seizures with COVID-19 and draw attention to evidence in other research of SARS-CoV-2 inclusions in nervous tissue samples [249].

The question arises of whether a direct invasion of the nervous system is responsible for strokes or else there are other factors including those relating to coagulopathy which are responsible. In the 56 main papers, we identified a number of cases with thrombi, sometimes extensive, arising in the carotid arteries and typically involving the middle cerebral arteries and being sufficient to account for the strokes. The role of direct invasion of the tissue has played a role in ischaemic damage in a case of necrotising encephalopathy Poyiadji, et al. and so this is a mediator for ischaemic damage but significantly less so than ischaemic stroke resulting from thromboembolism in the large vessels [250]. Indeed Kato, et al. in their comparison of neurological manifestations of SARS-CoV-2 with MERS and SARS suggest that strokes in COVID-19 most likely result from a combination of a hypercoagulable state and endothelial dysfunction [251]. Nevertheless the findings of Morassi, et al. raise the possibility of direct CNS invasion predisposing to stroke risk [115].

Cardiovascular

Direct invasion of the myocardium: Valderrama, et al. suggested that SARS-CoV-2 may directly invade the myocardium and lead to cardiac thrombi, atrial tachyarrythmias and ACE-2 receptor-mediated mechanisms [125]. A recent study identified abnormalities in 55% of echocardiograms of 667 patients supporting the notion of cardiac involvement in COVID-19 [252]. Momtaz-manesh, et al. provides strong evidence of myocardial involvement in COVID-19 in their systematic review and meta-analysis [253]. Hendren, et al. describe a COVID-19 related acute cardiovascular syndrome which can include acute coronary syndrome (STEMI or NSTEMI), acute myocardial injury without obstructive coronary artery disease, arrhythmias, and heart failure with or without cardiogenic shock, pericardial effusion with or without tamponade and thromboembolic complications [254].

Secondary effects on the myocardium-stress cardiomyopathy:

Yaghi, et al. have proposed stress cardiomyopathy as a potential mediator of coagulopathy in COVID-19 [109]. In stress cardiomyopathy, physical or emotional stressors place additional demands on the heart leading to a cardiomyopathy. Sattar, et al. report a case of COVID-19 presenting with Takotsubo Cardiomyopathy with atrial fibrillation [255]. Jabri, et al. report a significant increase in presentations of stress cardiomyopathy in patients compared to the pre-pandemic period [256]. As with atrial fibrillation, the additional stresses placed on the heart may be a marker of the critically unwell state of a patient and so this can also be considered under the heading of general factors. Okura reviews the diagnostic criteria for Takotsubo Syndrome and the occurrence in COVID-19. In the non-COVID-19 literature El-Battrawy, et al. found no difference in the rate of thromboembolic events including stroke between recurrent and non-recurrent Takotsubo Syndrome groups although finding an incidence of between 1.32 and 3.3% [257,258].

Cardioembolism 2nd to cardiac injury: In the 56 main papers, there was evidence of cardiac thrombi with a left ventricular thrombus being described [259]. Other authors have similarly identified cardiac thrombi in patients with COVID-19. Soltani and Mansour report a highly unusual case of COVID-19 presenting with biventricular thrombi [260]. Sethi, et al. report a case of clot-in-transit in the right ventricle and describe the implications for the pulmonary embolism response team [261]. Horowitz, et al. reports another case of clot-in-transit in the right ventricle in a proned patient with ARDS [262]. Sulemane, et al. report a case of pulmonary embolus with intramural right ventricular thrombus [263]. Although this is evidence of

cardiac thrombi this does not differentiate between an in-situ origin resulting from myocardial invasion or else an embolic origin.

Secondary to cardiogenic shock: Barrios-Lopez, et al. suggest cardiogenic shock in COVID-19 as a potential mediator of ischaemic stroke [100]. In their systematic review, Shafi, et al. provide evidence of cardiogenic shock in COVID-19. They cite evidence both of an association with high mortality and also with direct SARS-CoV-2 invasion of the myocardium [264].

Warkentin and Pai suggest 'shock liver' as a mediator for disseminated intravascular coagulation occurring with cardiogenic shock [265]. Akkus, et al. found evidence of increased plasminogen activator inhibitor-1 (PAI-1) in patients with cardiogenic shock after myocardial infarct [266]. Schiessler, et al.report their findings in shock-associated coagulopathy in a group of patients receiving mechanical circulatory support and heart transplantation [267]. Hanaki, et al. report increased levels of leucotoxin in two patients with infective endocarditis and cardiogenic shock [268]. Egbring, et al. investigated infection-related cardiogenic shock and identify proteinase inhibitor complexes as an important mediator and discuss the diagnostic and therapeutic implications [269].

Cardiovascular compromise: Cardiovascular compromise is a broad term which encompasses much pathology with the potential for coagulopathy including cardiogenic shock and myocardial involvement. Bansal mentions altered myocardial demand-supply ratio in a review of cardiovascular disease and COVID-19 in addition to other pathologies which impact on cardiovascular function [270]. At present we would consider this as a broad category meriting further characterization.

Myocarditis due to direct infection: Stefanini, et al. reported 11/28 cases of STEMI in which no culprit lesion was found and suggested a number of mediating mechanisms including myocarditis resulting from SARS-CoV-2 infection [111]. Myocarditis has been reported as an important feature of COVID-19 early in the pandemic (Inciardi et al, 2020). Shafi, et al. review the evidence for COVID-19 associated myocarditis in their paper [264].

Antoniak, et al. provide evidence that viral myocarditis is associated with a hypercoagulable state and that this is associated with expression of tissue factor in the myocardium [271]. Pickens and Catterall describe a case of disseminated intravascular coagulation and myocarditis with Mycoplasma pneumoniae infection lending evidence to the association of viral myocarditis with a coagulopathy although this does not discount the involvement of other mechanisms described here [272]. Chimenti et al. report on a case of infarct-like myocarditis resulting from Epstein-Barr virus [273]. Salacki and Wysokiński report on a case of acute myocardial ischaemia associated with myocarditis and antiphospholipid syndrome [274]. There is an established literature on Chagas disease which is divided into acute and chronic phases and can lead to a coagulopathy [275].

Gastrointestinal

Viral enteroneuropathy: Kaafarani, et al. suggests viral enteroneuropathy as a possible mediator of the GI pathology they have described [119]. However their case series encompasses different groups of pathology including disorders of gastrointestinal motility as well as mesenteric ischaemia. In the cited reference Wells, et al. enteroneuropathy is suggested as a mediator for pseudo-obstruction [276].

Bostancıklıoğlu suggests that various pathways between the gut and the central nervous system that could mediate spread of SARS-CoV-2 [277]. Briguglio, et al. discuss the potential role of the vagus nerve in transmitting infection from the enteric nervous system to the central nervous system whilst also noting that the physical barriers as well as the gut-associated lymphoid tissue afford protection to the enteric nervous system [278]. Nevertheless just as with the ischaemic strokes, the authors in the 56 main papers provided evidence of thromboembolic events in the splanchnic arteries which could account for the events including small bowel necrosis. In summary, viral enteroneuropathy may be more relevant to gastric dysmotility rather than mesenteric ischaemia.

Respiratory

Respiratory pathology: This term is broad and we will refer to this as requiring further characterisation.

Respiratory failure and hypoxia leading to myocardial injury: Siddameddy et al. report a case of STEMI with COVID-19 and suggest that respiratory failure with hypoxia can lead to myocardial injury [134]. As per Pascuale and Coleman, the myocardium is metabolically flexible although the association between hypoxia and cardiac arrest is well characterised [279,280]. Raad, et al. investigated the pattern of cardiac injury in patients with COVID-19 and in their discussion suggest a number of factors that may lead to myocardial infarct type II in COVID-19 including hypoxia [281]. Myocardial infarct can lead to complications including Atrial Fibrillation Gorenek and Kudaiberdieva which in turn predisposes to thromboembolism [282].

Hypoxaemia which can lead to hypoxia is a characterising feature of ARDS and many of the 56 main papers identified in our review provide examples of patients with COVID-9 and ARDS. Raad, et al. therefore provide indirect evidence of COVID-19 leading to hypoxia which in turn leads to myocardial damage as they identify evidence of an association between ARDS and myocardial injury expressed as high-sensitivity Troponin T levels [281].

Hypoxaemia/hypoxia with vasoconstriction: Many of the authors in the main paper comment on the significance of hypoxia in relation to the COVID-19 related coagulopathy. Jain, et al. describes cases of hypoxia in their retrospective cohort study [283]. Meza, et al. suggests hypoxia as one of many putative mediators of stroke in COVID-19 [284]. Helms et al. suggest hypoxia as a mediator of increased stroke risk and provide evidence of the increased thrombosis seen in ARDS [128]. ARDS is one of the most relevant examples of a COVID-19-related hypoxaemic state although the multitude of pathologies in the critically ill patient can complicate the interpretation. Helms et al. suggest a number of mechanisms by which hypoxia can lead to thrombosis [128]. Hypoxia can lead to vasoconstriction which predisposes to occlusion and they cite Grimmer and Kuebler who outlined the details of Hypoxic Pulmonary Vasoconstriction (HPV) [285]. HPV is an efficient homeostatic mechanism which ensures oxygenated areas of the lung are well perfused. HPV is influenced by a number of pharmacological agents which are relevant in anaesthetics [286]. However as a homeostatic mechanism, this would divert blood away from hypoxic areas and would therefore not be relevant to the coagulopathy unless the mechanism is dysregulated.

Hypoxia-Inducible Factors (HIF's) are transcription factors which alter gene expression including Tissue Factor and Plasminogen-Activator Inhibitor-1 (PAI-1). Evans suggests HIF's as a mediator between sepsis and thrombosis [287]. Gomez-Arbeleaz, et al. suggests a number of mechanisms for the increased risk of thrombosis in COVID-19 including increased viscosity of the blood secondary to hypoxia (sic) [113].

Pathology of the vasculature

Microangiopathy leading to ischaemia: Fara, et al. refers to a microangiopathy that may be associated with SARS-CoV-2 infection in their case series of macrothrombosis and stroke [106].

Makatsariya, et al. provide a useful overview of microangiopathy. They note that thrombotic microangiopathy is divided into primary and secondary [288]. There are two main forms of primary thrombotic microangiopathy: Haemolytic Uraemic Syndrome (HUS) and Thrombotic Thrombocytopenic Purpura (TTP). In TTP there is reduced activity of ADAMTS13, an enzyme which cleaves the procoagulant Von Willebrand Factor (VWF) while in HUS there is excessive release of VWF into the circulation. Secondary thrombotic microangiopathies also exist and result from a number of causes including autoimmune disorders.

Martinelli, et al. reported on a retrospective study of 50 patients with

COVID-19 and find evidence of a mild deficiency in ADAMTS13 suggesting that this is evidence of a secondary microangiopathy [289]. They also found evidence of an inverse relationship with D-Dimer levels. Baeck, et al. investigates the possibility that chilblains reported in COVID-19 may result from a microangiopathy and conclude that there is no relationship [290]. Jhaveri, et al. report a case of COVID-19 in which there is thrombotic microangiopathy together with alternative complement activation [291].

Song and FitzGerald suggest that microangiopathy in COVID-19 may be mediated by dysregulation of complement activation and draw comparisons with atypical haemolytic anaemia and paroxysmal nocturnal haemoglobinuria [292]. Ackermann, et al. report on a case series of 7 autopsies in which they found widespread evidence of thrombosis with microangiopathy in the pulmonary vessels [293]. They further identified vascular angiogenesis as a feature of COVID-19 which distinguishes it from severe influenza. Gavriilaki and Brodsky provide evidence of microangiopathy in COVID-19 and outline the pathological mechanisms [294].

Endotheliitis: A number of the authors in the main papers refer to either the possibility of endotheliitis or provide evidence of the same. Escalard et al. in their case series of mechanical thrombectomy for ischaemic stroke suggest that endotheliitis may be a reason why reperfusion was not achieved despite recanalization [105]. Varga, et al. in their case series report evidence of direct viral invasion of the endothelium and widespread endothelial inflammation [188]. They cite evidence of widespread expression of ACE-2 receptors on the endothelium as a facilitator of viral entry into endothelial cells. Fara, et al. in their case series note thrombosis in association with mild COVID-19 and discuss the possibility of endotheliitis and reference another paper providing evidence [106,295]. Sardu, et al. examines the evidence for endothelial involvement in COVID-19 although focusing on endothelial dysfunction [295].

Reitsma, et al. provide an overview of the endothelial glycocalyx noting that it is membrane-bound layer consisting of proteoglycans (predominantly), glycosaminoglycans and glycoproteins in dynamic equilibrium with soluble glycosaminoglycans and proteins in the plasma [296]. Important components of the glycocalyx are hyuluronan and heparin sulfate. Hyuluronan has a significant ability to bind to water molecules and various clinical applications including as dermal filler. Semeraro and Colucci outline the evidence of anticoagulant properties of the endothelium involving the protein C pathway, Tissue Factor pathway inhibitor and heparin sulfate and other Glycosaminoglycans (GAGS) [297].

An example of how endothelial cells and the glycocalyx in particular are specialised is provided [298]. In their review they outline the contribution of the endothelium and the glycocalyx in particular to the Glomerular Filtration Barrier (GFB) in the kidneys. Furthermore they suggest that the glycocalyx can be disrupted by processes such as inflammation and by such means can contribute to the development of Focal Segmental Glomerulosclerosis (FSGS). Interestingly this is of particular significance in COVID-19.

Goshua, et al. provides evidence of endotheliopathy in COVID-19 with elevated markers, find a difference between critically ill and non-critically ill patients with COVID-19 and provide evidence of soluble thrombomodulin as a prognostic indicator [299]. Tong, et al. found evidence of increased levels of serum endothelial cell adhesion molecules in severe COVID-19 which decreased with recovery [300].

Yamaoka-Tojo suggests endothelial glycocalyx damage as a mediator of systemic inflammatory microvascular endotheliopathy in COVID-19 and relates this to the clinical findings in COVID-19 [301]. Fraser, et al. found evidence of glycocalyx degradation in critically ill patients with COVID-19 [302]. Cipolloni, et al. from 2 autopsies found evidence of Factor VIII positivity and endothelial and alveolar damage which they suggest leads to different forms of ARDS [303]. Nikbakht, et al. note the presence of endothelial cells in the blood-brain barrier and suggest that this is relevant to CNS involvement in COVID-19 [304].

Endothelial dysfunction: Many authors in the main papers suggest endothelial dysfunction as a mediator of COVID-19-related coagulopathy. Endothelial dysfunction is well-characterised and describes a reduction in the availability of vasodilators such as nitrous oxide and an increase in endothelial-derived vasoconstrictors resulting from the action of various cardiovascular risk factors. Endothelial dysfunction is a precursor for atherosclerosis and predisposes to a number of pathologies including thrombosis [305].

With regards to COVID-19 Varga, et al. provides evidence of apoptosis in association with endothelial dysfunction in their case series [188]. As per the previous section Sardu, et al. examines the evidence for endothelial dysfunction in COVID-19 [295]. Smadja, et al. identified elevated Angiopoetin-2 and E-selectin on admission as prognostic for ICU admission in patients with COVID-19 [306]. They note that both are markers for endothelial dysfunction. Further they suggest that an intact endothelium is antithrombic and disruption of the endothelium is therefore prothrombotic and that an analogy can be drawn with pre-eclampsia.

Vasculitis or vasculitis-like mechanism: Morassi, et al. in their case series of stroke with COVID-19 suggest vasculitis as a possible mediating mechanism [115]. They cite research in both SARS and New Haven Coronavirus. In SARS there was evidence of fibrinoid necrosis and inflammatory cells in the vessel walls in three cases [229].

The relationship between vasculitis and thrombosis is well-established and Emmi, et al. provides an overview of the evidence for increased risk of thrombosis in a number of vasculitides [307]. Iba, et al. suggest macrophage activating syndrome as a cause of coagulopathy in COVID-19-related vasculitis [308]. Tahir, et al. report a case of Cutaneous Small Vessel Vasculitis (CSVV) secondary to COVID-19 after exclusion of other differentials [309]. Hussein, et al. report a case of COVID-19 with pulmonary haemmorhage secondary to ANCA vasculitis although the association with COVID-19 was unclear [310].

Becker reviews the evidence for vasculitis in COVID-19 and provides an overview for the pathogenesis of vasculitis [311]. Becker references the histopathological findings of endotheliitis. As per Becker we will group vasculitis and endotheliitis together in this paper [311].

SARS-CoV-2-induced small vessel thrombosis: Kaafareni, et al. suggest two mechanisms in particular that would merit further investigation one of which is the possibility of a SARS-CoV-2-induced small vessel thrombosis [119]. They cite Connors and Levy who writes about thromboinflammation and who in turn reference Fox, et al. whose autopsy findings include small vessel thrombosis [189,312]. There are numerous studies identifying evidence of small-vessel thrombosis in COVID-19 and this appears to be a robust finding [41,293,313,314]. Many of these findings describe pathology in the lungs. Wang, et al. report two cases of COVID-19 with digital gangrene mediated by small-vessel thrombosis [315].

Iatrogenic

Pharmacological adverse events: Kaafareni, et al. describe a case series of patients with COVID-19 and gastrointestinal symptoms and suggest a number of explanatory mechanisms including pharmacological side-effects although this could also cover non-coagulopathy-related clinical features [119]. Nevertheless there are a number of pharmacologically-active agents with thrombophilic properties and this includes licensed medications and illegal drugs. Girolami, et al. have reviewed the subject and comment on the paucity of published literature. However they identify 21 classes of pharmacologically active agents with possible thrombophilic properties [316]. The licensed medications include the antipsychotic Clozapine, oral contraceptives, Tamoxifen and Heparin which can lead to Heparin-induced Thrombocytopenia (HIT). They also cite a number of case reports of arterial thrombosis with the use of Marijuana. The possibility that there may be a synergistic thrombophilic effect involving thrombophilic pharmaceutical agents and COVID-19-specific thrombophilic mechanisms should be considered. An association between severe COVID-19 and polypharmacy was found in one pre-print paper. Osteonecrosis of the femoral head was reported in SARS and has been attributed to the use of steroids but not yet described in COVID-19 on the basis of our examination of the literature

[317,318].

Mechanical ventilation: Pulmonary coagulopathy occurs secondary to lung injury. The aetiology of lung injury is broad and includes mechanical ventilation. Indeed the treatment of mechanical ventilation-associated pulmonary coagulopathy was evaluated in a meta-analysis [319].

Immune-mediated syndromes

Antiphospholipid syndrome: Zayet, et al. reported elevated anticardiolipin antibodies in one case whilst noting that a diagnosis of antiphospholipid syndrome cannot be made unless positive antibodies have been present for several months. This has presented a challenge in the early stages of the pandemic [120].

There are a number of suggested mechanisms by which antiphospholipid antibodies can potentially mediate coagulopathy. Salmon and de Groot discuss a number of these mechanisms in their paper including inhibition of Proteins C activity, inhibition of Protein S activity, inhibition of antithrombin activity and Tissue Factor induction [320].

Devreese, et al. in their case series of 31 patients in ICU identified positive antiphospholipid antibodies in 10 patients at initial testing but these tests were negative at repeat testing one month later [321]. Xiao, et al. report antiphospholipid antibodies in 47% of the critically ill patients in their study and arising at a median of 39 days after disease onset [322]. Those with multiple antibodies experienced a higher incidence of ischaemic stroke. Cavelli, et al. argues that secondary antiphospholipid syndrome is the cause of the coagulopathy in COVID-19 [323].

Borghi, et al. demonstrate a low prevalence of antiphospholipid antibodies in their study involving 122 patients with severe COVID-19 [324]. Zuo, et al. found evidence of antiphospholipid antibodies in their series of 172 patients with COVID-19 and correlated higher levels with the severity of respiratory disease and increased neutrophil activity with release of neutrophil extracellular traps [325]. Rodriguez, et al. note that as well as antiphospholipid syndrome, other autoimmune conditions have been reported in COVID-19 [326]. Iba, et al. outline 5 different coagulopathies associated with COVID-19 including an antiphospholipid antibody syndrome-like coagulopathy amongst four other coagulopathies [308].

Maria, et al. report a case of flare-up of primary antiphospholipid syndrome with adrenal haemmorhage and acute limb ischaemia in a male patient with COVID-19 and suggest an interaction between COVID-19 and antiphospholipid syndrome [324]. Cavalli, et al. note that antiphospholipid antibody syndrome can result from viral infections [323].

We distinguish between antiphospholipid antibody syndrome-like coagulopathy for which there is evidence and antiphospholipid antibody syndrome for which there is not sufficient evidence.

Type-1 interferonopathy: Bouaziz, et al. noted similarities between the dermatological presentation of COVID-19 and type-1 interferonopathy [327]. Chilblains for instance occur in Aicardi-Goutiéres Syndrome (AGS) [328].

This hypothesis is further developed [329,330]. Damsky, et al. suggest that sporadic pernio in COVID-19 reflects a strong host interferon-I response and that patients experiencing acral pernio or chilblains are experiencing a milder course of illness due to the immune response [330]. Histopathological findings were presented in Kolivras, et al. as well as a hypothesis about the interferon-1 response [331].

Muskardin and Niewold review the role of type-1 interferons in rheumatic diseases including Systemic Lupus Erythematosus (SLE) and also note 12 different type-1 interferons [332]. The type-1 interferons contrast with the type-III interferons which are preferentially activated in the respiratory epithelium and other barrier surfaces [333]. Interestingly there is evidence to suggest that type-1 interferon can impair the response to secondary bacterial infections [334]. Nagafuchi, et al. suggest the need for precision medicine in profiling the immune response in SLE [335]. Chen, et al. reviews the relationship of type-1 interferons to outcomes with atherosclerosis and notes a role in endothelial dysfunction [336]. Martin-Fernandez, et al. identified type-1 interferon-induced necrotic skin lesions in their study of five families with a deficiency in ISG15 [337].

Rodero and Crow review the type-I interferonopathies and outline the different groups of clinical features (Table 31) as well as the associated genotypes (Table 32) and their posited role [328]. They suggest that interferon is potent in action but also difficult to detect. In their review they state that there is insufficient evidence to support a causal relationship between an upregulation of type-I interferon signalling and the associated clinical features at that time (Tables 31 and 32).

Table 31. Presentations of type-I interferonopathies as per (Rodero and Crow).

Presentations of type-I interferonopathies
Lupus
Spastic paraparesis
Lung inflammation
Developmental Delay
Malignancy
Glaucoma
Skin vasculopathy

Table 32. Genotypes of type I interferonopathies as per (Rodero and Crow).

Genotypes of type I interferonopathies
TREX1
SAMHD1
RNASEH2A
RNASEH2B
RNASEH2C
PSMB8
MDA5
ADAR1
TRAP
C1q
ISG15
USP18
POLA1
STING
PSMB4
PSMA3

Schreiber divides type-1 interferon signalling into robust and tunable and outline the details of the signalling cascade [338].

Xia, et al. found three SARS-CoV-2 proteins that functioned to evade the host's type-1 interferon response while Gemcioglu, et al. report a mild progression of COVID-19 in a patient treated with type 1 interferon for multiple sclerosis. Another perspective on interferon and COVID-19 is found in interventions [339,340]. Yu, et al. in their systematic review and meta-analysis note that although there is a role for interferons for first-line therapy in coronavirus infections within local protocols there is also a need for robust trials [341].

General factors

Critical illness encephalopathy: Deliwala, et al. note the association of critical illness encephalopathy, cytokines and stroke in their case report and literature review and suggest that this may represent a precursor state [219]. Aggarwal, et al. investigates the relationship between pre-existing

cerebrovascular disease and severity of COVID-19 [342]. Helms, et al. provide evidence of an association between severe COVID-19 with ARDS, critical illness encephalopathy and stroke although noting that they have not demonstrated a causal relationship [125]. Deliwala, et al. present a case of encephalopathy associated with ARDS where the imaging does not initially reveal evidence of ischaemic stroke although this is subsequently identified [219]. The relationship between encephalopathy and delirium has been outlined by Slooter, et al. who describe acute encephalopathy as a pathological brain process which may lead to a number of clinical conditions including delirium although having other associations also [343].

Hypotension: Zhou, et al. in their case report of DVT and acute limb ischaemia note that hypotension is a risk factor for DVT [344]. Momtazmanesh, et al. did not report hypotension as a finding in their systematic review and meta-analysis of 10,898 patients with COVID-19 [253]. Wu and Song, et al. identify a significant role for the order in which vasopressors are discontinued in the treatment of septic shock [345,346]. Hypotension is however a cardinal feature of septic shock and so this is best considered under the heading of septic shock [347]. Additionally hypotension is a recognised cause of ischaemia [348].

Hypertension: Yaghi, et al. suggests relative hypertension secondary to mechanical ventilation leading to posterior reversible encephalopathy syndrome as a mechanism for ischaemic stroke in COVID-19 [109]. Momtazmanesh, et al. in their systematic review and meta-analysis note the significance of pre-existing hypertension as a risk factor for prognosis [253]. Jain and Yuan in their systematic review and meta-analysis similarly identify hypertension as a comorbidity which was predictive for severity of COVID-19. In terms of modelling this is considered under vulnerabilities [283].

Lymphopenia and Leucocytosis: Zayet, et al. describe lymphopenia and leukopenia in their cases of COVID-19 with stroke and relate this to the associated stroke risk [120]. They cite a study demonstrating that the lymphocyte-to-monocyte ratio is a prognostic indicator in acute ischaemic stroke [349]). Urra, et al. found an association between lymphopenia and ischaemic strokes involving the superior and middle temporal gyri [350]. The phenomenon of post-stroke immune depression has been described but this temporal relationship would therefore not account for initial strokes in COVID-19 [351]. Nevertheless both post-stroke immune depression and infection may be important in the characterisation of the consequences of COVID-19 coagulopathy in cases of stroke particularly in terms of the long term consequences of COVID-19 [352,353]. In a meta-analysis Huang, et al. found higher leukocyte counts and lower lymphocyte counts in patients with severe COVID-19 compared to patients with mild illness. In terms of modelling, this is best considered in terms of the thrombophilic state [354].

Atrial fibrillation: Arrigo, et al. in their review of Atrial Fibrillation note that this is a common condition in an ICU setting and they identify several mechanisms leading to atrial fibrillation: myocardial stretch, inappropriate oxygen delivery, electrolyte disturbances, inflammation, adrenergic overstimulation, endocrine disorders and hypothermia [355]. They outline a number of treatment approaches depending on the underlying mechanism. Lazzeri, et al. report a series of 28 patients with COVID-19 and ARDS [356]. Two of the patients presented with chronic atrial fibrillation while 11 of the remaining 26 presented with paroxysmal atrial fibrillation. Holt, et al. report a reduction in the incidence of atrial fibrillation during the early period of lockdown but suggests that this may be due to the effects of the pandemic on healthcare access [357]. Schnaubelt, et al. report on a case of atrial fibrillation complicating a suspected cytokine storm [358].

Immobilisation and bed rest: Immobility and bed rest are well recognized risk factors for DVT and this relationship is an important contributor to the practice of thrombophrophylaxis in the hospital setting. McLendon, et al. Zhou, et al. and Prevatali, et al. review the risk factors for DVT (Table 33) and cite evidence for immobility and bed rest as risk factors for DVT [344,359,360]. In the 56 main papers, the authors note that patients experienced thromboembolic events despite thromboprophylaxis. There is no doubt that this is an important consideration in the ICU setting. McLendon, et al. note a hierarchy of DVT risk with immobility in order from highest to lowest: Hip, knee, ankle, shoulder, and elbow (Table 33) [359].

Table 33. Deep vein thrombosis risk factors (McLendon et al) (Zhou et al) and (Prevatali et al).

Vein thrombosis risk factors
Age
Bed rest
Respiratory failure
Acute coronary syndrome
Congestive heart failure
Chronic kidney disease
Chronic disease
Indwelling catheters
Long distance travel
Major trauma
Non-infectious inflammatory conditions
Obesity
Varicose vein in lower extremity
Prior Venous Thromboembolism
Smoking
Stroke
Thrombophilias
Surgery
Immobility
Oestrogen use
Pregnancy
Initial postpartum
Family History
Infection
Impaired blood flow
Malignant tumor
Chemotherapy
Air Pollution

The veins are valved which influences the dynamics of blood flow and periods of stasis can predispose to thrombosis. However the arterial anatomy is substantially different and in our findings the arterial ischaemic events significantly outnumbered those affecting the veins. Reddy, et al. describe a case of arterial ischaemia in the lower limb secondary to thrombosis involving both the deep and superficial veins-phlegmasia cerulean dolens [361]. This mechanism may be of minor relevance in COVID-19 but in the majority of the 56 main papers describing acute limb ischaemia, deep vein thrombosis was not reported as a comborbidity. Zhou, et al. was the exception [344].

Air travel presents a special case of immobility and the occurrence of deep vein thrombosis has been well documented in this setting and the efficacy of interventions investigated [362]. Sohail and Fischer reiterate the finding of deep vein thrombosis in their review of air travel and health-related conditions but also cite cases of arterial thrombi although less frequent [363].

Dehydration due to fever, diarrhea: Zhou, et al. suggests fever and diarrhoea as relevant risk factors for DVT in COVID-19 [344]. In a retrospective study of 25 patients with COVID-19 diarrhoea was reported in 8% of patients [364]. Parasa, et al. in a systematic review and meta-analysis which looked at the prevalence of gastrointestinal symptoms

found that 12% of patients with SARS-CoV-2 infection experienced gastrointestinal symptoms including diarrhoea, nausea and vomiting [365]. In another systematic review and meta-analysis looking at gastrointestinal involvement in COVID-19, the prevalence of diarrhoea was 10.4% (95% CI 7.7-13.9) [366]. Hajifathalian, et al. identified prevalence for diarrhoea of between 10 and 29% in patients with COVID-19 in their review of the literature [367]. In another systematic review and meta-analysis, the authors looked at the outcomes in 61, 742 patients. In a subset of 18 studies they found a prevalence of diarrhoea of 8% (95% confidence interval 4.6-11.4) [368]. Kaur, et al. found a prevalence of diarrhoea of 9.2% in their systematic review [369].

In terms of the relationship between diarrhoea and dehydration, this is well-established and the importance of oral rehydration has been emphasised across a range of settings. Giddings, et al. provide an overview of traveller's diarrhoea including the central role of oral rehydration therapy in addressing dehydration [370]. Dehydration can increase the likelihood of coagulation. Shi, et al. found that dehydration mediated ischaemic stroke risk via activation of coagulation [371]. Borgman, et al. demonstrated that dehydration leads to central hypovolaemia with increased clotting in a trial involving 11 volunteers [372]. Li, et al. identified dehydration as a predictor for prognosis in ischaemic stroke over the long term [373].

Fever has been well characterized in COVID-19 as per the introduction and can lead to fluid loss through sweating thereby providing an additional mechanism which can lead to dehydration.

Metabolic/electrolyte disturbance: Kaafareni, et al. in their description of gastrointestinal complications of COVID-19 including mesenteric ischaemia suggest a number of mechanisms including metabolic and electrolyte disturbances seen in critically ill patients [119]. Numerous metabolic and electrolyte disturbances have been described in critically ill patients and may have a relationship with thromboembolic events.

In more general terms Gawalko, et al. suggest a number of mediators of atrial fibrillation including hypoxaemia, electrolyte imbalance, endothelial dysfunction, ACE-2-related pathways and the cytokine storm [374]. Renal function is an important consideration for electrolyte disturbances and there are a number of findings on urea nitrogen levels (BUN) where BUN is approximately twice the value of serum urea levels. Shao, et al. undertook a meta-analysis (n=24527) of acute kidney injury in patients with COVID-19 and found that acute kidney injury was significantly associated with mortality and BUN and creatinine were significantly associated with mortality [375]. Post, et al. report two cases of kidney infarcts associated with elevated LDH [376]. Liu, et al. found that urea nitrogen (BUN) levels, D-Dimers and lymphocyte ratio (expressed as a percentage of white cell count) were prognostic in COVID-19 [377]. Oussaleh, et al. analyzed the biochemical parameters in a prospective cohort study of 162 patients with severe COVID-19 and found that only urea Nitrogen >0.42 g/L was prognostic for death. Thus there may be an indirect relationship with coagulopathy via critical illness and the associated risks [378].

In terms of sodium Corwin and McIlwaine note that in critically ill patients, hypernatraemia may be associated with reduced cerebral volume which can lead to mechanical stress on the cerebral blood vessels [379]. However Berni, et al. found evidence of hyponatraemia in COVID-19 and that it was inversely correlated with IL-6 levels which they suggest is mediated by an IL-6-induced vasopressin release [380]. Post, et al. cites evidence that low sodium levels may cause upregulation of the renal membrane bound ACE-2 receptors [381]. In turn they suggest that this would increase the risk of SARS-CoV-2 binding to renal ACE-2 receptors. They also cite evidence of an association between hyponatraemia and severity of COVID-19 [382]. In another paper Post, et al. also cites evidence of geographical differences in sodium intake and suggests that dietary intake may play a role in illness severity [381]. Królicka, et al. reviewed the evidence for hyponatraemia in infections including COVID-19 [383]. They cite evidence for hyponatraemia in COVID-19 and more generally identify hyponatraemia as a risk factor in infections for longer hospital stay and mortality. Ghahramani, et al. in their meta-analysis of 22 studies (n=3396) found evidence of a significant association of decreased sodium in patients with severe COVID-19 compared to non-severe COVID-19 [384]. Hyponatraemia is also noted in patients with stroke and suggested mediators include the syndrome of inappropriate ADH secretion and cerebral salt wasting syndrome [385]. Hyponatraemia occurred in 30% of patients in a retrospective observational cohort study Frontera, et al. with increasing severity correlated with mortality, encephalopathy and mechanical ventilation with lower levels being correlated with IL-6 levels [386].

Liu, et al. found evidence of hyponatraemia in 25.8% of 93 patients with COVID-19 [387]. Tezcan, et al. found that hyponatraemia was the most common electrolyte disturbance in their study of 408 hospitalised patients with COVID-19 [388]. In their study, hyponatraemia, hypochloraemia and hypocalcaemia were prognostic for outcomes. Zimmer, et al. in contrast with other studies found evidence of hypernatraemia in COVID-19 and this was associated with prognosis as well as hypokalaemia and hyperchloraemia [389]. They suggest that this results from elevated angiotensin II levels. Suso, et al. report a case of IgA Vasculitis with Nephritis [390]. Carriazo, et al. draw attention to the occurrence of SIADH in COVID-19 [391]. Khan, et al. presents a case of hypovolaemic hyponatraemia in COVID-19 [392]. Ata, et al. presents a case of hyponatraemia in COVID-19 and suspect that this reflects SIADH [393]. Kumar, et al. presents a case of hyponatraemia with adrenal infarction in COVID-19 [394]. Habib, et al. report a case of symptomatic hyponatraemia in COVID-19 which was determined to be secondary to SIADH after further investigation [395]. Ravioli, et al. report 2 cases of SIADH in COVID-19 [396]. Thus there are consistent findings with the vast majority of studies identifying hyponatraemia but when hyponatraemia or hypernatraemia occur they are both prognostic in COVID-19. A key point here is that if sodium homeostasis is working effectively then hyponatraemia or hypernatraemia would be avoided and it is likely that this is related to a disruption in the RAA system.

Frise and Salmon note the relationship between hypokalaemia and cardiac arrythmias and these in turn may give rise to thromboembolic events (e.g. atrial fibrillation) [397]. Chen, et al. completed a cohort study looking at hypokalaemia in COVID-19 (n=175) [398]. They found that 85% of severely and critically ill patients had hypokalaemia and that patients with higher levels of hypokalaemia were more likely to have elevated creatine kinase, lactate dehydrogenase, C-reactive protein levels and higher body temperature. They suggest that hypokalaemia is difficult to correct because of ACE-2 degradation and that the hypokalaemia is mediated via the renin-angiotensin system. Vena, et al. in a retrospective cohort study in a tertiary care hospital (n=317) identified hypokalaemia in 25.8% of patients [399]. Yang, et al. found a significant relationship between corticosteroid treatment and hypokalaemia in patients with COVID-19 in their meta-analysis of 15 studies (n= 5270) [400]. Chen, et al. found a high prevalence of hypokalaemia in COVID-19 which was responsive to potassium supplementation [401]. They suggest that this may result from disruption of the renin-aldosterone system. Moreno-P, et al. found evidence of hypokalaemia in 30.7% of 301 patients with COVID-19 and this was associated with need for mechanical ventilation [402].

Prabhu, et al. present a case of BRASH syndrome (bradycardia, renal failure, AV nodal blockade, shock, and hyperkalemia) in COVID-19 [403]. Chen, et al. looked at the characteristics of 113 deceased patients compared to those who survived in their study (n=799) and found that renal failure, hyperkalaemia and alkalosis were more common in those who died [401]. Thus in the case of potassium, there are mixed results. With the RAA system, sodium retention is accompanied by potassium excretion whereas hypokalaemia and hyponatraemia are commonly reported in studies. Taken together with the evidence about the RAA system, the most plausible explanation is that there is a disruption of sodium and potassium regulation due to a disruption in the RAA system.

Rosengart outlines the consequences of hypocalcaemia and hypercalcaemia in critically ill patients and the association of hypocalcaemia with hypotension is noted [404]. Hypotension is independently associated with stroke risk [405]. The role of Vitamin D in the immune system is well documented and there is also a well-established causal link with

hypocalcaemia in Vitamin D deficiency in keeping with the homeostatic functions of Vitamin D [406]. Chakhtoura, et al. highlight the importance of Vitamin D in infections and suggest that Vitamin D may play a role in COVID-19 susceptibility [407].

Bossoni, et al. report a case of hypoparathyroidism in a lady with a thyroidectomy who developed COVID-19 and the authors suggest that the COVID-19 was the precipitant [408]. Elkattawy, et al. report a case of hypoparathyroidism with normal calcium and hyperphosphataemia which they suggest as secondary to SARS-CoV-2 infection [409]. Liu, et al. found evidence of hypocalcaemia in 62.6% of 67 patients with severe COVID-19 and was inversely correlated with D-Dimer and IL-6 levels [410]. Sun, et al. found evidence that hypocalcaemia was prognostic in COVID-19 and associated with a higher incidence of septic shock and that calcium levels were correlated with Vitamin D levels [411].

Liu, et al. found that calcium levels were lower in severe COVID-19 and that calcium levels negatively correlated with CRP, D-Dimer and IL-6 levels [410]. In a retrospective cohort study (n=241), 74.7% of patients with COVID-19 were hypocalcaemic on admission [411]. Furthermore calcium was lower in those with severe illness and those with low calcium experienced higher 28-day mortality and were more likely to develop septic shock.

Another consideration for calcium homeostasis is medication. Vila-Corcoles, et al. found no significant reduction in the hazards ratio for developing COVID-19 in patients taking calcium channel blockers [412]. There was a reduction for patients taking Angiotensin II receptor blockers but this was not statistically significant. Similarly Sardu, et al. found no significant effect of antihypertensive medication on prognosis in COVID-19 in their prospective cohort study [413]. Reynolds, et al. looked at patients taking one of five classes of antihypertensives and found no significant reduction in incidence of COVID-19 or in severity in those with COVID-19 [414]. Solaimanzadeh did find a significant reduction in mortality as well as a significant reduction in intervention with mechanical ventilation and intubation in older adults admitted with COVID-19 who were receiving treatment with calcium channel blockers compared to those who were not [415].

Rotman, et al. report a case of a rare syndrome of calciphylaxis and COVID-19 in which calcium was deposited in the vasculature and associated in this case with ischaemic dermopathy [416]. In retrospective cohort study in a tertiary-care hospital Di Filippo, et al. found hypocalcaemia in 82% of 531 patients with COVID-19 [417]. They also identified a correlation of hypocalcaemia with LDH levels and suggest a cytopathic viral lysis syndrome to account for this. Kumar, et al. and Kumaran, et al. report cases of pancreatitis with hypocalcaemia [418,419]. Demir, et al. present a case of hypocalcaemia and hypoparathyroidism with COVID-19 presenting with Fahr's syndrome [420].

Magnesium as a group 2 element in the periodic table competes with calcium which is relevant physiologically. Tang, et al. review the role of magnesium in the management of different conditions and suggests a role for magnesium supplementation for specific indications in COVID-19 [421].

Kim, et al. present two cases of acute hyperglycaemic crises in Diabetes in COVID-19, of which there are many other cases in the literature [422].

Outline the relationship between hypomagnesaemia and arrythmias in critically ill patients. Again this may similarly mediate thromboembolic events via atrial fibrillation. We did not identify evidence of hypomagnesaemia in COVID-19 in our literature search [423].

Low platelet count: Meza, et al. cite a number of factors which predispose towards a hypercoagulable state including low platelet count [424]. One study which has been cited to support this assertion [425]. This paper references a low platelet count, relating this to the ACE-2 receptor and also to an increased risk of cerebral haemmorhage when combined with hypertension. This in turn relates to another paper [426]. This paper described a family cluster of SARS-CoV-2 infection and is one of the earlier descriptions of the clinical features. Levi and Opal consider the low platelet count in the critical care setting and identify a number of mediators including disseminated intravascular coagulopathy, microangiopathy and sepsis [427].

Firstly looking at the relationship between platelets and thrombosis in the non-COVID-19 literature one of the conditions associated with both thrombocytopenia and thrombosis is Heparin-Induced Thrombocytopenia (HIT). The relationship of heparin to thrombocytopenia is well-established and the experimental evidence dates back to 1942 [428]). The negatively charged heparin binds to the positively charged PF4 (which is released from platelet alpha-granules) forming a complex which due to the nature of the electrostatic interactions is dependent on the concentrations of heparin and PF4 [428]). The heparin-P4 complex is the target of antibodies (HIT). PF4 is expressed on the endothelium and is prothrombogenic. HIT is associated with thrombosis and more people develop antibodies when treated with heparin than develop thrombocytopenia or thrombosis suggesting a subclinical presentation also exists [428]. The heparin/PF4/antibody complex binds to platelets and causes platelet activation via a spleen tyrosine kinase-mediated mechanism and procoagulant microparticles are released [428]. Gollomp, et al. provides experimental evidence to support several neutrophil-mediated prothrombotic mechanisms in HIT including formation of PF4/NET/HIT antibody complexes and neutrophil-binding to inflamed endothelium [429]. Perdomo, et al. provides evidence that neutrophil activation and NET's are predominantly responsible for the thrombosis in HIT [430]. Hsieh, et al. report a case of pneumopathy associated with antiphospholipid antibodies, HIT and cerebral venous thrombosis [431]. The absence of platelet alpha-granules is found in the grey platelet syndrome and is associated with a bleeding tendency [432].

Multivessel coronary artery thrombosis has been described in a case of idiopathic thrombocytopenic purpura [433]. Antiphospholipid antibodies have been detected in primary immune thrombocytopenia even in the absence of antiphospholipid syndrome and thrombocytopenia is seen in primary antiphospholipid syndrome [434]. Katz, et al. note an incidence of thrombocytopenia in intensive care settings of up to 50% [435].

They also note that thrombocytopenia occurs in up to 50% of cases of ARDS, is predictive of mortality in sepsis and septic shock, correlates with hypoxemic respiratory failure and is also seen in SARS. They suggest a range of causes may be responsible for the association of thrombocytopenia with critical illness including splenic sequestration.

Donahue, et al. reported on a novel approach to treating hypersplenism-associated thrombocytopenia in unresectable pancreatic cancer [436]. They performed splenectomy and chemotherapy and they cite another study in which splenectomy enabled the continuation of interferon therapy in patients with hepatitis C, liver cirrhosis and portal hypertension [437]. DVT and pulmonary embolism occurred in a lady being treated for idiopathic thrombocytopenia purpura with intravenous immunoglobulin [438]. Hally, et al. provides an overview of the platelet TOLL-like receptors including their response to PAMPS and DAMPS [439]. They note that fibroblast stimulating lipopeptide-1 (FSL-1) is found to stimulate platelet production of IL-6 via the TLR2/6 receptors. Li, et al. note some of the ways in which platelets interact with microbes including sequestration [440].

Hottz, et al. identified platelet activation and platelet-mediated induction of Tissue Factor in monocytes in patients with severe COVID-19 compared to those with mild COVID-19 [441]. They provided evidence of mediation by integrin αIIb/β3 receptors and platelet p-selectin. Manne, et al. found evidence of increased p-selectin expression in platelets in people with COVID-19 compared to those without [442]. There were found to be increased circulating aggregates of platelet-neutrophils, platelet-T-cells and platelet-monocytes in people with COVID-19. Platelet activation markers were not correlated with IL-6, IL-8, and TNF-α levels but demonstrated platelet hyperreactivity and there was evidence that this was related to both thromboxane generation and MAPK pathway activation.

Becker, et al. suggests that the megakaryocytes found circulating in

the pulmonary microvasculature may be an important source of platelets in COVID-19 [443]. Rapkiewicz, et al. find evidence of platelet-rich thrombi in multiple organs and megakaryocytes [444].

Plaques unstable due to mononuclear infiltrates, hypoxia, turbulence: Cai, et al. suggest that plaques may rupture in the context of COVID-19 associated hypoxia, haemodynamic turbulence and mononuclear infiltrates and thrombosis in microvessels [445]. They cite two papers [446,447]. Restrepo, et al. provides evidence of 20 different cardiac-injury mechanisms resulting from organisms which cause pneumonia [447]. This includes instability of coronary atheromas, acute coronary syndromes and thrombin formation. Xu, et al. report on post-mortem findings in a male patient with Covid-19 but found no evidence of cardiac pathology [446]. Taken together these papers provide evidence of established mechanisms of cardiac injury by organisms that cause pneumonia but this evidence is not specific to COVID-19. We will consider this as best placed within the possible consequences of secondary infection in COVID-19 depending on the causative organisms.

Secondary infection

Septic embolisation with bacterial superinfection: Yaghi, et al. suggests a number of mechanisms that may mediate the increased risk of stroke seen in the cases they presented [109]. They suggest that the critical care period has established associations including septic embolisation in the case of superinfections.

With reference to the non-COVID-19 literature, Elsaghir and Khalili review the evidence for septic embolisation with the most notable example being infective endocarditis. In an autopsy series Grosse, et al. found evidence of gram-negative and positive as well as fungal bronchopneumonia in cases of COVID-19 [448]. They also describe fungal colonisation with septic pulmonary thromboemboli.

Strictly speaking, septic embolisation is not coagulopathy-related and although there is strong evidence for ischaemic events resulting from septic emboli, we will not include this in the model of COVID-19-related coagulopathy.

Secondary infection: Meza, et al. report 4 cases of diabetic ketoacidosis in COVID-19 without respiratory symptoms but with bacterial coinfection in 2 cases [424]. Zhou, et al. present a case of DVT with acute limb ischaemia and discuss the possible cause of DVT in COVID-19 and include secondary bacterial and fungal infections as risk factors [344]. Many of the risk factors overlap with those of mentioned previously including infection. DVT's in turn can predispose to pulmonary emboli [359].

Manna, et al. provides an overview of viral infections with secondary bacterial infection. They cite evidence of an elevated risk of secondary bacterial infection with viral infection and also outline some of the mechanisms by which this may occur [449].

Given the size of the pandemic it is unsurprising that there is a significant evidence base for coinfection with COVID-19. Verroken, et al. found bacterial co-infection in 40.6% of patients admitted to ICU with COVID-19 with the main bacteria being Staphylococcus Aureus, Haemophilus Influenza and Moraxella Catarrhalis [450]. Kim, et al. found that 20.7% of 116 specimens from patients with SARS-CoV-2 were positive for co-infection. Rhinovirus, enterovirus, respiratory syncytial virus and non-SARS-CoV-2 Coronoviridae were the most common co-infections [451]. Interestingly they found that co-infections were more likely in samples without SARS-CoV-2 infection but this relationship was not significant for any of the individual organisms using a Chi squared test ($P<0.05$).

Lansbury completed a systematic review and meta-analysis of coinfections in people with COVID-19 (n=3834). They found that 7% of patients with COVID-19 in hospital had bacterial infection and that this figure was higher in ICU compared to the wards and the most common bacteria were Mycoplasma Pneumonia, Pseudomonas Aeruginosa and Haemophilus Influenza while Respiratory Syncytial Virus and Influenza A were the most common viruses. Fungal coinfections were also identified. Arastehfar, et al. report on 35 published cases of COVID-19 Associated Pulmonary Aspergillosis (CAPA) [452]. Cucchiari, et al. report on a case series of 5 patients with COVID-19 and pneumococcal pneumonia superinfection identified with urinary antigen [453]. Peddu, et al. demonstrated viral and bacterial coinfection with SARS-CoV-2 using metagenomic analysis [454]. He, et al. found that in severe COVID-19 with reduced T-cell count there was a higher risk of bacterial and fungal infection [455].

There are numerous case reports identifying coinfection and providing evidence of unusual coinfections, comorbidities or other insights. Shah, et al. report a case of COVID-19 with coccidioidomycosis [456]. Langerbeins, et al. report a case of chronic lymphocytic leukemia with SARS-CoV-2 infection with parainfluenza coinfection [457]. Jose and Desai report a case of COVID-19 with rapid deterioration following an E.Coli superinfection [458]. Menon, et al. report a case of SARS-CoV-2 comorbid with Pneumocystitis Jirovecci and note that this is commonly seen when there are deficiencies in T-cell immunity [459]. Lehmann, et al. found a rate of coinfection of 3.7% of patients but this increased to 41% in those admitted to ICU [460]. Blaize, et al. report a case of COVID-19 with invasive pulmonary aspergillosis [461]. Poignon, et al. report a case of COVID-19 with invasive pulmonary fusariosis [462]. Castiglioni, et al. report a case of superinfected pneumatocoles in a case of COVID-19 [463]. The pneumatoceles were suspected to have resulted from the SARS-CoV-2 infection Muller, et al. report a case of Covid-19 comorbid with hepatitis C and HIV [464]. Konala, et al. present 3 cases of coinfection with COVID-19 and influenza [465].

Stroke risk with infection: Morassi, et al. discusses the importance of the relationship between stroke and infection [114]. They cite a paper examining this relationship in more detail [466]. Emsley and Hopkins suggest that up to one third of strokes are preceded by infections [466].

Miller and Elkind provide an overview of the relationship between infection and stroke [467]. They identify 22 infectious organisms where evidence has been found of an association with stroke and which include viruses, bacteria and fungi. The pathological mechanisms include arachnoiditis, vasculitis, compression of large arteries by cysts, arterial occlusion by infected erythrocytes, cardioembolism, microembolic infarction, larval obstruction of small vessels, meningitis, arteritis, vascular necrosis, aneurysmal dilatation, opportunistic CNS infections, accelerated atherogenesis, enhanced platelet aggregation, prothrombotic state and chronic inflammation.

Elkind, et al. identified an increased risk of ischaemic stroke with increasing infection burden involving five common infections in the Northern Manhatten Study [468]. Benjamin, et al. review the evidence for stroke in HIV infection noting that 1-5% of patients with HIV experience stroke and cerebral ischaemic lesions are found in up to 34% of autopsies [469]. They suggest a number of possible mediators for stroke risk in HIV: HIV associated vasculopathy, vasculitis, accelerated atherosclerosis, opportunistic infections, neoplasia, bacterial endocarditis, marantic endocarditis, HIV-associated cardiac dysfunction, HIV-associated hyperviscosity and ischaemic heart disease. In a systematic review and meta-analysis of studies looking at Hepatitis C infection and stroke risk, found an odds ratio of stroke with HCV infection of 1.97 (95% CI 1.64-2.30) [470].

Cowan, et al. published their findings in the Atherosclerosis Risk in Communities (ARIC) cohort [471]. The odds ratio for stroke following a hospitalised infection in the previous 14 day-period was 7.7 (95% CI: 2.1-27.3). Erskine, et al. completed a meta-analysis which included 7.9 million patients who had been infected with herpes zoster [472]. They found increased odds of up to 40% of experiencing a cerebrovascular event at between 3 months and 1 year after the infection onset.

Autopsy/Biopsy finding related mechanisms

Pyroptosis: Pyroptosis was described as a potential mechanism [188]. Pryoptosis is a form of programmed cell death which involves inflammation. Li, et al. noted that the pathways mediating pyroptosis are poorly understood and they investigated the signalling pathways involved in Pneumonia associated sepsis [440]. They found an important role for

IL-17 and outline details of the signalling pathway. Yang, et al. in their comparison of SARS and SARS-CoV-2 propose a role for pyroptosis in the pathogenesis of SARS-CoV-2 [473]. We have included this under the broader heading of sepsis.

Apoptosis: Apoptosis was described [188]. Apoptosis is programmed cell death and is associated with characteristic histopathological findings. There is a suggestion that apoptotic pathways may be important in cases of severe sepsis. Luan, et al. characterised apoptotic pathways in immune cells in severe sepsis in their study [474]. We have included apoptosis within the broader topic of sepsis.

Additional mechanisms

Alternative complement pathway: More recently evidence has emerged for an important role of the alternative complement pathway. The complement pathway is part of the innate immune response and is divided into three pathways-the classical, alternative and lectin complement pathways. Brodszki, et al. provide a guideline for the complement deficiencies and their management and review the evidence on complement deficiencies and the regulation of complement [475]. They note a thrombotic microangiopathy associated with dysregulation of the alternative complement pathway. Furthermore there are a number of complement deficiencies that are associated with autoimmune disorders such as SLE.

Chatzidionysiou, et al. consider the question of whether COVID-19 is a complementopathy [476]. Rambaldi, et al. report initial findings in an investigation of a lectin pathway inhibitor in patients with COVID-19-related ARDS and suggest the results support a role for the lectin pathway in COVID-19-related pathophysiology [477]. Magro, et al. reported on a case series of 2 post-mortems and biopsies from 3 patients with skin involvement all with COVID-19 [91]. They found evidence from the lungs and skin of marked involvement of the lectin and alternative complement pathways. They suggest that a COVID-19-related generalised thrombotic microvascular injury results from complement activation. Numerous cases of collapsing glomerulopathy have been described in COVID-19 [291,478-483]. Collapsing glomerulopathy as a morphological variant of focal segmental glomerulosclerosis is in turn associated both with thrombotic microangiopathy and alternative complement pathway activation [484,485]. C3 glomerulopathy is another condition involving the kidneys and resulting from a dysregulated alternative complement pathway activation [486].

General factors relating to arterial thrombosis: Lowe and Tait identify a number of risk factors relating to arterial thrombosis and suggest that it is the role of all healthcare practitioners to reduce these events through pharmacological prevention and education [487]. The risk factors they identify are traditional risk factors for cardiovascular disease and include dyslipidemia, psychosocial factors, diabetes, hypertension, smoking and abdominal obesity as well as protective factors including fruit and vegetables and exercise. Whilst smoking and obesity are also risk factors for DVT as per Table 25, dyslipidemia, psychosocial factors, diabetes and hypertension are not listed in Table 25 and suggest a more chronic aetiology and a role for endothelial dysfunction. This however is contrast with the acute nature of arterial thromboses in COVID-19.

Medical device-related coagulopathy: In the 56 main papers, there were multiple examples of medical device-related coagulopathy (including catheters). We suggest a number of mechanisms are involved. Firstly catheters may result in subtle vascular wall damage that ordinarily would not present any problems but when combined with the vasculopathy of COVID-19 acts synergistically to increase the risk of thrombosis. Secondly in the case of the ECMO centrifuge, suggest that this is due to a combination of ultrafiltration and high fibrinogen levels [125]. Kowalewski, et al. compare coagulation and inflammation in COVID-19 and ECMO and note the pro- and anticoagulant properties of ECMO [488]. Thirdly when the blood is in contact with artificial surfaces this can trigger the intrinsic pathway which amplifies the extrinsic pathway.

Vulnerabilities: There are a number of factors that act as modifiers of risk of mortality in COVID-19. Williamson, et al. looked at 10,926 COVID-19-related deaths in 17,278,392 adults using pseudonymised records from primary care [489]. They identified a number of risk factors for death in COVID-19 (Table 34).

Table 34. Risk factors from (Williamson et al).

Risk factors
Diabetes
Haematological malignancy
Non-haematological malignancy
Age
Male
Black, South Asian & Mixed and Other Ethnicity
Obesity
eGFR<= 60 ml/min per 1.73 m2
Chronic respiratory disease
Chronic liver disease
Stroke & Dementia
Other neurological disease
Conditions associated with immunosuppresion
Rheumatoid arthritis, lupus or psoriasis
Hypertension up to age 70
Stroke
Thrombophilias
Surgery
Immobility
Oestrogen use
Pregnancy
Initial postpartum
Family History
Infection
Impaired blood flow
Malignant tumor
Chemotherapy
Air Pollution

Marazeula, et al. examined the endocrine and metabolic aspects of COVID-19 [490]. They suggest four ways in which obesity may worsen outcome in COVID-19-reducing respiratory reserve, comorbidities, increased viral shedding and chronic inflammation. However a key factor for consideration with vulnerabilities is endothelial dysfunction and this relates to coagulopathy.

Amraei and Rahimi suggest that endothelial dysfunction is a common factor in a number of comorbidities that impact on COVID-19 severity including obesity, diabetes and cardiovascular disease including hypertension [491]. They suggest that endothelial cell injury by SARS-CoV-2 both in the lungs and elsewhere may be an important consequence of infection and would explain the elevated Von Willebrand Factor levels. Bansal, et al. review the evidence for worse outcomes in COVID-19 with hypertension, diabetes and obesity [492]. They further highlight the presence of endothelial dysfunction in diabetes type 2 and obesity. One study found an odds ratio of 1.67 for severe COVID-19 with obesity compared to non-obesity (95%CI: 1.43, 1.96; P<0.001) [493].

Hayden reviews endothelial activation and dysfunction in diabetes Type 2, metabolic syndrome and COVID-19 [494]. Type 2 diabetes is noted to affect a number of tissues including the lungs through a range of mechanisms including endothelial activation and dysfunction. Furthermore the Blood Gas Barrier (BGB) is formed by the fusion of the basement of the type I pneumocytes and alveolar endothelial cells and plays a role both in oxygen exchange and after endothelial activation also plays a role in the immune response to SARS-CoV-2. The BGB endothelium is activated

by cytokine storms, binding of SARS-CoV-2 to the ACE-2 receptors on the pulmonary endothelium and via a SARS-CoV-2 induced redox storm mediated via reactive oxygen and nitrogen species (RONS). A key finding is the loss of the pulmonary epithelial glycocalyx in both diabetes type 2 and the metabolic syndrome and it is suggested that this could account for the vulnerability of people with type 2 diabetes to more severe COVID-19.

Of note in splenectomy was associated with increased risk of mortality in COVID-19 although this did not reach statistical significance [489]. Nevertheless post-splenectomy there is an increased risk of arterial thrombosis [495]. Zhou, et al. in their review cite evidence of destruction of secondary lymphoid tissue in autopsy findings including splenic atrophy and focal haemmorhagic necrosis [344].

Falasca, et al. report on a number of post-mortem findings including splenic congested red pulp and lymphoid hypoplasia whilst many of the remaining findings relate to apparent non-coagulopathy-related pathologies in COVID-19 [496]. Qasim, et al. report a case of splenic artery thrombosis and infarct in COVID-19 [497]. Shaukat, et al. report a case of atraumatic splenic rupture in COVID-19 [498]. In terms of genetic susceptibility Zeberg and Pääbo identified a haplotype that presents increased risk for severe COVID-19 [499].

Type-III hypersensitivity reaction: In the type III hypersensitivity reaction, antibody complexes are deposited in various tissues in the body. The complement pathway can be involved in the pathogenesis of the type III hypersensitivity reaction and so this can be considered together with the section on the alternative complement pathway. Granger, et al. review the evidence on the relationship between NET's and autoimmune diseases [500]. They note that with deficiency in DNAase 1 activity which results in elevated NET's there is an association with active lupus and provide additional evidence of the relationship between NEs and lupus. They also note that difference in the components of NET's in patients with and without SLE.

There is evidence that when senescent neutrophils are not cleared through apoptosis this is associated with the development of autoimmune disease [501]. Tanaka, et al. has demonstrated an association between apoptosis-associated release of autoantigens and SLE [502]. Yang, et al. note that autoantigens and Damage Associated Molecular Patterns (DAMPS) are released after apoptosis, pyroptosis, necroptosis and by NET's resulting in inflammation and with a potential for autoimmune reactions [503].

Roncati, et al. describe a case of ischaemic bowel and spleen [504]. They describe the histopathological findings and demonstrate evidence of fibrinoid necrosis. They suggest that naïve helper T-cells switch the immune system to a type-2 helper T-cell response rather than a type-1 helper T-cell response which then escalates to a type-III hypersensitivity reaction with immune-complexes deposited in the blood vessel walls resulting in a systemic vasculitis.

Mahdi proposes a model of COVID-19-related type-III hypersensitivity [505]. Favelli, et al. draw parallels between rheumatoid arthritis and COVID-19 and ask whether the latter can be consider an autoimmune condition [506]. Deshmukh, et al. report a case of collapsing glomerulopathy with COVID-19 in which there were no pre-existing risk factors and they attributed the pathology to COVID-19 [507]. Cossey, et al. note that there are many causes of collapsing glomerulopathy [508]. Gupta, et al. report two cases of collapsing glomerulopathy with podocytopathies and Sharma, et al. presents two cases of COVID-19-associated collapsing focal segmental glomerulosclerosis [509,510].

Towards a model of COVID-19 related coagulopathy

In our paper, we draw together the findings from many studies to develop a testable model as per Table 35 and the diagram mapping (Figures 10-21). This is a simple model with several components and is described by causal relationships but without quantitative descriptions of those same relationships. The purpose of this model is to serve as a starting point for further enquiry and to enable other researchers to refute or confirm these relationships or to quantify and expand upon them, thereby improving the understanding of the COVID-19-related coagulopathy (Table 35) (Supplementary Figures 10-21).

Table 35. A model of coagulopathy in COVID-19 colour coded according to Virchow's triad: Purple- three elements of Virchow's triad combined, yellow- hypercoagulability, blue-stasis, green-endo- thelial damage, black-not applicable, white-no category of Virchow's criteria, red- combination of endothelial damage and hypercoagulability, General evidence- evidence for relationship with coag- ulopathy independently of COVID-19, Evidence in COVID-19- evidence of relationship with coag-ulopathy in COVID-19.

Revised Taxonomy for COVID-19-related Coagulopathy Mechanisms	General Evidence	Evidence in COVID-19
A. Viral Life Cycle		
A1. Attachment		
A2. Penetration		
A3. Uncoating		
A4. Gene Expression and Gene Replication		
A5. Assembly		
A6. Release		
B. Host Immune Response		
B1. Non-Pathological Response		
B2. Cytokines		
B2a. IL-6		
B2a1.IL-6-associated coagulopathy	Moderate	Weak
B2b. Cytokine storm	Strong	Moderate
B3. Innate immunity-mediated mechanisms		
B3a. Alternative complement pathway activation	Moderate	Moderate
B3b. Neutrophil extracellular traps	Strong	Strong
B4. Adaptive immunity-mediated mechanisms		
B5. Antiphospholipid Antibody Syndrome-Like Coagulopathy	Strong	Strong
B6. Immunothrombosis	Strong	Strong
B7. Type-III hypersensitivity	Strong	Moderate
B8. Sepsis-induced coagulopathy	Strong	Moderate
B9. Sepsis-associated DIC	Strong	Weak
C. Hypercoagulable state		
C1. Hyponatraemia	Strong	Strong
C2. Hypokalaemia	Strong	Strong
C3. Calcium	Strong	Strong
C4. Dehydration	Strong	Nil
C5. Immune-mediated mechanisms (B2-B10)		
C6. Angiotensin II	Strong	Moderate
C7. Clotting cascade	Strong	Strong
C8. Hypoxaemia	Strong	Strong
C9. Hyperviscosity	Strong	Moderate
D. System Involvement		
D1. Cardiovascular		
D1a. Vasculature		
D1a1. Microangiopathy with thrombosis	Strong	Strong
D1a2. Endotheliitis	Strong	Strong

D1a3. Vasculitis	Strong	Strong
D1b. Myocardium		
D1b1. Direct invasion of the myocardium		

Revised aetiologies for COVID-19

The revised aetiologies are shown in Table 35. The revised aetiologies have been organised into categories following the preceding analysis. The general evidence is then considered for each potential aetiology and categorised as weak, moderate or strong. The general evidence refers to the evidence for this aetiology leading to a coagulopathy independently of COVID-19 and this is contrasted with the evidence for this aetiology leading to a coagulopathy in cases of COVID-19. The revised aetiologies then form the basis for the development of the model together with the corresponding narrative descriptions.

Discussion

We will now discuss our results, dividing this up into a general discussion of the findings, gaps in knowledge, a model of COVID-19-related coagulopathy, drawbacks of the study and then the next steps followed by a summary.

General findings on the nature of the COVID-19 related coagulopathy

In our mixed-methods scoping review, we were able to identify clinical evidence of a COVID-19-related coagulopathy. We found evidence of ARDS, sepsis and disseminated intravascular coagulation in cases with thromboembolic events (TBE). However we also found evidence of cases where ARDS, sepsis or disseminated intravascular coagulation had either not been confirmed or else had been excluded. Since ARDS, sepsis and disseminated intravascular coagulation have well-established causal links with TBE's they are likely to account for a subset of the events seen in COVID-19. Given the evidence for additional mechanisms associated with coagulopathy, we can demonstrate more generally that COVID-19 is a polycoagulopathy mediated by multiple coagulation mechanisms (MCM's).

The mechanisms for Sepsis-Induced Coagulopathy (SIC) were unclear. Nevertheless Liao et al found that sepsis-induced coagulopathy typically preceded DIC [511]. The non-overt DIC criteria may similarly be useful in COVID-19. Pulmonary thromboinflammation has been suggested as one of the main mechanisms leading to respiratory failure in COVID-19 and although the relationship of pulmonary thromboinflammation to endothelial inflammation elsewhere is not yet clear [512].

We found that pulmonary arterial embolism was one of the most frequent thromboembolic events. Benito, et al. found an incidence of PE's in COVID-19 of 2.6% in a cohort of patients in Barcelona [513]. Mackman, et al. report on the incidence of thrombosis in COVID-19 in various studies and find rates differ in ICU and non-ICU settings [514]. In ICU settings, the rates are VTE (4.8-69%), PE (16.7-35%), DVT (0.5-69%), arterial thromboembolism (3.8%), ischaemic stroke (2.7%). In non-ICU settings the rates are VTE (0.9-6.5%), DVT (0-46%).

Thromboembolism is unlikely to spare any vascular territory in COVID-19 although the pulmonary vasculature is likely to be commonly affected given the transmission dynamics of SARS-CoV-2 together with the anatomical considerations of the pulmonary vasculature. Natelello, et al. found evidence of microthrombi and microhaemmorhages from analysis of nailfold capillaries in patients with COVID-19 or else recovered from the acute illness [515]. Borczuk, et al. found the pulmonary vasculature was commonly involved in COVID-19 in their autopsy cohort and this includes macro and microthrombi [516]. Patel, et al. found evidence of reduced pulmonary perfusion in COVID-19 and suggested this as indirect evidence of thrombosis [517]. Chi, et al. found 23.9% of patients in 11 cohorts developed VTE [518].

Our findings suggest that there is evidence that the thrombi formed in COVID-19 may have unusual properties which merit further investigation. Kalinskaya, et al. investigated patients with COVID-19-related coagulopathy and found that in patients with COVID-19 compared to the control group the clots grew quickly, to a larger size and were lysed more quickly [519].

We suggest the construct of 'residual COVID' to describe residual irreversible ischaemic damage from thromboembolic events. The transience of the coagulopathy in COVID-19 also requires clarification. Garg, et al. report a case of a patient who had recovered from COVID-19 but developed pulmonary emboli despite treatment with warfarin although they suggested that the PCR result may have been a false negative [520].

Virchow's triad in relation to the COVID-19 related coagulopathy

The application of the model of Virchow's triad to the COVID-19-related coagulopathy highlights an important distinction between the arterial and venous system. Arterial thromboembolic events are usually a result of many decades of pathology, predominantly through the development of atherosclerotic plaques. Deep vein thromboses however can occur relatively acutely and more frequently and this reflects the importance of stasis. The veins are valved and contrast anatomically with the elastic, pulsatile arteries and the blood is more prone to coagulation in the venous system with reduced mobility. With COVID-19, we see this pattern is reversed and arterial thromboembolic events occur relatively frequently and acutely even in the absence of plaques.

There are three factors that are likely to account for this. Firstly there is the marked hypercoagulability. Secondly there is also involvement of the vasculature with combination of different pathologies that have been identified representing the endothelial involvement in Virchow's triad. A third more minor factor may be stasis secondary to cardiac involvement (e.g. atrial fibrillation).

The significance of the ACE-2 receptor

SARS-CoV-2 requires the ACE-2 receptor for entry into the cells. From our literature review, we identified evidence of a potentially significant role for the ACE-2 receptor in terms of the COVID-19-related coagulopathy. Firstly there is the location of the ACE-2 receptors which determines which tissues are directly involved (particularly the respiratory and cardiovascular systems). The second point relates to the effect on Angiotensin-II which is thought to be upregulated. Angiotensin-II has many effects including vasoconstriction and is thrombogenic. Thus by gaining entry to the cells via the ACE-2 receptor, SARS-CoV-2 sets in process a chain of events leading to an increase in the levels of circulating angiotensin thereby potentially contributing to hypercoagulability of the blood.

Mortality

The in-hospital mortality although high is in keeping with other studies [399]. The hospital sample likely represents the most severely unwell patients. We have thus characterized a syndrome that can occurs in severe cases although this does not negate this occurring in cases that are classed as less severe and this is discussed further in the next section. Whilst we had a small sample population from the subset of 34 studies there were a number of findings that would benefit from further replication studies. We found a particularly high mortality in association with acute limb ischaemia and it was not clear to us why this was. For other thromboembolic events such as strokes and STEMI's there are well-established care pathways informed by evidence-based policies. Given the high infection rate of COVID-19 even rare consequences of the infection will result in high case numbers due to the size of the infected population.

Characteristics of the population

The sample in the 56 main papers were all hospitalised patients and given the high mortality it is reasonable to assume that they represent the most unwell patients with COVID-19. Not all severely ill patients will be hospitalised due a variety of factors depending on the local healthcare

provision which varies significantly internationally. Not all patients seen in hospital may be severely ill. Additionally thromboembolic/ischaemic events may be subclinical. The question of how relevant the syndrome is to the wider population of all patients with SARS-CoV-2 infection would require additional information. This information could be gained retrospectively but ideally with a prospective cohort study with a comprehensive sequential assessment for thromboembolic events through the course of the acute illness.

Abridged thematic analysis

Thematic analysis is a method used in the analysis of qualitative data which can utilise both qualitative and quantitative approaches. There are three main approaches to thematic analysis: Coding book approach, coding reliability and reflexive/organic [94]. All of these approaches have one thing in common-the coding step which is considered central to the contemporary thematic analysis approach. Although thematic analysis has been referenced as far back as the 1950's in psychoanalysis and further back in other fields, the modern origins of thematic analysis are cited as 'The Thematic Origins of Scientific Thought' by Gerald Holton [521,522]. Merton notes that Holton appears to have used an inductive approach to the thematic analysis. Thematic analysis is a flexible method for analysis that has been used with a variety of different approaches [523].

Yardley draws attention to the variety of qualitative methodologies together with a diversity of philosophical underpinnings whilst also recognizing the importance of pluralism and the risks around evaluation [524]. Whilst (Yardley, 2000) highlights objections to the standardization of qualitative research, Greenhalgh and Taylor maintain that qualitative research should utilize "explicit, systematic and reproducible methods" [524,525].

The Abridged Thematic Analysis (ATA) solved an important problem in analyzing the content of a large number of papers with limited resources. The absence of the coding depends on an intuitive understanding of the material and a trust in the rater to identify the salient themes. We based the removal of the coding step on the philosophy of pragmatism [526]. We argue that in a pandemic, there is a strong ethical imperative to utilize and make available a methodology for rapidly analyzing clinical literature to gain invaluable insights and generate understanding and testable models. The coding approach becomes impractical due to the large number of papers and sampling would omit valuable material. Thus pragmatism has provided the philosophical underpinning for the carefully considered step of removing coding.

ATA is justified by analyzing material which is linked to an established theoretical infrastructure. Whereas the usual aim of thematic analysis is to describe the themes within the material, our further aim is to gain insights into COVID-19 in the midst of a pandemic. This further aim provides resource constraints including time and also the limited resources we had available to undertake the analysis. The analysis of the clinical material is most likely to be undertaken by clinicians working with limited resources. ATA is a suitable tool in these situations, meeting the need for clinicians to rapidly develop a clinical knowledge base to provide care for those with COVID-19. A more recent study confirmed a subset of the findings from our abridged thematic analysis including COVID-19-associated clots being refractory and susceptible to rethrombosis and reocclusions [527].

Turning to VATA, we needed to pivot firstly from understanding the perspectives of clinical experts in various fields and then hold in mind that our aim is to understand a viral illness. We therefore needed to validate our taxonomy as well as the themes themselves through the wider perspectives of experts across diverse fields. Whilst this may seem an ambitious undertaking, it is contextualized by the reality of the pandemic facing medical practitioners, allied healthcare professionals and the general public (Tables 36-38).

Gaps in knowledge

There are many knowledge gaps identified from this scoping review and we have included a selection of specific knowledge gaps that may help to inform future studies.

A. What is the role of the microvasculature in COVID-19?

For example Tibirica and De Lorenzo, suggest ways to investigate the microvasculature in critically ill patients with COVID-19 [528].

B. Does splenectomy predispose to increased severity of COVID-19 and if so is this mediated via coagulopathy?

C. Is coagulopathy a feature of Long COVID-19?

D. Do different permutations such as venous-arterial and venous-venous ECMO impact differently on thrombosis risk?

E. Do drugs that act on the Renin-Angiotensin-Aldosterone System (RAS) reduce the state of hypercoagulability?

F. What is the role of Endothelial stabilizing agents in COVID-19?

Weinbaum, et al. review the role of glycocalyx in various vascular-related diseases and note that the glycocalyx is a target for influenza viruses as well as SARS-CoV [529]. They also review a number of therapeutic agents for stabilising the glycocalyx. Wilson, et al. note that Adrenomedullin plays an important role in stabilising the endothelium in infection and call for an investigation of the role of Adrenomedullin in COVID-19 [530]. One study found that Adrenomedullin RNA was increased in patients with severe COVID-19 compared to mild illness [531].

G. Is there an association between mesenteric ischaemia and mesenteric fat in COVID-19?

Kaafareni, et al. has presented a case of mesenteric ischaemia with a pattern of yellow tissue overlying areas of ischaemia [119]. This can be seen clearly [532]. A case report may be of relevance here with the association of a congenital band associated with mesenteric ischaemia where they had earlier identified strands of fat [533]. Stanifer, et al. draw on experimental findings to suggest that intestinal cells are an active site of SARS-CoV-2 replication [534].

Ha, et al. suggests a mechanism whereby mucosa-associated gut bacteria in the fat may translocated to extraintestinal locations [535]. Coffey, et al. created a metric for mesenteric pathology which included 'fat wrapping' [536]. They found a significant correlation between this metric (mesenteric disease activity index) and the Crohn's disease activity index and argued for inclusion of mesentery in ileocolic resection for Crohn's disease. There is evidence for the involvement of adipose tissue in inflammation and immunomodulation [537,538].

Limitations of the study

There were a number of drawbacks in the study [539].

The search strategy to identify the main papers was not rigorous.

The search strategy was simple. A more rigorous approach may have yielded more results. Nevertheless we identified a number of robust studies and our methodology allowed for us to optimise the extraction of useful information from identified papers.

The search terms in the main search may have biased the outcome.

We used search terms which could have biased the study towards identifying thromboembolic events in specific anatomical locations such as strokes and pulmonary emboli. Nevertheless we identified other anatomical locations through the search.

The search strategy for exploring the various hypotheses for the aetiology was unstructured and prone to bias.

We acknowledge the limitations of the unstructured search strategy. The goal of this search was not to be definitive in answering questions but primarily to explore and test the various hypotheses that had been generated as the validation stage of the Validated Abridged Thematic Analysis (VATA). The diverse hypotheses cover many theoretical domains

and analysis requires a pragmatic approach but also enables triangulation and quality assurance.

Publication bias may be expected but we discounted hypotheses. We included systematic reviews and meta-analyses that typically address bias.

In the qualitative analysis, the absence of coding increases the risk of omissions from the identified themes or else misinterpretation.

The omission of coding was a pragmatic decision which is based on theoretical considerations. Content validity is tested by triangulation with an established evidence base. Whilst there is a risk of omission due to oversight, we have judged the benefits to outweigh the risks in terms of rapidly summarizing themes.

The patients in the 56 main papers were all hospital-based and therefore the findings do not generalize to all patients with COVID-19.

We acknowledge that more severe COVID-19 featured in many of the papers. Nevertheless a number of patients experienced thromboembolic events after an asymptomatic period or else having mild symptoms. The VATA and model-building drew on a wider literature base. Although not generalizable to all patients with COVID-19 we have characterised a syndrome that results from COVID-19 [540-579].

Hypotheses

We have developed a number of hypotheses for further investigation (See Appendix A).

Next Steps (See Appendix B)

The purpose of a scoping review is to review the subject area in preparation for further research. In this regards, we divide the proposed next steps into three. Firstly there are the immediate recommendations for reporting in papers in this area so as to move towards a standardized approach which will facilitate data aggregation. Secondly we recommend specific processes that will facilitate a Decentralized Research Program (DRP). Thirdly we make recommendations about developing a symbolic representation of causal links. This has a more general usage case than the COVID-19-related coagulopathy but this recommendation results from the problems that have been encountered both in terms of healthcare delivery in the pandemic as well as the challenges we have faced in writing this paper. This third type of recommendation requires a more profound change in practice and may not be achievable in the short-term but is particularly well-suited to meeting the challenges of a pandemic. The next steps are covered in more detail in the appendix.

Recommendations

We have developed a number of recommendations for future research studies in this area (See Appendix C)

Conclusion

We conclude with a summary of the main findings in this paper and determine from our evidence that SARS-CoV-2 infection leads to a viral clotting fever syndrome with high mortality although the prevalence is unclear from this data. COVID-19 is a polycoagulopathy with multiple clotting mechanisms (MCM's) causing serious clinical thromboembolic sequalae. Our findings are based on a population that was hospitalised and of more advanced age. Fever occurred in most but not all of the patients with this presentation and therefore the clotting fever syndrome is an indication that if both fever and clotting events occur that COVID-19 should be considered as a differential. The absence of fever or thromboembolic events should not discount COVID-19. The D-dimer is a key prognostic indicator in COVID-19 and bears special significance as a marker of underlying thromboembolic events. In the most severe cases, the D-Dimers were elevated up to some 200-fold over the upper limit of the reference range with significant clinical correlates.

Overall we found an average of 1.3 thromboembolic events per patient but these were predominantly arterial rather than venous in nature albeit where we had classified pulmonary emboli as arterial rather than venous on the basis of the vessel anatomy rather than the consideration of the flow of blood towards or away from the heart. This is particularly relevant in COVID-19 given the distribution of ACE-2 receptors in the smooth muscle cells which in turn are more densely arranged in the arterial vasculature. Of note is that we found not a single case of pulmonary vein thrombosis in the 56 main papers whilst pulmonary arterial emboli were found in abundance.

We found that there were five main groups of arterial thromboembolic events according to arterial territories-splanchnic arteries, coronary arteries, pulmonary arteries, the femoral and other arteries of the lower limbs as well as the cortical and subcortical arterial supply but particularly the middle cerebral arteries. The involvement of these territories leads to characteristic signs and symptoms which are well-established in the literature and where further work can lead to clinical algorithms and the development of public health messages with sufficient evidence. We also identified carotid artery thromboemboli in association with strokes and many authors drew attention to this important finding. Thrombi were also found in the aorta and the heart. We found sporadic reports of the involvement of the veins with the exception of the deep veins in the lower limbs which were more frequently identified. Of special note is the occurrence of thromboembolic/clotting events in association with medical devices which we use broadly to include catheters, ECMO centrifuges and dialysis machines. The occurrence of upper limb DVT's was predominantly associated with catheters.

A combination of more general factors in the setting of either mild or severe illness may also contribute. The insensible fluid loss from diarrhoea and vomiting may lead to dehydration and electrolyte disturbances. Periods of immobility may increase the risk of a lower limb DVT. Hypokalaemia and hyponatraemia may both predispose to atrial fibrillation which in turn results in cardiac muscle stasis and generation of thrombi and subsequent thromboembolic events. The disruption of the RAA system may impact on the correction of these disturbances.

On analysis of a subset of papers, we were able to quantify other findings albeit on the basis of a small sample size which limits our ability to generalise these findings and suggests that these findings need to be further validated. We found sex differences amongst the occurrence of arterial thromboembolic events as well as differences in mortality. We draw special attention to the occurrence of acute limb ischaemia in COVID-19 which is associated with a particularly high mortality albeit with evidence of selection bias in the data we analysed and which merits further attention.

The qualitative analysis identified the general clinical findings with an experiential (clinical) account. Thus clots were described in unusual locations, occurring in multiple territories and with unusual findings such as desert foot. During interventions, the thromboemboli were found to be friable, breaking away and further embolising into new territories. Repeated occlusion of arteries was identified after recanalisation and in one case the clot was altogether undetachable from the arterial wall necessitating an alternative surgical procedure. Thromboemboli occurred despite prophylactic anticoagulation. Patients would present with serious clinical thromboembolic events after being either asymptomatic or else with an apparently mild course of the illness.

In terms of the validated abridged thematic analysis, we were able to assess the content validity of the proposed aetiological mechanisms by means of an examination of the literature. This was not limited to the papers screened in an exploratory literature search but also with reference to the other papers we had examined for the purposes of this scoping review. By means of an iterative process utilised in thematic analysis we were then able to assemble the selected mechanisms into taxonomy. Furthermore we were able to translate the taxonomy into a rudimentary symbolic representation, a process which may be of use to other clinicians and researchers investigating this field of enquiry as the model can be extended and refined.

In theoretical terms, we utilised Virchow's triad as a means of structuring the taxonomy. We were able to confirm overarching themes of hypercoagulability, vascular wall involvement and to a lesser degree stasis. The primary pathology would appear to be the viral invasion of the endothelium which is mediated via the ACE-2 receptors which together with heparin sulfate affords the virus a route for entry into the cells. Once inside the cells, the virus appropriates the cellular machinery and escapes RNA intracellular sensing mechanisms by means of the construction of replication organelles including double membrane vesicles. The RNA sensing mechanisms typically trigger an interferon response upon successful detection and it should be noted that the interferon response or lack thereof appears critical in determining the subsequent course of the illness. An exaggerated interferon response may result in a mild illness and possibly chilblains as a dermatological finding. A delayed interferon response may result in a more severe course and this may be of more relevance to the risk of coagulopathy and the concept of immunosenescence may also be relevant.

Following the invasion of the endothelium, there is found to be endotheliitis and also various degrees of thrombosis in the small blood vessels. From our examination of the literature there appear to be many details requiring clarification but there are a few events which appear to be more robustly supported in the literature. Firstly the endothelium is specialised according to the organ in which it is located. In the lungs, the blood vessels have a physiological function of ventilation-perfusion matching whilst in the kidneys this forms part of the filtration mechanism. The viral invasion appears to degrade the function of the endothelium and it would appear that together with a disruption of the RAA axis likely resulting from the utilisation of the ACE-2 receptors, there is a subsequent degradation of ventilation-perfusion matching and glomerulofiltration if those organs are affected. The ventilation-perfusion mismatch is likely to account for the phenomenon of silent hypoxia which is of significant consequence in clinical management and hypoxaemia contributes to the risk of a coagulopathy. A disruption in glomerulofiltration results in impaired plasma filtration with significant consequences for various homeostatic mechanisms including those of the electrolytes.

The consequences of the invasion of the endothelium by the virus can also be considered in terms of thromboinflammation. The construct of thromboinflammation is well supported in the literature and it is clear that platelet activation plays a significant role in COVID-19. The key question here is the role of the endothelial glycocalyx. There is evidence of disruption of the glycocalyx in COVID-19 and this would result in a local prothrombotic environment and would lead to platelet activation. One of the components of the glycocalyx is heparin sulfate which is required for viral entry into the cells and so the disruption of the glycocalyx would be more likely secondary to viral invasion of the endothelium. A special role may be played by hyaluronan with evidence that in COVID-19 it leads to the creation of a gel in the lungs which may contribute to hypoxaemia. With the seeding of the virus in the lungs and then in the endothelium of other blood vessels, thromboinflammation would result in the generation of a thrombus. The properties of the thrombus would predispose to embolisation including a possible contribution from components of the locally disrupted glycocalyx. The arterial wall would be an ongoing source of thrombogenesis. The role of susceptibility factors is also of importance and in particular endothelial dysfunction is related to the metabolic syndrome. This likely contributes to a low grade inflammatory, prothrombotic potential and a possible vulnerability to viral invasion.

Another important aspect of the pathology is the role of the neutrophils. One clear finding is the presence of NETs and when taken together with the evidence of apoptosis and related mechanisms, a key feature of COVID-19 is exposure of intracellular material to the extracellular environment. Thus while the virus has carefully avoided detection in the intracellular space through the replication organelles, the intracellular material of the host cells is exposed. There is thus the potential for the host immune system to generate an autoimmune response. Furthermore if the tissue destruction is overwhelming and the clearance insufficient then there may be a large amount of circulating antibody complexes leading to a type-III hypersensitivity response in a minority of cases. This in turn can lead to deposition of immune complexes in the skin, kidneys and vasculature with the latter resulting in a vasculitis which can predispose to further thromboembolic events.

Finally returning to the original question in this paper, we found evidence of thromboembolic events with and without each of sepsis, DIC and ARDS.

We conclude with Tables 37 and 38 which summarise the main results of the qualitative and quantitative analysis and these should be used in conjunction with Table 35 and Figures 10-21 and with the section on the limitations of the study.

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