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Immune Mediated of Pulmonary Intravascular Coagulopathy (PIC) in COVID-19 Penumonia

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Abstract.

The lung pathology seen in patients with COVID-19 shows significant microvascular thrombosis and haemorrhage linked to extensive alveolar and interstitial inflammation, which shares features with macrophage activation syndrome (MAS). We have termed the lung-restricted vascular immunopathology associated with COVID-19 as diffuse pulmonary intravascular coagulopathy (PIC), which is distinct from disseminated intravascular coagulation (DIC) in its early stages. Raised D-dimers and cardiac enzymes— respectfully reflecting pulmonary vascular bed thrombosis with fibrinolysis and emergent pulmonary hypertension-induced ventricular stress—in the face of normal fibrinogen and platelet levels, are key early features of severe COVID-19-related PIC. Extensive immunothrombosis over a wide pulmonary vascular territory with lack of confirmation of COVID-19 viraemia in early disease best explains the adverse impact of male sex, hypertension, obesity and diabetes on the prognosis of patients with COVID-19. The immune mechanisms that underlie diffuse alveolar and pulmonary insterstitial inflammation in COVID-19 includes a MAS-like state that triggers extensive immunothrombosis, which might unmask subclinical cardiovascular disease and is distinct from the MAS and DIC that is familiar to rheumatologists.

Keywords: COVID-19; pulmonary intravascular coagulopathy (PIC); disseminated intravascular coagulation (DIC); macrophage activation syndrome; thrombosis; immunothrombosis; diffuse alveolar damage.

Introduction

The COVID-19 pneumonia pandemic and earlier coronavirus outbreaks have been associated with adult respiratory distress syndrome (ARDS) and a worse outcome in older subjects than in younger ones.[1,2] The severity of the systemic inflammation in response to the human coronavirus family members has features reminiscent of a cytokine storm or macrophage activation syndrome (MAS), also known as secondary haemophagocytic lymphohistocytosis (HLH).[3,4] This has inspired use of directed anti-cytokine therapy strategies for severe COVID-19 pneumonia, as these agents are known to be useful in MAS spectrum disease[4,5]. A key feature of HLH/MAS is haemophagocytosis and an acute consumptive coagulopathy leading to disseminated intravascular coagulation (DIC), which has also been reported in COVID-19 pneumonia, but usually as a pre-terminal event.[6,7] Indeed, the hypercytokinaemia with extreme hyperferritinaemia that is typically seen with viral HLH is evident in some patients with COVID-19 pneumonia.[8]

COVID-19 Pneumonia is distinct from Macrophage Activation Syndrome

We recently described how the MAS-like pulmonary immunopathology characteristic of COVID-19 pneumonia is distinct from classical HLH.[9] Haemphagocytosis is a cardinal feature of MAS,[10,11] and has also been reported in SARS.[12,13] In SARS, this process might involve phagocytosis of extravascular red blood cells consequent to severe lung micro-vascular damage, micro-haemorrhage with physiological haemophagocytosis of extravascular red blood cells (Figure 1B), or possibly very advanced disease with frank MAS-like pathology and DIC (Figure 1). The hypercytokinameia of MAS/HLH is often associated with extremely high serum ferritin concentrations (10,000 - 100,000 ng/mL or higher), whereas in patients with COVID-19, serum ferritin concentrations are typically in the 500 - 3,000 ng/mL range, at least early in the illness. Another clear distinguishing feature between COVID-19 pneumonia and MAS/HLH is the liver function derangement that is characteristically seen in MAS/HLH and can contribute to coagulopathy secondary to loss of liver syntethic function (Figure 1).

Extensive lung infiltration by macrophages and other immune cells has been reported in SARS pneumonia, with similar findings emerging in patients with COVID-19 pneumonia,[13-16] leading to diffuse alveolar damage. The extensive nature of SARS-CoV-2 viral infection results in diffuse inflammation that involves the large juxtaposed pulmonary vascular network,[17] and this diffuse, slowly evolving COVID-19 pneumonia has similarities to a MAS-like clinical and laboratory picture. These clinical findings suggested to us that an initial pulmonary intravascular coagulopathy (PIC) occurs in patients with COVID-19 pneumonia that is distinct from DIC.[17] Herein, we propose a model for the pathophysiology of this PIC and describe how extensive coronavirus infection and age-related changes in immunity, combined with diffuse pulmonary immunothrombosis, explains the cardiovascular mortality in these patients (Table 1).

Pulmonary Vascular Pathology Patterns in SARS and COVID-19

Acute respiratory infections are associated with a higher risk of cardiovascular related death, especially in the weeks immediately after infection, and particularly in older patients, and those with pre-existing cardiovascular disease. Severity of pneumonia in these patients is linked to an increased risk of death.[18,19] Of particular note, one pathological study demonstrated similar vascular changes in post-mortem tissue obtained from subjects succumbing to non-SARS-related bronchopneumonia as in those who died from SARS,[20] indicating that vascular thrombosis triggered by infection, rather than the infection itself, may be key (Figure 2).

Coronavirus family members show tropism for ACE2 on type II pneumocytes. This tropism, along with the close anatomical juxtaposition of type II pneumocytes and the pulmonary vascular network and severe, multifaceted inflammatory reactions, likely drives the generalised pulmonary hypercoagulable state in a pneumocyte-interstitium-pulmonary endothelium-small pulmonary vessel axis[17,21] (Figure 2). It has recently emerged from single cell sequencing analysis that the vast majority of pulmonary ACE2 gene expression is confined to a small population of type II pneumocytes and is largely excluded from endothelial cells and alveolar macrophages.[22] From a clinical perspective, diffuse alveolar changes (determined by CT scan) are distinct from bronchopneumonia and show how COVID-19 interfaces with a large area of the pulmonary microvasculature. This likely explains the propensity for diffuse pathology in patients with COVID-19 pneumonia. Indeed, extensive air space changes on CT associate with a worse prognosis in patients with COVID-19 pneumonia;[23] indeed diffuse disease on CT is also a feature of subjects who succumbed to SARS infections (Figure 2).[24]

ACE2 has been shown to regulate innate immunity and, in mice, genetic deletion of Ace2 leads to more severe pulmonary inflammation after acid inhiliation.[25] These findings suggest that ACE2 downregulation could aggravate extensive inflammation over a wide alveolar-capillary network. Indeed it was subsequently shown that injecting the SARS spike protein in mice leads to similar lung pathology, likely due to internalisaiton of the Ace2 receptor and subsequent inhibition of Ace-2-mediated generation of the immunoregulatory angiotensin 1-7 peptide, which signals via the Mas receptor.[24] Ace2 deficiency was also associated with a more severe pneumonitis and a higher mortality in a mouse model of influenza infection.[25] Theoretically, a similar mechanism could increase the proclivity towards immunothrombosis in man. In humans, the MERS coronavirus principally uses the DPP4 receptor, which is not restricted to type II pneumocytes; this virus results in clinical features and pathology similar to SARS and SARS-CoV-2, including a high mortality rate.[26] Analogous to ACE2, in some experimental systems the DPP4 receptor may negatively regulate lymphocyte function, which could point to shared coronavirus mechanism contributing to PIC (Table 3) [27].

Pulmonary Vascular Disease in SARS and COVID-19

The SARS-CoV-2 and SARS virus genomes are highly homologous and patients infected with these viruses appear to share common clinical and pathological features.[28,29] Initial post-mortem reports from three SARS cases indicated diffuse alveolar damage and small pulmonary vessel thrombosis and haemorrhage, but also a more generalised small vessel thrombosis;[30] a second study of 6 cases reported vascular pathology in 2 cases.[13] A later

study of pathological specimens from 20 patients with SARS confirmed the presence of diffuse alveolar damage but also noted fibrin thrombi, small vessel occlusion, and pulmonary infarction in upwards of 80% of cases.[20] A review of aggregated SARS pathology reports shows evidence for vessel wall oedema, inflammatory cell infiltration into the walls of the pulmonary microvasculature, significant haemorrhagic necrosis, and vessel microthrombus mostly confined to the lung and pulmonary tissue infarction, in the context of septal inflammation and diffuse alveolar damage.[31] Limited data have emerged from patients with COVID-19 pneumonia, and these data paint a similar pulmonary vascular picture with blood vessel wall oedema, modest vessel wall immune cell infiltration, hyaline thrombosis, haemorrhagic change and infarction.[15,32,33] Emergent data have also emphasised prominent capillary thrombosis,[33] and one study also reported cardiomegaly and right ventricular dilatation, pointing toward the expected development of pulmonary artery hypertension.[31]

Lack of Evidence for Coronavirus Myocarditis or Coronary Vasculitis

Myocarditis may occur after severe respiratory viral pneumonia; this is relatively rare but well documented, especially in younger females following influenza infection (Table 2). Understandably, raised cardiac enzymes in patients with COVID-19 have been taken to potentially represent myocarditis or virus-associated cardiac vasculitis. In SARS virus infection, most evidence points away from cardiac involvement.[34,35] The ACE2 receptor is also expressed on endothelial cells, and one in situ hybridisation study suggested that pulmonary endothelial cells are infected.[36] Other studies showed a complete absence or very low level of potential endothelial cell infection.[34,35] Moreover, another study in patients with SARS suggested a close link between infection of pneumocytes and inflammatory cytokine expression in the same cells,[37] but this was not reported for endothelium. Recent publications indicate that SARS-CoV-2 RNA was undetectable in the blood[39] or was detected in only 15% of cases,[40] again arguing for a pathology centred around pneumocytes and adjacent tissue pathology rather than systemic viral infection (figure 2).[38,39]

A role for the ACE2 receptor in cardiovascular biology predates the link between pulmonary pathology and COVID-19 pneumonia. Genetic deletion of ACE2 in rodents was associated with ventricular contractility defects but no evidence of cardiomyopathy or fibrosis.[40] The link between ACE2 downregulation in lung tissue, either in genetically manipulated mice or mice treated with SARS-spike protein, and increased inflammation suggests a relatively simple model whereby coronavirus infection of ACE2-expressing cardiomyocytes or cardiac endothelium may trigger a similar inflammatory pathology. In the most comprehensive study of cardiac involvement in patients that succumbed to SARS, viral RNA was detectable in a third of post-morten cardiac tissues and was associated with decreased ACE2 expression and increased macrophage infiltration.[41] The same study showed no evidence of myocyte necrosis or lymphocytic infiltration, both hallmarks of viral myocarditis[42]. Overall autopsy reports, including those emerging in COVID-19, vary from showing no significant pathology, infiltrating macrophages, and some reports of occasional infiltrating CD4+ T cells[33].
The cardiac pathology in SARS-Cov-2 pneumonia needs evaluation in the light of known cardiovascular comorbidities including hypertension and PIC and the MAS-like state with associated hypoxaemia and secondary pulmonary artery hypertension. The hypercytokinaemia that is part of the MAS-like state and is independent of viraemia may also

influence ACE2 tissue expression. One key cytokine characteristic of MAS-like pathology, IFNγ, has been shown to downregulate ACE2 expression on am epithelial cell line, but this has not been reported for heart cells.[43] Therfore, reported changes in the heart tissue including endothelium could represent a cytokine and hypoxia effect rather than viral infection.

Laboratory data point towards early Pulmonary Intravascular Coagulopathy

The key early laboratory observations in patients with COVID-19 pneumonia are an elevated plasma D-dimer concentration in conjunction with elevated cardiac markers, including brain natriuretic peptide, creatinine kinase, and troponin-T; elevation of the latter at hospitalisation is linked to a poor prognosis.[44] In keeping with this, a previous study has reported that elevated plasma levels of fibrin degradation products, including D-dimers, constitutes a significant independent biomarker of poor prognosis.[6] For example, Zhou and colleagues reported that 90% of patients presenting with COVID-19 had increased activation of coagulation, as indicated by elevated D-dimer concentrations at presentation.[23] Importantly, D-dimer concentrations above 1μg/ml were associated with an 18-fold increased odds ratio for fatal outcome.[23] Furthermore, progressive elevation of D-dimer and fibrin degradation products were seen in non-survivors.[23] However, despite this increase in D-dimers, patients with COVID-19 do not typically develop overt systemic DIC. In rare cases of COVID-19 in which overt DIC does develop, it tends to be restricted to late-stage disease. This is reflected in the consistent observation that platelet counts and fibrinogen concentration are not significantly reduced in patients with COVID-19 despite marked increases in D-dimer concentrations[45]. Indeed, fibrinogen generally remained elevated in these patients, in keeping with an ongoing acute phase response.

Extensive Pulmonary Inflammation and thrombosis in COVID-19 Pathology

As mentioned, severe COVID-19 sepsis is associated with a marked MAS-type picture with increased inflammatory markers and ferritin concentrations that undoubtedly results in local activation of pulmonary vasculature endothelial cells. For example, interleukin (IL)-1, IL-6 and TNF have all been shown to trigger acute endothelial cell activation.[46] Given the critical roles played by endothelial cells in maintaining normal haemostasis, regulating fibrinolysis, and determining vessel wall permeability, local endothelial cell dysfunction in the pulmonary microvasculature is likely to play an important role in the thrombo-inflammatory processes that ultimately results in COVID-19 vasculopathy, V/Q mismatch, and a clinical phenotype of refractory ARDS.

In addition, the MAS-like picture associated with COVID-19 pneumonia will trigger expression of active tissue factor on endothelial cells and activated infiltrating macrophages and neutrophils.[46] The net effect will be local presentation of blood-borne tissue factor within the lungs, which will further amplify activation of the coagulation cascade. Importantly, endothelial cell disruption, tissue factor expression, and activation of the coagulation cascade activation will all be progressively exacerbated by development of local hypoxia,[47] establishing a deleterious positive thrombo-inflammatory feedback loop within the small

vessels of the lungs with thrombosis and haemorrhage (figure 3). Beyond these coagulopathic changes occurring within the pulmonary vasculature, previous studies of broncoalveolar lavage have shown that both severe pneumonia and ARDS are associated with enhanced thrombin generation and fibrin deposition within the bronchoalveolar system.[48] These changes correlate with severity of inflammation[49] and are primarily driven by upregulation of tissue factor expression within the alveoli, coupled with a reduction in fibrinolysis induced by plasminogen activation inhibitor-1.[50] The biological mechanisms responsible for the extremely elevated plasma D-dimer concentrations in patients with severe COVID-19, together with the marked inter-individual variations observed, remain unclear. Nonetheless, these data clearly suggest hyperactive fibrinolysis with increased plasmin generation. Collectively, these findings have led to the recent suggestion that elevated plasmin(ogen) levels may represent a risk factor for COVID-19 susceptibility.[51]

Hypoxaemia development secondary to COVID-19-induced ARDS might also activate the coagulation cascade and could be important in endothelial dysfunction beyond the capillary network; hypoxaemia might also play a role in adjacent small pulmonary vascular thrombosis.[52,53] Other factors including mechanical ventilation in patients progressing to ARDS might contribute to this picture. The role of vascular microrthrombi formation, or immunothrombosis, in containment of bacterial infection and spread is well established, but its role in viral infection remains less well established.[54] Likewise, the role of local pulmonary intravascular immunity and its impact on the PIC phenotype is completely unknown.[55] Nevertheless, adenoviral access to the circulation in an artificial model system triggers a MAS-like phenomenon with DIC.[56] The role of positive pressure ventilation as a factor driving release of viral nucleic acids and proteins across damaged alveolar-endothelial cell barriers is another factor that needs consideration as an iatrogenic contributor to immunothrombosis and poor outcomes.

Finally, it has also been demonstrated in experimental SARS models that normal aged primates have a similar degree of viral replication as younger primates, but that aged primates have more pulmonary damage and lower activation of type 1 interferon responsive gene pathways.[57] At the molecular level, aged mice showed exacerbated innate immune responses associated with NF-kB gene pathway activation. including elevated IL-8, and also elevated expression of tissue factor—the key extrinisic clotting pathway protein.[57] It is well established that type 1 interferon responses decrease with age in humans,[58] including in response to viral infection, but at what age this transition occurs needs better definition.[59] Viral or age-related impairment in type 1 interferon cytokine production appears to be associated with a second wave of inflammatory cytokine production and tissue factor expression that might substantially contribute to PIC.

Implications of PIC

The role of anti-coagulation in the setting of COVID-19 PIC is of considerable interest. Expert recommendations for the use of anti-coagulants have already been published, reflecting the recognition of clotting dysregulation.[60] The potential relevance of anti-

cardiolipin antibodies in the COVID-19 critical care setting is also recognised but is of uncertain significance.[61] However, some data are available, mostly derived from prospective non-randomised cohort studies. In a study of nearly 450 COVID-19 cases, low molecular weight heparin (mostly used in prophylactic rather than therapeutic doses) did not confer an overall survival advantage but was associated with improved survival in the group with a high sepsis induced coagulopathy (SIC) score and also in those with D-dimer concentrations more than 6 times the upper limit of normal.[45] The role and timing of anticoagulation in this extensive virus-related immunothrombosis, especially where pulmonary haemorrhaging occurs, needs very careful consideration. In DIC, thrombosis and bleeding may occur simultaneously, and the same scenario appears to also arise in PIC (Figure 3).

Given the MAS-like pathology of COVID-19 pneumonia, the question arises whether anti-cytokine therapy will ameliorate the diffuse immunothrombosis process associated with severe cases. In the translational setting, the use of the IL-1β blocker canakinumab is associated with a decreased risk of all-cause cardiovascular mortality,[62] with an increased benefit in patients with the most dramatic reductions in serum IL-6.[63] Unlike in low grade arterial inflammation in the absence of overt infection, it remains to be seen whether the severe COVID-19-associated MAS with PIC will be successfully targeted using these strategies, but ongoing viral infection might represent a major hurdle.[17] Recently it has also emerged that the the coagulation and immune systems are directly linked via thrombin cleavage of IL-1α from macrophages and platelets. This novel mechanism is of special interest with regard to anakinra, which blocks both the IL-1α and IL-1β pathways, whereas monoclonal antibodies such as canakinumab selectively block IL-1β.[64]

The most critical question is whether the emergent early activation of coagulopathy and fibrinolysis in patients with COVID-19 pneumonia is purely due to an appropriate immune response to the virus, or whether there is a degree of excessive inflammation that could be targeted to help prevent PIC progression. The potential survival advantage of drugs pioneered to treat inflammatory and hyper-inflammatory states needs to be viewed through the lens of severe diffuse pulmonary immunothrombosis. The combination of immunomodulatory and anti-coagulant strategies in patients with high D-dimer concentrations and evidence of myocardial stress warrants especially close attention. The use of JAK pathway inhibition needs careful scrutiny given the association between JAK inhibitors and thromboembolic disease.

Some bleeding complications outside of the lung have been described in patients with COVID-19. This is perhaps unsurprising in the minority of PIC cases that progress to systemic DIC. Reports of acute necrotising encephalopathy, which is associated with haemorrhage, are emerging.[65] However, this rare condition is well recognised in association with viral infections in general.[66] Given that ACE2 is expressed on endothelial cells, the notion of thrombosis outside PIC or DIC needs further consideration.

This PIC model has implications for understanding cardiovascular mortality in the current pandemic. It shifts the focus away from COVID-19-related myocarditis or coronary vascular

involvement secondary to viral infection of ACE2-expressing myocytes or endothelial cells, with cardiac injury and toward a scenario of multisite pulmonary vascular thrombosis with progressive myocardial ischaemia. The immunthrombotic pathology that evolves over several days will more likely manifest in patients with underlying cardiovascular risk factors such as obesity, hypertension, and type 2 diabetes, and will be compounded by the cardiac ischaemia that accompanies ARDS development. Cardiovascular mortality is significantly higher in men than women aged 30 to 64 years in many different populations.[67] These well known risk factors might also account for racial differences in COVID-19 mortality [68,69]. The COVID-19 pandemic with profound immunological changes that constitute a pulmonary MAS-like picture is revealing a large burden of subclinical cardiovascular disease in predisposed subjects by slowly triggering an extensive pulmonary immunothrombosis. Our model offers a different and more robust alternative to the proposed impact of medications on ACE2 expression with increased viral infectivity.[70] It is also important to determine to what degree COVID-19-mediated diffuse alveolar damage with ARDS development in the absence of coagulopathy may also contribute to outcomes since emerging post-mortem reports do not report this pathology in all cases.

Finally, diffuse PIC is not unique to the MAS-like pattern of inflammation. Diffuse alveolar infection, activation of innate immune mechanisms, including dysregulation of ACE2 protein expression, and marked adaptive anti-viral immune responses could contribute to extensive pulmonary immunothrombosis without a clinically evident MAS (Table 3). Will this translate into differential efficacy, if any, of immunosuppressive therapy between the MAS-like subgroup and those without MAS? Ultimately, the tropism of COVID-19 for type II pneumocytes, along with evidence for extensive microvascular thrombosis during a global pandemic in subjects without natural immunity points towards an explanation for the increased cardiovascular mortality following respiratory infection that has been recognised for some time in other settings. We believe that this PIC, or pulmonary immunovascular coagulopathy, represents the best explanation for the COVID-19 pneumonia risk factors for poor survival including cardiovascular disease in the present scenario where there is little evidence for systemic viraemia in early disease[39].

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Authors contributions:

DM+CB - conception, literature review, final draft writing, critical revision
JSO - first draft writing, literature review, critical revision, editing.
KS - first draft writing, figures, editing.
PE- final draft editing and final approval

All the authors have participated sufficiently in this work, take public responsibility for the content and have made substantial contributions to this research. This manuscript has not been submitted to another journal and has not been published in whole or in part elsewhere previously

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Table 1-Differences and Similarities Between DIC and PIC

Clinical Features	**Disseminated Intravascular Coagulation (DIC) linked to HLH/MAS**	**Pulmonary Intravascular Coagulopathy (PIC) linked to COVID-19**
Onset	Acute	Subacute
Hepatosplenomegaly	+++	
Adenopathy	++	
Pulmonary Involvement	50%	100%
Thrombosis	Multi-organ clotting	Mainly lung (Occasional central nervous system and peripheral thrombosis reported- related to DIC evolution?)
Bleeding	Generalised	Intrapulmonary micro-haemorrhage
Active Infection Considerations	Yes- usually for primary HLH Secondary HLH may not have driving infection	Thought to be ongoing alveolar infection
Laboratory Parameters		
Liver Function	Raised Transaminase +++ Decreased synthetic function including fibrinogen and other clotting factors	+/- Preservation of liver synthetic function
Anaemia	+++	-
Thrombocytopenia	+++	Normal/low
Immune Cell Cytopenia	++	No- but lymphopenia a feature of COVID-19 in general
Creatanine Kinase	+ (skeletal and cardiac origin)	+ (worse prognosis)
Troponin-T	+	++ with higher levels associated with worse outcome
Haemophagocytosis	Generalised to marrow, liver and other sites detectable in 80%+	Occasional intrapulmonary and regional lymph node haemophagocytosis reported
Evolution	 DIC secondary to MAS	PIC may evolve into DIC PIC may occur without MAS
Coagulation & Immunology		
Elevated PT/ APTT	+++ / +++	+/normal
Fibrinogen levels	Decreased	Normal/slight increase
FDPs/D-Dimer	Increased	Increased
CRP	Elevated	Elevated
Ferritin Elevation	+++	Elevated
Hypercytokinaemia	+++	++

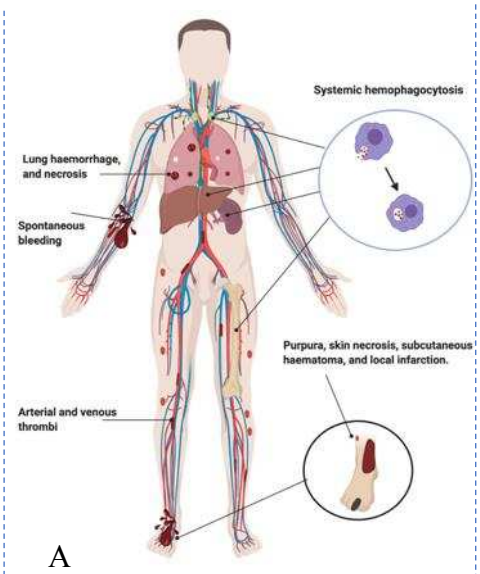
Table 2- **Cardiovascular Disease, Myocarditis and Infection**

	Findings	Ref.
Cardiac Injury not specific to COVID-19	Cardiac injury in 60%+ with Avian Influenza (H7N9) suggesting that cardiac disease linked to infection. Also linked to history of cardiovascular disease but not male sex or diabetes (Note myocarditis well documented with influenza in other studies summarised below)	[71]
	pandemic (H1N1) 2009 virus 46% Cardiac Injury Mean age 34 Female more common than male Presumed Myocarditis- No histology/ No post mortem data	[72]
COVID-19 Viral Access to Heart	No Viraemia in 9 cases in COVID-19	[39]
	"RNAemia in only 15%" Cardiac injury linked to ICU admission and not RNAaemia	[38]
Endothelial cells	Express ACE2 but cytopathic changes that are seen in pneumocytes not reported	[37]
Cardiac Myocytes in Human	With SARS no cytopathic change Lack of SARS viral protein detection	[34]
Community Acquired pneumonia Bronchopneumonia	Increased risk of cardiovascular death	[18,19]
Other factors linked to cardiac Pathology	Older age, Male sex, Hypertension, Obesity, Diabetes Hypoxia from ARDS development Emergent DIC late in COVID-19 disease	
Viral Myocarditis	H1N1 Influenza A Virus. Rare link to Fulminant Myocarditis Reported	[73]
Viral Myocarditis	47 Cases of Fatal Influenza Virus, Children/ Female predominant Myocarditis deemed to be cause of death in 5 cases	[74]

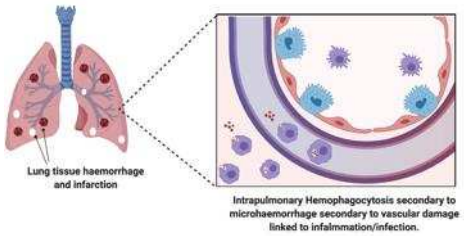
Table 3- Immune Factors contributing to Pulmonary Intravascular Coagulopathy

• Diffuse alveolar damage and inflammation
• Diffuse interstitial inflammation
• Extensive pulmonary macrophage activation “MAS-like”
• Dysregulation of pulmonary innate immune e.g. ACE2 receptor expression downregulation?
• Adaptive Immune Responses to COVID-19
• “Inflammaging”- activation of innate immunity with greater age
• Age related coagulation cascade changes
• Mechanical Ventilation forcing viral immunostimulatory molecules into micro-vasculature increasing the propensity towards immunothrombosis

Figure 1



A



B

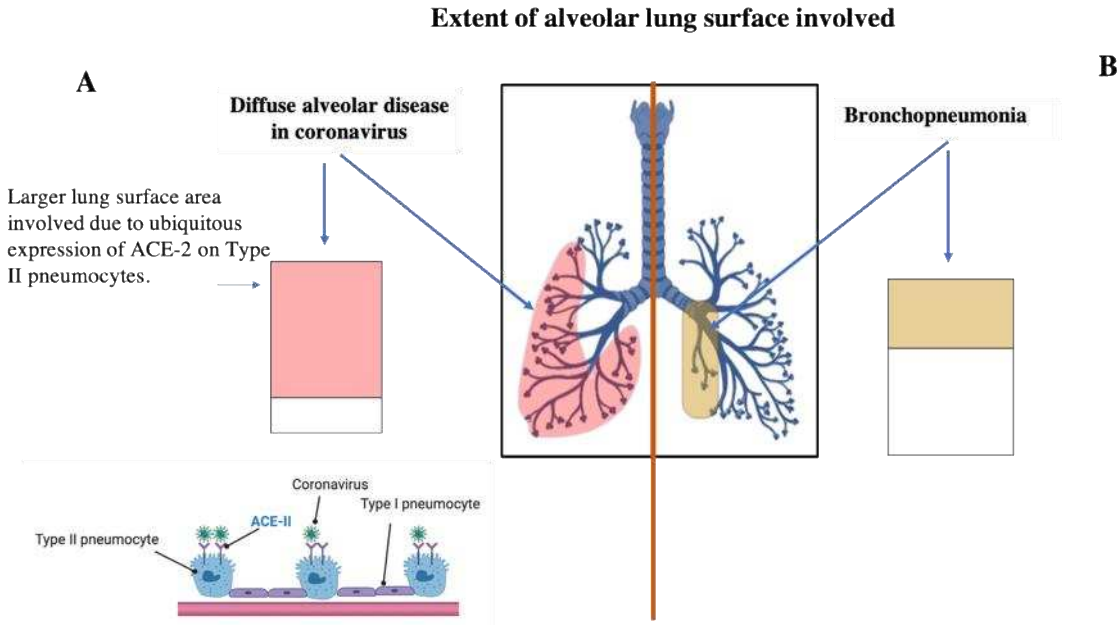
	Early MAS Picture	Early COVID-19 Picture
Clinical	Hepatosplenomegaly, lymphadenopathy	Pneumonia
Cardiac	Usually Normal	Raised Troponin-T and Brain Natriuretic Peptide
Blood	Anaemia, low platelets	Normal
Clotting	Low Fibrinogen/ high FDPs	Normal fibrinogen/High FDPs
Inflammatory Markers	CPR/ESR Elevated	CPR/ESR Elevated
Bleeding	Diffuse clotting and bleeding	Clotting and haemorrhage confined to pulmonary vasculature
Immunotherapy	Treat Cause e.g. EBV Suppression of inflammation	No effective anti-viral therapy Inflammation Suppression?
Anti-Coagulation	Suppression of inflammation	Role of anti-coagulation?
Evolution		May evolve into DIC

Legend for Figure 1

Figure 1A. Secondary HLH/MAS is associated with organomegaly, thrombocytopenia and haemophagocytosis and disseminated intravascular coagulation (DIC) with pulmonary involvement in half the cases[75]. Activation of bone marrow, lymphoid organ, hepatic Kupffer cells and circulating mononuclear cells leads to a severe consumptive coagulopathy with low fibrinongen levels and increased fibrinogen degradation. In addition, liver dysfunction exacerbates the consumptive coagulopathy. A rapid onset DIC pattern with hyperferritinaemia reflecting generalised haemophagocytosis with erythrocyte degradation, sequestration and export with diffuse clotting and bleeding.

Figure 1B. Pulmonary involvement without generalised lymphoid organ hyperplasia is typical of COVID-19 pneumonia. Haemophagocytosis, albeit intrapulmonary has also been reported in coronavirus family infection[13]. But in the early stages the systemic coagulopathy is not a feature. Such intrapulmonary haemophagocytosis and that in regional nodes indicates activated macrophage mediated removal of extravascular red blood cells secondary to vascular injury. A DIC picture may also develop late in the course of COVID-19 pneumonia in cases with ARDS development.

Figure 2

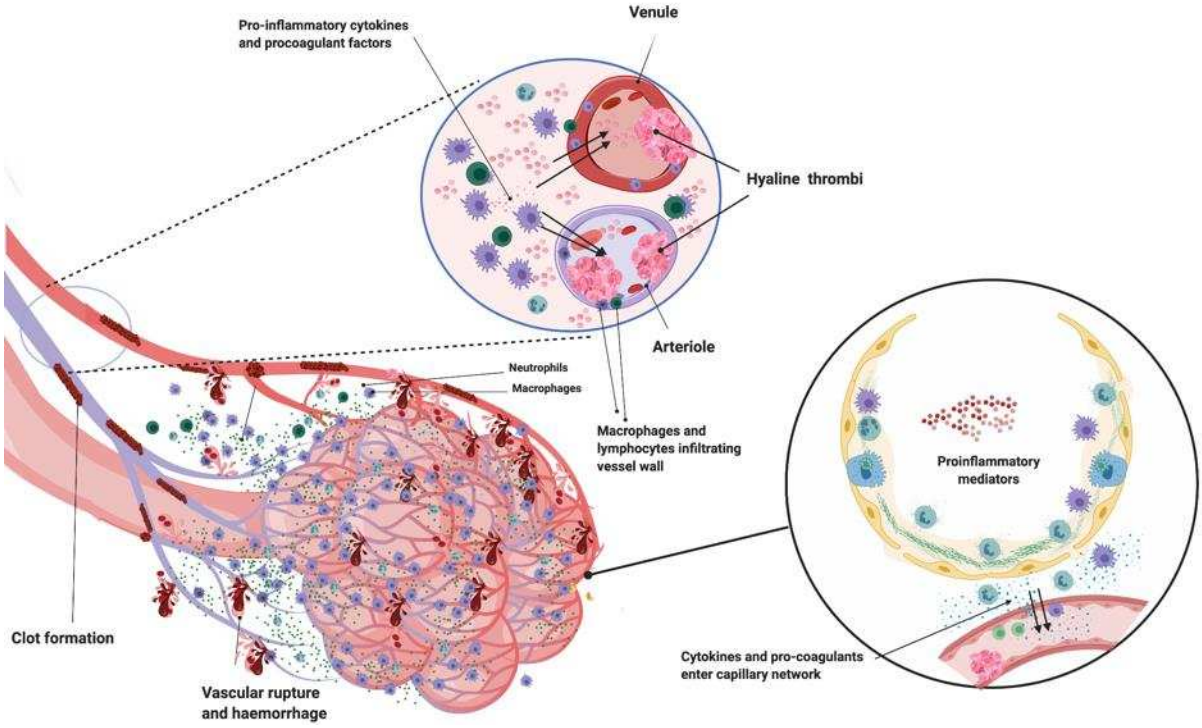


Legend for Figure 2

Figure 2A. Coronavirus family members gain access to the lungs via the ACE-2 receptor that is expressed most abundantly on a subpopulation of type II pneumocytes. The shaded boxes on the left and right indicate the much greater capability for immunothrombosis given the alveolar tropism for COVID-19.

Figure 2B. Segmental bronchopneumonia including bacterial and influenza more typically has a different lung distribution, with prominent bronchial tree involvement including haemorrhagic destruction of trachea and large airways[74] and generally more patchy alveolar network disease. As shown in Figure 2B there may be larger areas with normal perfusion. The slow evolution of COVID-19 infection with alveolar hypoxia and micro thrombosis may result in pulmonary arterial hypertension and the cardiac picture that mostly occurs with hypoxaemia and raised D-dimers. The scale of alveolar and microvascular inflammation rather than systemic viral infection per se determines the cardiovascular pattern of disease. Of course segmental bronchopneumonia could results in a degree of immunothrombosis sufficient to cause a cardiac event especially in older subjects with known or silent cardiac disease.

Figure 3



Legend for Figure 3

Scheme showing how extensive COVID-19 lung involvement with large anatomical interfacing between infected type II pneumocytes, extensive interstitial immunocyte MAS-like activation and the extensive pulmonary microvascular network, triggers diffuse pulmonary bed extrinsic inflammation with immunothrombosis leading to a microthrombotic immunopathology that leads to right ventricular stress and contributes to mortality.
Diffuse type II pneumocyte centric pathology with extension into the intestituim leads to extensive pulmonary macrophage recruitment and activation leading to a local MAS-like picture. Pro-inflammatory and pro-coagulants gain access to the capillary network (lower circle). The low pressure nature of the vascular system and thin vessel walls in and proximal to the alveolar network triggers immunothrombosis by a variety of mechanisms including local elevations in pro-inflammatory cytokines, vessel wall tissue damage with tissue factor production and direct injury to small vessels. Vigorous fibrinolytic activity (detected early by D-dimer elevation) may not keep check with the extensive microthrombi formation and lead to the evolution of COVID-19 inflammation driven pulmonary infarction, haemorrhaging and pulmonary intravascular coagulopathy induced pulmonary hypertension. Risk factors for cardiovascular disease may thus increase the likelihood of death in severe COVID-19 inflammation.