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Appendix A

Hypotheses

Here we outline hypotheses generated from the findings. The purpose of this section is to provide clinicians and scientists with hypotheses for further testing. We provide comments on the strength of the evidence informing these hypotheses.

Hypothesis 1: COVID-19 causes an arterial vasculopathy that promotes a hypercoagulable state.

Our findings revealed a significant difference in the frequency of reported venous and arterial thromboembolic/ischaemic events in the selected papers we identified. An adult case of Kawasaki-like disease in COVID-19 has been reported and we have reviewed the evidence for endothelial dysfunction, endotheliitis and vasculitis all of which suggest the involvement of the vasculature in the pathogenesis of COVID-19. The above hypothesis does not negate the presence of venous thromboembolism but instead refers to the strong evidence for arterial thromboembolism. In so doing, we have also taken the unusual step of including the pulmonary arteries as separate from the venous circulation purely on the grounds of the anatomical structure of the arteries which shares an embryological origin with the aorta. This distinction is important in terms of the location and density of the ACE-2 receptors in smooth muscle cells in arterial walls in comparison with the veins as well as the difference in blood flow dynamics and shear stress.

Hypothesis 2: COVID-19 is associated with arterial thromboembolic events in five main 5 territories-mesenteric ischaemia, cerebrovascular events including the carotid artery involvement, myocardial ischaemia/infarct, pulmonary emboli and acute limb ischaemia From the 56 main papers, we found evidence for thromboembolic events in all of these territories. This does not negate the occurrence of thromboembolic events in other arterial territories including the aorta but it emphasises clinically important locations with evidence from the literature. In most of the studies there was not a control group although there was indirect evidence of an increase in local incidence and where there were control groups this provided further supportive evidence. The occurrence in these territories would have implications for diagnostics, community and hospital surveillance and public health campaigns and it is therefore important to test this hypothesis further. Systematic reviews or meta-analyses could investigate the question of incidence, the involvement of other territories as well as the likelihood of diagnosis in different settings. Further case studies and case series would be invaluable in providing further supporting evidence, data on key variables as per the recommendations section and also providing additional clinical acumen for qualitative analyses.

Hypothesis 3: The arterial ischaemia pathology in the 5 main territories identified in COVID-19 cases is associated with high mortality.

From the analysis of 34 papers, we found that the arterial ischaemic pathology in the 5 main territories was 7.6-35%. The overall mortality is much higher than expected in COVID-19 and suggests that the sample is not representative of the total population of people who develop COVID-19 (we include asymptomatic people in this generalisation). This may be due to selection bias in the cases that have been selected for publication all of whom are in a hospital setting. However the arterial ischaemic pathology may be less likely in the total population than the hospital setting alone.

Hypothesis 4: COVID-19 predisposes to large vessel stroke particularly involving the middle cerebral arteries.

From the analysis of 34 papers, we found that stroke occurred in 27.7% of cases. This owed partly to the selection bias from the search strategy. Of those cases that were reported, the majority were large vessel strokes predominantly affecting the middle cerebral arteries. Additionally as this is a select population in a hospital setting with more severe COVID-19, the significance of the percentage of cases is limited to this setting and severity. However Oxley, et al. draw attention to the unusually high incidence of large vessel stroke in young patients in their case series and find a large increase in comparison with other time periods [124]. Additionally a number of patients presented after a period of being asymptomatic in the community.

Hypothesis 5: The carotid arteries may be a source of large vessel thromboembolism in COVID-19-related stroke.

From the analysis of the 56 main papers, we identified a number of cases affecting the carotid arteries even in the absence of plaques and this together with the location is of significance. Further case reports would be helpful in identifying any associations such as cardiac emboli, evidence of direct viral invasion of the carotid endothelium or physiological evidence of involvement of the carotid body. Additionally it has been suggested that in the case of large vessel strokes, carotid involvement is excluded in COVID-19. Competing hypotheses would include carotid artery involvement as an incidental finding or extension of vascular involvement to neighbouring arterial territories (e.g. middle cerebral artery) consistent with a vasculopathy.

Hypothesis 6: Thrombi extend into multiple arterial branches producing multi-territory ischaemic events including multi-territory stroke and desert foot.

From the qualitative analysis of the 56 main papers, we identified multi-territory involvement in the same patient. These findings were commented on by authors. Further evidence would be needed in the form of case reports and estimation of prevalence.

Hypothesis 7: Thrombi have a high risk of embolisation compared to thrombi resulting from common thrombogenic pathologies.

From the qualitative analysis of the 56 main papers, one group reported a high risk of embolisation during mechanical thrombectomy in large vessel stroke confirmed by different surgeons and using varied techniques. If the thrombi have a high risk of embolisation then in combination with a putative extension of vascular involvement along arterial walls this would increase the risk of involvement of multiple territories. Further case reports and quantification of the effect would provide further valuable evidence and the latter could be investigated using a meta-analysis or systematic review.

Hypothesis 8: Women are more likely than men to die from pulmonary emboli in COVID-19.

This hypothesis is based on an analysis of 34 studies and with a relatively small number of cases. This is not an a priori hypothesis and would need to be tested in a more robust way with a systematic review or meta-analysis or with original data and should be regarded with an abundance of caution until such evidence is available.

Hypothesis 9: Men are more likely than women to die from acute

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myocardial infarcts in COVID-19.

This hypothesis is based on an analysis of 34 studies and as with hypothesis 8 is not an a priori hypothesis, and is based on small numbers and should again be viewed with an abundance of caution.

Hypothesis 10: Women are more likely than men to die from thromboembolic/ischaemic events involving the splanchnic artery territories in COVID-19.

Again this is based on the analysis in the 34 studies and should be considered with due caution.

Hypothesis 11: Women are more likely than men to die from strokes in COVID-19.

Again this is based on the analysis in the 34 studies and should be interpreted with the caveats for hypothesis 8.

Hypothesis 12: Women are more likely than men to die from acute limb ischaemia in COVID-19.

This is based on the analysis in the 34 studies and should be considered with the caveats for hypothesis 8.

Hypothesis 13: Women are more likely than men to die from aortic thromboembolic events in COVID-19.

This is based on the analysis in the 34 studies and should be considered with the caveats for hypothesis 8.

Hypothesis 14: Thromboembolic events are underreported in COVID-19.

Lodigiani, et al. makes this suggestion. Our findings from the analysis of the 56 main papers would support this hypothesis as we found that the average number of thromboembolic/ischaemic events in each patient was 1.3 [103]. There are a number of reasons why thromboembolic events may be underreported including changes in service provision during the pandemic, occurrence in the community setting and diagnostic overshadowing.

Hypothesis 15: A subset of patients with Long-COVID will experience residual consequences of ischaemic lesions which we term Residual-COVID.

Following on from Hypothesis 2, arterial thromboemboli in the five main territories would be expected to be associated with characteristic findings which include ischaemic events such as stroke. Whilst there is a degree of plasticity with stroke depending on a number of factors, there is also an element of irreversibility due to tissue destruction. We would term this irreversible loss of function as Residual-COVID as recovery of function would not be expected. Ischaemic lesions could be thus described on the basis of the established literature in other conditions. There may be other aspects of the pathology in COVID-19 that would fit into this category.

Hypothesis 16: The two-hit hypothesis

Based on our findings, we hypothesise that a pre-existing vulnerability to coagulopathy combines synergistically with COVID-19 to increase the risk of coagulopathy further.

Appendix B - Next Steps

The purpose of a scoping review is to review the subject area in preparation for further research. In this regards, we recommend basic standards for reporting on clotting pathology in COVID-19 which will aid further research in this area including systematic reviews and meta-analyses.

Recommending Standards for Reporting on COVID-19 clotting pathology

A scoping review is limited in comparison with a systematic review or meta-analysis in the recommendations that can be made. Here we make recommendations for clinical research on COVID-19 clotting pathology.

There has been criticism of case reports and case series as lacking the rigour of randomised controlled trials (RCT's) [580]. However as we have demonstrated, such publications can bring valuable insights that not even RCT's may offer. Indeed the problems posed by the COVID-19 pandemic have disrupted research and caused a reappraisal of the role of different types of evidence [524]. ARDS is an important pathology to exclude or confirm when evaluating clotting disorders in COVID-19. Whilst this is mainly seen in the ICU setting, ARDS exists along a continuum and cases may develop in the general ward setting. The potential for silent hypoxia which has been described in COVID-19 reinforces the need for an exclusion of ARDS when reporting clotting disorders in COVID-19. Since the PaO2/FiO2 interpretation involves the positive end-expiratory pressure (PEEP) or CPAP values or which are typically available only in an ICU or HDU settings an alternative is required for general settings. The Kigali modification of the Berlin definition allows the calculations to be made using the ratio SpO2/FiO2 and is a simple practical tool for clinician when reporting on an important differential in a case report or case series [581]. D-Dimers are used in the diagnosis of DIC and the evidence previously discussed demonstrates a significant elevation in D-Dimers in many cases of venous and arterial thromboembolism and the D-Dimers are prognostic in COVID-19. There has been discussion in the literature about standardising the reporting of D-Dimers [582]. We would recommend that the D-Dimers should be reported with the corresponding laboratory reference range, the units and whether this is expressed in D-Dimer units (DDU's) or Fibrinogen Equivalent Units (FEU's). In a number of cases the location of ischaemic areas was reported rather than the arteries supplying those areas. Attempts to estimate the arterial territories are prone to errors due to anatomical considerations (e.g. circle of Willis connecting arterial territories) as well as individual anatomical variation although the latter is less likely to result in error. Given the controversies around the IL-6 levels, we recommend using the Dublin-Boston score given the prognostic value (Tables 36-38) [583].

Table 36. Checklist for reporting in publications, TE -Thromboembolic event.

Reporting in publications	
Checklist for repo0072ting in publications	
Is individual data listed?	Y/N
Is gender reported?	Y/N
Is age reported?	Y/N
Is survival reported?	Y/N
Has ARDS been excluded?	Y/N
Has ARDS been confirmed?	Y/N
Is the Kigali modification relevant?	Y/N
Has DIC been excluded?	Y/N
Has DIC been confirmed?	Y/N
Has sepsis been excluded?	Y/N
Has sepsis been confirmed?	Y/N
Was mechanical ventilation used?	Y/N
What were the O2 sats at the time of TE?	-
Was there evidence of CXR consolidation?	Y/N/NA
Were there new onset cardiac abnormalities?	Y/N

Were new cardiac conditions treated prior to TE?	Y/N
Was the patient immobile?	Y/N
Did the patient have fever?	Y/N
Was the fever treated?	Y/N
Did the patient have diarrhoea	Y/N
Was the diarrhoea treated?	Y/N
Was there evidence of dehydration?	Y/N
Was dehydration treated?	Y/N/NA
Was there evidence of stroke?	Y/N
Was there evidence of mesenteric ischaemia?	Y/N
Was there evidence of DVT?	Y/N
Was there evidence of myocardial infarct?	Y/N
Was there evidence of acute limb ischaemia?	Y/N
Was there evidence of pulmonary embolism?	Y/N
Was there evidence of vasculitis?	Y/N
Was there evidence of cardiogenic shock?	Y/N
Was there evidence of myocarditis?	Y/N
Was there evidence of stress cardiomyopathy?	Y/N
Was there evidence of medical device-related coagulopathy?	Y/N
Was there evidence of new onset renal-failure?	Y/N
Was there evidence of coinfection?	Y/N
If coinfection, which organism?	-
Was medication procoagulant?	Y/N
What was the blood-pressure?	-
What were the fibrinogen levels?	-
What were the D-Dimer levels?	-
What was the APTT?	
What were the platelet levels?	
Was there normo/hypo/hypercalcaemia?	Y/N
Was hypo/hypercalcaemia corrected?	Y/N
Was there hyponatraemia or hypernatraemia?	Y/N
Was hypo/hypernatraemia corrected?	Y/N/NA
Was there hypo/hyperkalaemia?	Y/N
Was the hypo/hyperkalaemia corrected?	Y/N/NA
Was there evidence of aPL antibodies?	Y/N
What were the IL-6 levels?	-
What were the levels of non-IL-6 cytokines?	-
Was there evidence of hyperviscosity?	Y/N/NA
What were Angiotensin II levels?	-
Were there markers of glycocalyx disruption?	Y/N
What were the vWF levels?	-

Table 37. Main findings of quantitative analysis, F-Female, M-Male, TE-Thromboembolism.

Main findings of quantitative analysis
10523 patients in all 56 studies
456 patients with COVID-19 and thromboembolic events
586 thromboembolic events (TE's)
Average of 1.3 events per patient
Breakdown of thrombembolic events in Table 8
Thromboembolism with and without ARDS
Thromboembolism with and without septicaemia
Thromboembolism with and without DIC
34 studies with detailed demographic data on 119 patients
Average age of 119 patients - 67
Average age of patients who died-73
Average age of patients who survived-63
% of deaths in group with aortic thromboembolism-33%
% of deaths in group with myocardial infarct-36%
% of deaths in group with pulmonary embolism - 25%
% of deaths in group with splanchnic artery thrombembolism - 60%
% of deaths in group with acute limb ischaemia - 79%
% of deaths in group with DVT -26%
Higher % of f v m deaths with aortic thromboembolism
Higher % of m v f deaths with myocardial infarcts
Higher % of f v m deaths with pulmonary emboli
Higher % of f v m deaths with splanchnic thromboemboli
Higher % of f v m deaths with acute limb ischaemia
Significance for mortality v survival with splanchnic TE's
27 published values for D-Dimers with reference range
Mean D-Dimer of 22 x upper limit of reference range with TE's
91/150 patients with COVID-19 and TE's with fever

Table 38. Main findings of abridged thematic analysis, ALI- Acute Limb Ischaemia.

Main findings in abridged thematic analysis
No known risk factors
Thromboembolic event despite anticoagulation/antiplatelet therapy
High in-hospital mortality
Aysmptomatic prior to thrombembolic event
Cryptogenic/Without any source of thromboembolism
Multiterritory stroke
Rethrombosis
Mild symptoms prior to presentation
Minimal or no improvement after revascularisation for stroke
No recanalisation after one pass for stroke
Clot fragmentation with embolisation with intervention
Unusual location of clots
Desert foot
Low rate of successful revascularisation for ALI
Thrombosis of a graft
Clotting of medical devices

Standardising the Communication of Pathological Mechanisms In COVID-19-related Coagulopathy

Developing rules for diagram mapping in a DRP: We have used a rules-based framework for mapping the pathology onto diagrams. Thus a simple line is an 'example of', causality is colour coded into weak, moderate and strong evidence both for COVID-19 specifically and separately for the more general non-COVID-19-related cases. Through iterations of use, the framework can be expanded. The non-COVID-19 related evidence is generalised (i.e. using induction) to COVID-19. Thus the diagrams encompass induction and deduction. The former is essential in a pandemic involving a new virus. Additionally the framework of rules enables symbolic manipulation of the diagrams.

Developing a symbolic clinical notation: We made a number of observations about the process of characterising the COVID-19-related coagulopathy. In the reviewed literature, aetiological mechanisms were described with diagrams and text in a non-standardised way. The need for a descriptive convention is highlighted by a number of factors: already in 2020 there had been over 1 million deaths globally, there are at least 7097 living languages, evidence-based medicine/practice draws on findings from specialised communities, these specialised communities have their own terminologies and paradigms but where knowledge can be siloed and where COVID-19 is a complex multi-faceted illness that affect multiple systems [584-586]. The above factors lead us to conclude that there is a need for standardisation of the descriptive notation for clinically relevant pathological processes using a symbolic clinical notation.

In the pandemic, diagnostic overshadowing is possible given the multi-system nature of COVID-19. Diagnostic overshadowing as a term was originally used in the field of Learning Disability and in other areas of mental health to describe the attribution of physical illness to mental illness [587]. We use the term diagnostic overshadowing in a more general sense to describe the attribution of one illness to another regardless of whether this is a physical or mental illness and as a result of factors including symptom overlap, incapacity (e.g. to provide a history) and urgency of treatment for main differential (e.g. in the resuscitation setting). The occurrence of diagnostic overshadowing in the original context is likely to represent the challenges of hierarchical as opposed to multiaxial diagnostic systems and an analogy can be drawn with polycoagulopathy.

The consideration of a polycoagulopathy as opposed to a unitary coagulopathy presents the same challenges both clinically and in the research setting. A combination of induction, deduction and abduction is used in clinical thinking as it deals with systems biology in real time and is distinct from a restricted hypothetico-deductive method. An example of some of the hidden steps in thinking is described in [588].

We may also draw parallels with the works of Professor Van der Groot who investigated the abilities of chess players. He found that expert players were able to recall substantially more of chess positions than novices even after a short glance at the board [589]. Subsequent work by Chase and Simon determined that the brain divided the chess positions into chunks and that stronger players utilised 'larger' chunks [590]. Dr Sigmund Freud and Dr Carl Jung both understood the importance of symbols in the unconscious mind [591,592]. When clinical symbols are attached to a set of logical rules they have computable properties with numerous applications.

There are more generalised applications such as in precision medicine which is the application of "individual variability in genes, environment, and lifestyle" into the treatment of cancer and then into other areas of medicine [593]. Precision medicine spans the interfaces between clinical practice and the application of knowledge from specialist scientific communities. Education could be transformed. Sadler and Regan have written about the success of AlphaZero, an artificial intelligence chess program that was programmed to teach itself to play chess achieving significant success [594]. Humans are able to derive valuable insights from the games of AlphaZero to enhance their skills. Similar applications may be possible with the use of a well-developed clinical symbolic notation. The field of semiotics which is closely related to the philosophy of pragmatism is the study of symbols [595]. A good example of a rapidly developed symbolic system is Emojis [596]. Thus Karl Jaspers transformed the practice of psychiatry by developing the field of psychopathology after he observed different approaches to psychiatric history taking [597]. The International Statistical Institute was responsible for the development of the International Classification of Diseases demonstrating that other disciplines can have a profound influence on the course of medicine. Both examples show the success of standardisation and potential of symbolic systems.

Decentralised Research Program: We propose a model for a decentralised research program based on the approach in this paper. During the COVID-19 pandemic there have been a number of challenges. There have been profound impacts on research ranging from suspension of activities through to diversion of funding [598-600]. Clinical staff has been redeployed to other areas of practice including those outside of the domain of their clinical training and services have been disrupted [601-605]. Students have been graduated early in order to undertake clinical work during the pandemic [606]. COVID-19 is increasingly recognised as a complex multi-system disorder which spans multiple areas of clinical specialism and where a variable course gives rise to obscure pathologies in a small proportion of cases. Multisystem diseases, rare disease and diseases which are not well characterised are recognised as some of the most challenging to manage [607,608]. Given the scale of the pandemic, a small proportion of cases translate into a very large number of actual cases.

Clinicians are on the frontline of this pandemic and the experience of clinicians is essential both in publishing findings and also translating research findings including trial outcomes into clinical practice. Our proposal focuses on the frontline clinician who is typically not well-resourced for research unless participating in large trials and who will have varying degrees of clinical research experience. We propose a crowdsourcing approach to facilitate COVID-19 research in the pandemic. Crowdsourcing approaches have already been utilised in a number of clinical areas and with a crowdsourcing approach it is possible to equal or even surpass large scale well-resourced endeavours in terms of outcomes [609-611].

The crowdsourcing approach is organised through the underlying clinical model we have provided. The clinical model offers the fulcrum around which the research program is organised, negating the need for centralised oversight. Thus clinicians and researchers can identify part or

all of the model to address and then update this aspect of the model at the conclusion of their input. In this manner, the clinical model can be viewed as a dynamic model which is in a state of continuous improvement from the clinical/research community. We would anticipate that after a few revisions, the clinical model may be unrecognisable from the original as the model more closely approximates reality with subsequent expert review as well as clinical and basic research findings.

Appendix C

Recommendation 1: Case reports or case series on clotting disorders in COVID-19 have a valuable role in advancing knowledge of COVID-19.

Recommendation 2: Clinical researchers reporting on clotting disorders should use a standardised approach.

Recommendation 3: We recommend reporting of individual data for large cohort studies. We found that case studies offered a rich albeit heterogenous source of data and with cohort studies, aggregation of data removed the possibility of secondary analyses of certain aspects of the data.

Recommendation 4: We recommend reporting the gender of the patient when reporting on COVID-19-related coagulopathy.

Recommendation 5: We recommend reporting on whether a diagnosis of ARDS was present or had been excluded.

Recommendation 6: We recommend reporting on ARDS using the Kigali modification of the Berlin definition in a non-ICU setting.

Recommendation 7: We recommend reporting on whether a diagnosis of Disseminated Intravascular Coagulation had been confirmed or excluded and including non-overt DIC where available.

Recommendation 8: We recommend reporting on whether a diagnosis of sepsis has been made.

Recommendation 9: We recommend reporting on whether mechanical ventilation was used.

Recommendation 10: We recommend reporting on the oxygen saturation at the time at which thromboembolic events are diagnosed.

Recommendations 11: We recommend publishing evidence of coinfection where possible.

Recommendation 12: We recommend publishing evidence of cardiac structural or ECG abnormalities where available and specifying whether the pathology existed prior to the SARS-COV2 infection.

Recommendation 13: We recommend that pharmacologically active agents that may increase the risk of coagulopathy are included in the reported data in studies.

Recommendation 14: We recommend that data on the mobility of patients are reported in publications.

Recommendation 15: We recommend that blood pressure measurements are reported in publications.

Recommendation 16: We recommend that Fibrinogen levels are reported. Fibrinogen levels are used in the diagnosis of DIC and evidence discussed previously demonstrates an elevation in COVID-19.

Recommendation 17: We recommend that D-Dimer levels are reported.

Recommendation 18: We recommend that platelet levels are reported.

Recommendation 19: We recommend that prothrombin time is reported.

Recommendation 20: We recommend that alternative complement pathway biomarkers are reported where available.

Recommendation 21: We recommend that Protein C levels are reported where available. Protein C is useful for the evaluation of non-overt DIC which may be relevant in COVID-19 but where further information will be needed.

Recommendation 22: We recommend that Antithrombin III levels are reported where available.

Recommendation 23: We recommend reporting on IL-6 if available.

Recommendation 24: We recommend reporting on the full extent of investigations to exclude venous and arterial thromboembolic events.

Recommendation 25: We recommend reporting on the location of the thromboembolic events.

Recommendation 26: We recommend reporting the Dublin-Boston score if IL-6 and IL-10 levels are available.

Recommendation 27: We recommend using the checklist in Table 36 when publishing original data on COVID-19-related coagulopathy and refining the checklist where necessary.

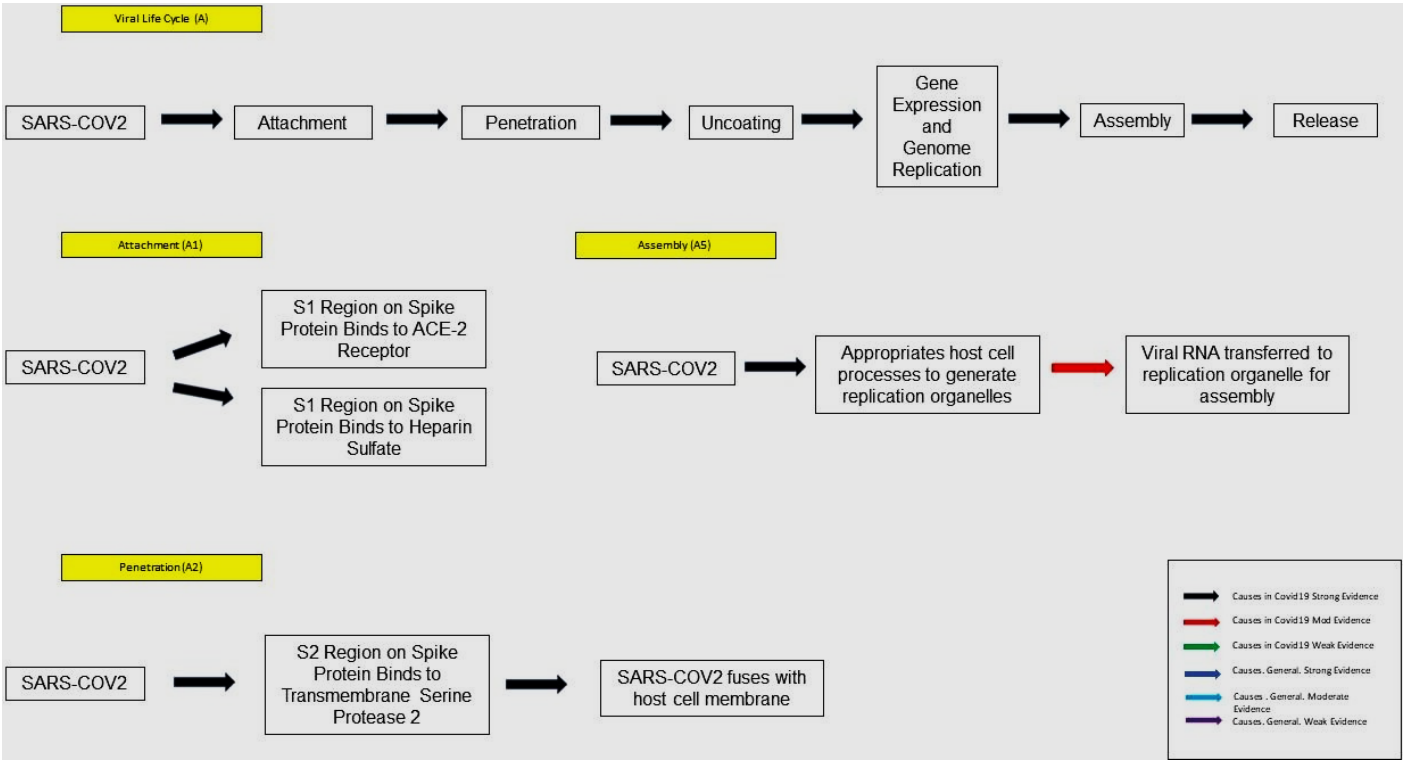

Figure 10. Viral life cycle. **Note:** ( ) Causes in Covid-19 strong evidence; ( ) Causes in Covid-19 mod evidence; ( ) Causes in Covid-19 week evidence; ( ) Causes. General. Strong evidence; ( ) Causes. General. Moderate evidence ( ) Causes. General. Weak evidence.

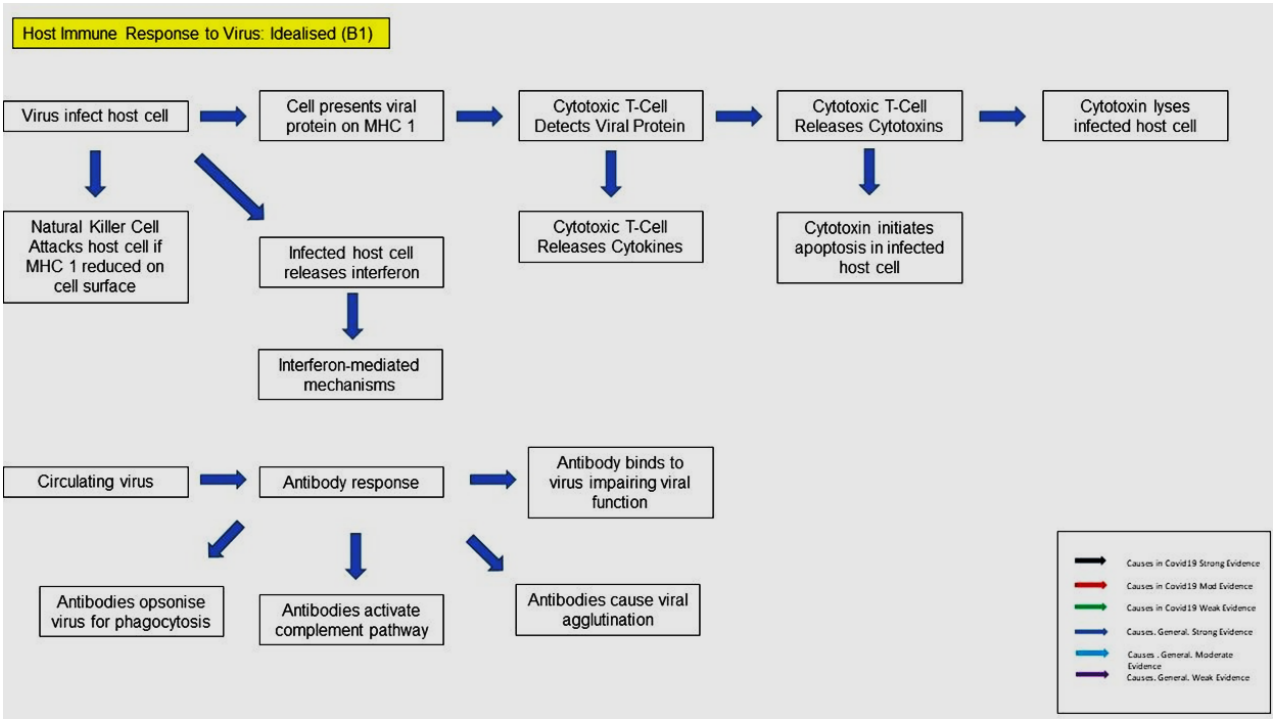

Figure 11. Idealised viral host immune response (non-pathological).

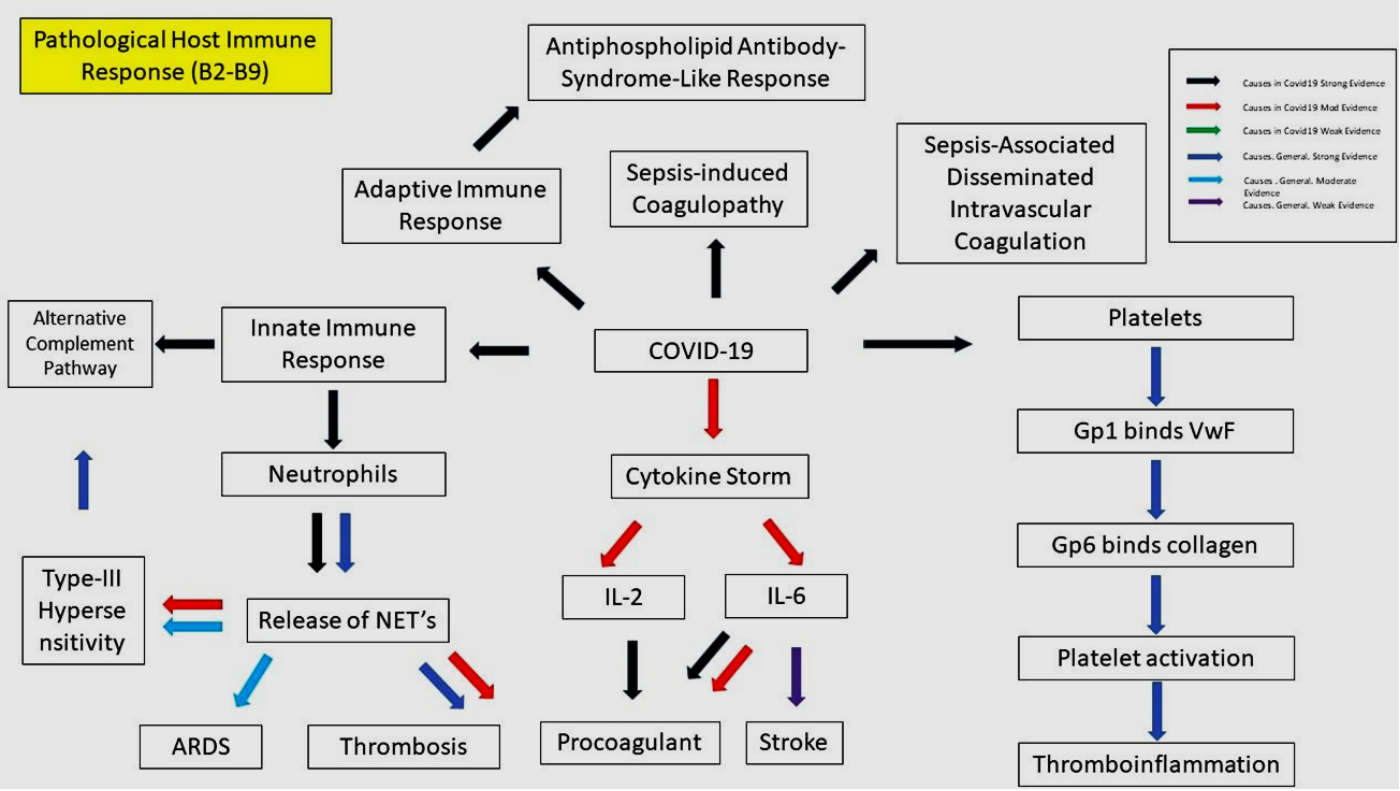

Figure 12. Pathological host immune response in COVID-19.

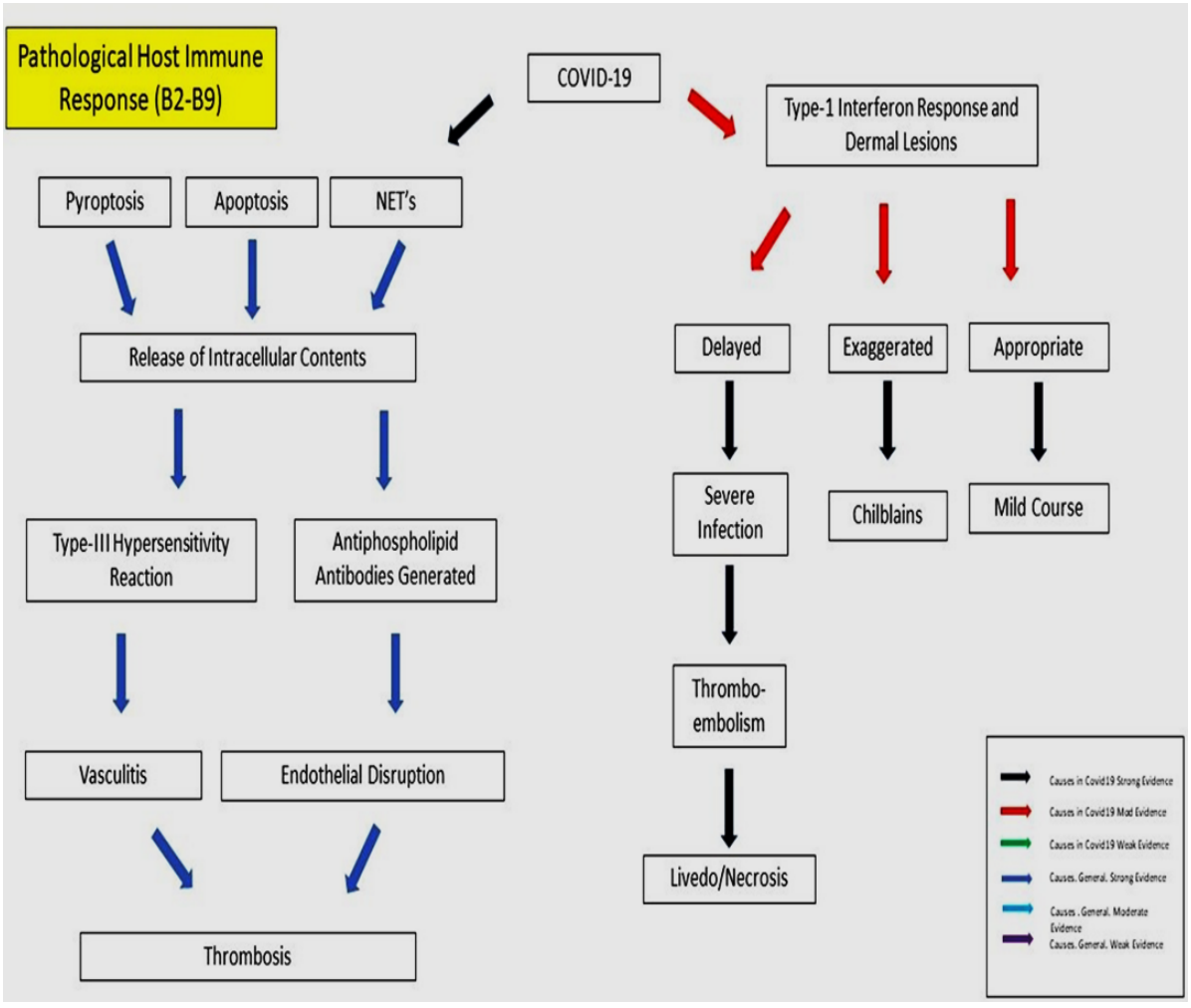

Figure 13. Pathological host immune response in COVID-19: 2nd diagram.

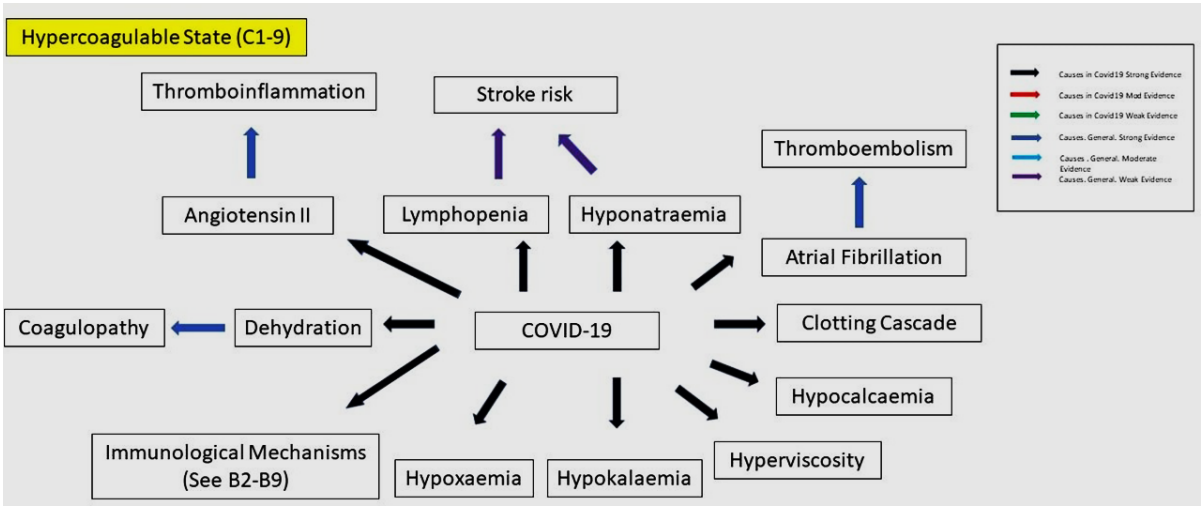

Figure 14. Hypercoagulable state in COVID-19.

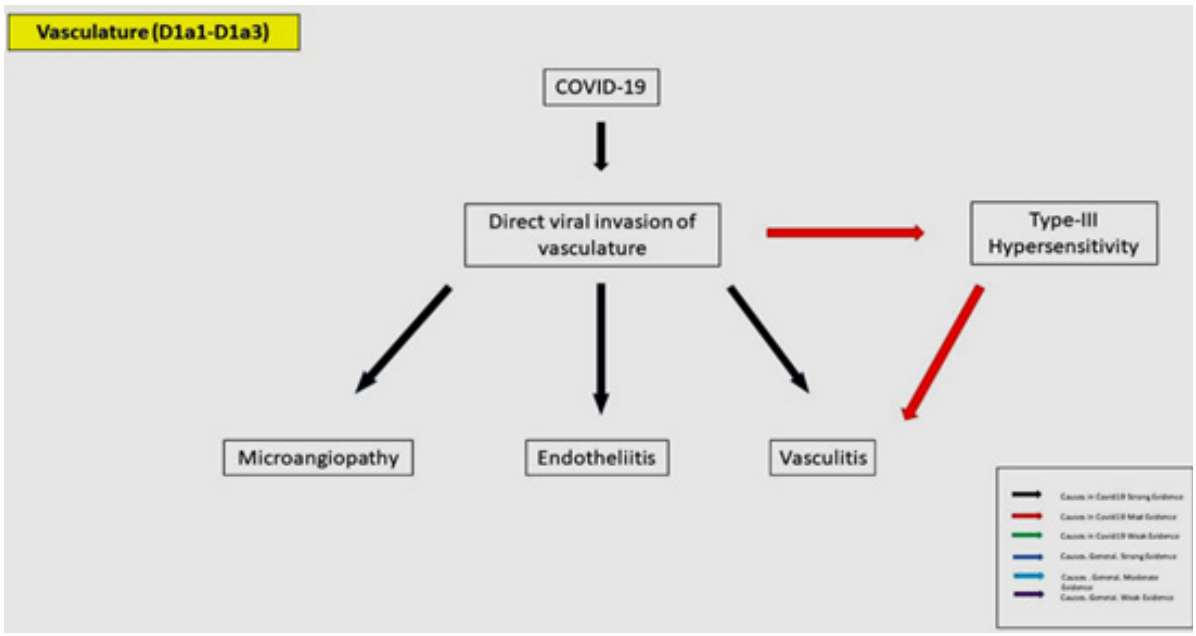

Figure 15. Involvement of the vasculature in COVID-19.

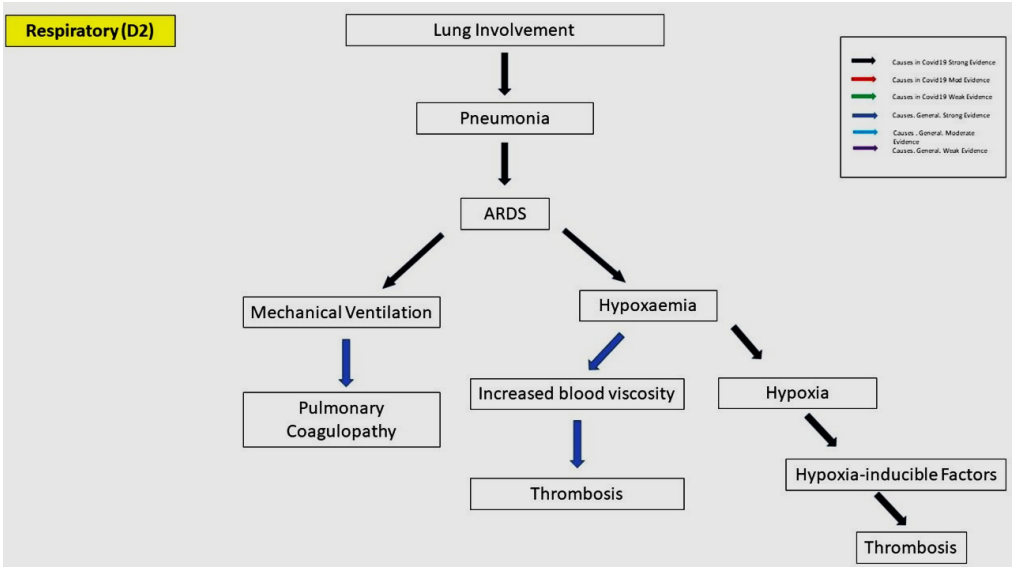

Figure 16. Respiratory involvement in COVID-19.

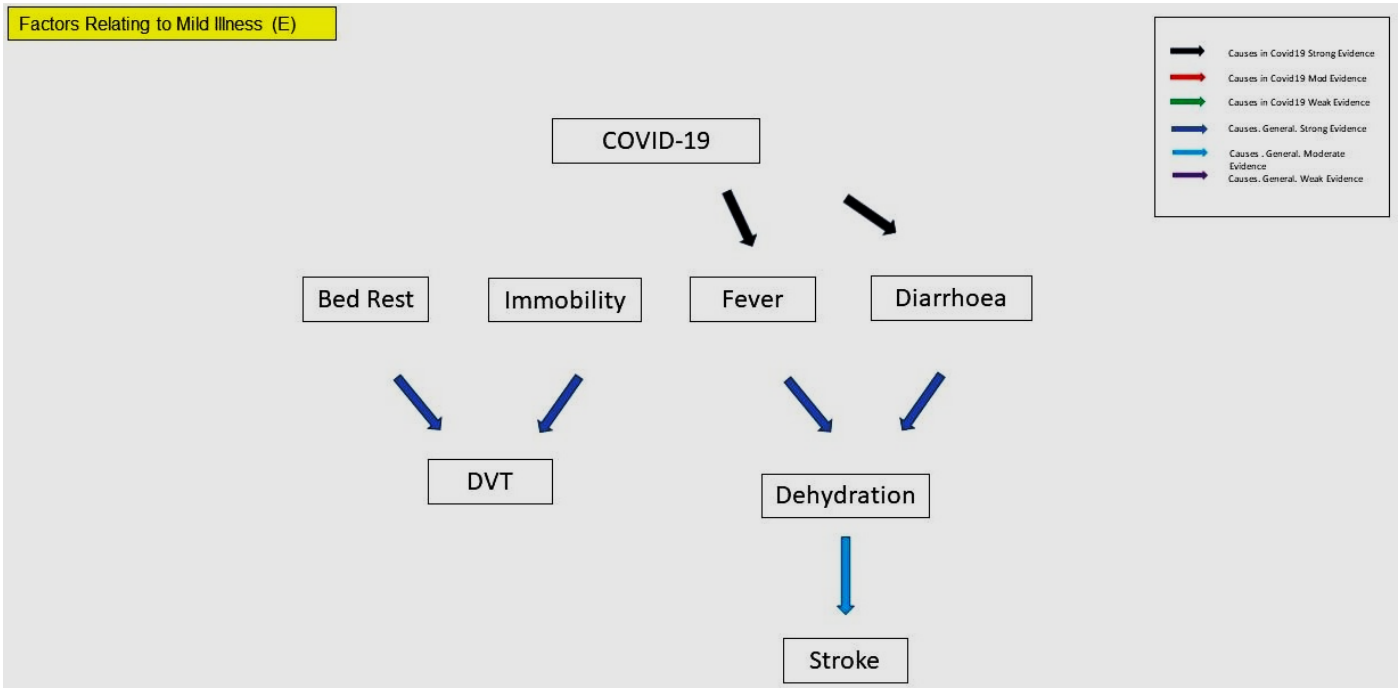

Figure 17. Factors relating to mild illness in COVID-19.

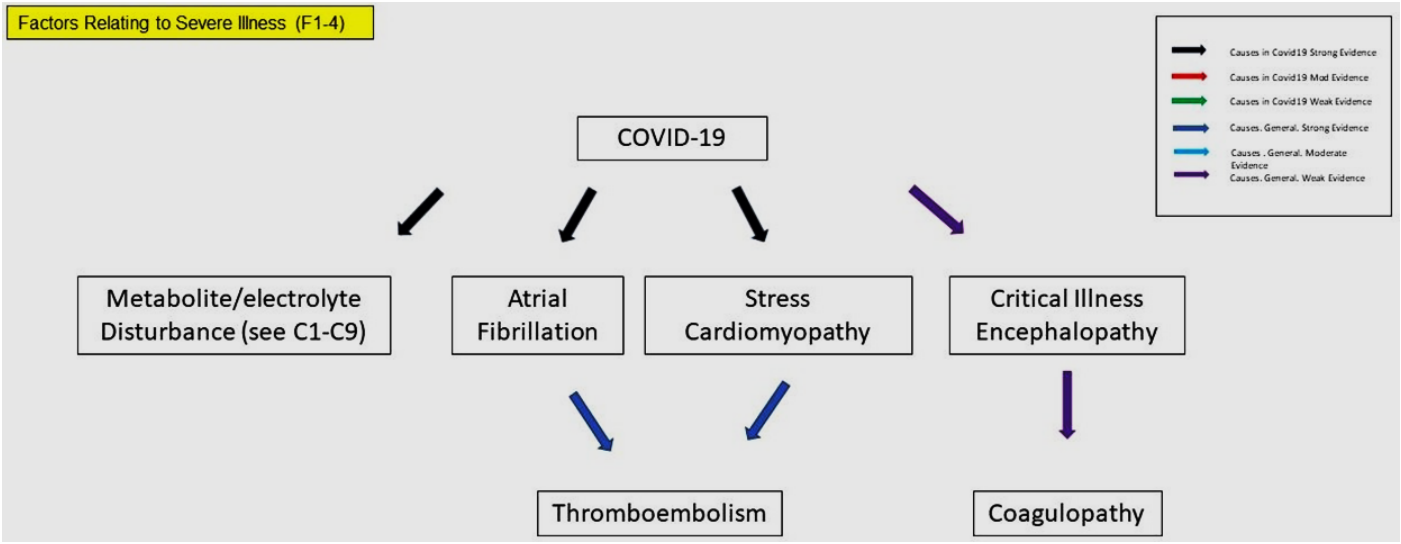

Figure 18. Factors relating to severe illness in COVID-19.

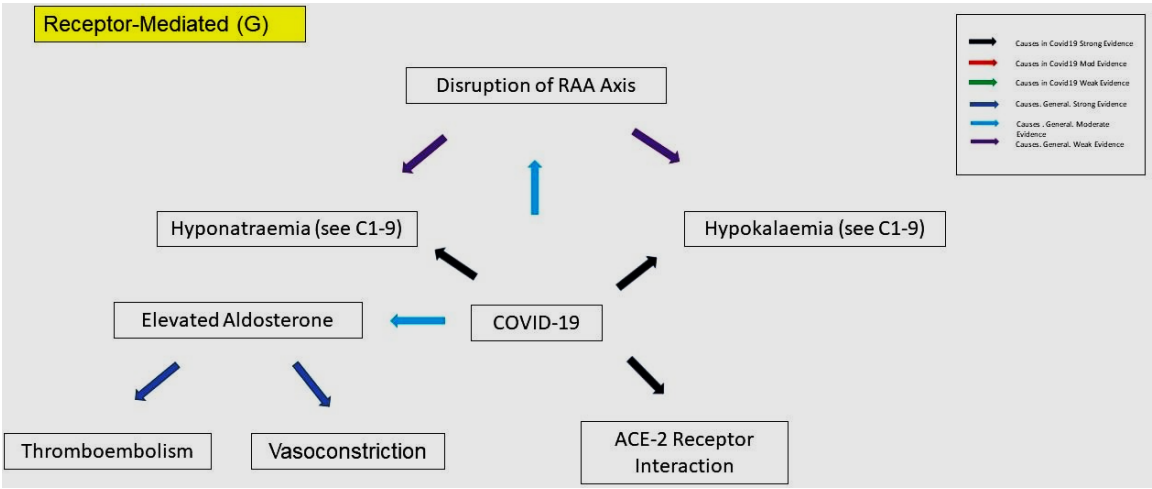

Figure 19. Receptor-mediated mechanisms in COVID-19.

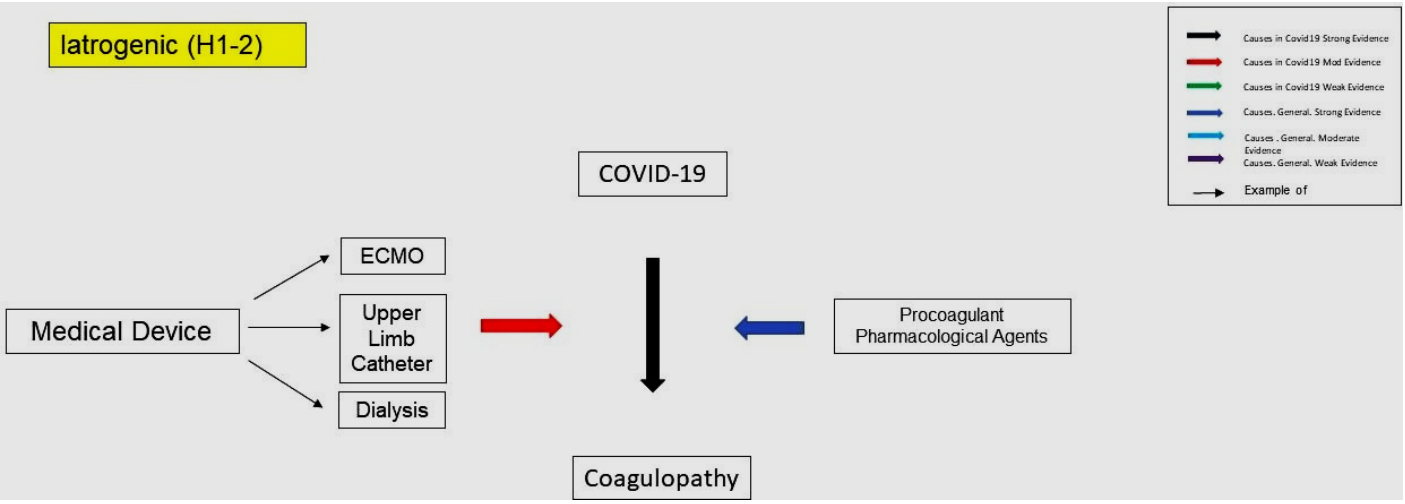

Figure 20. Iatrogenic Mechanisms in COVID-19.

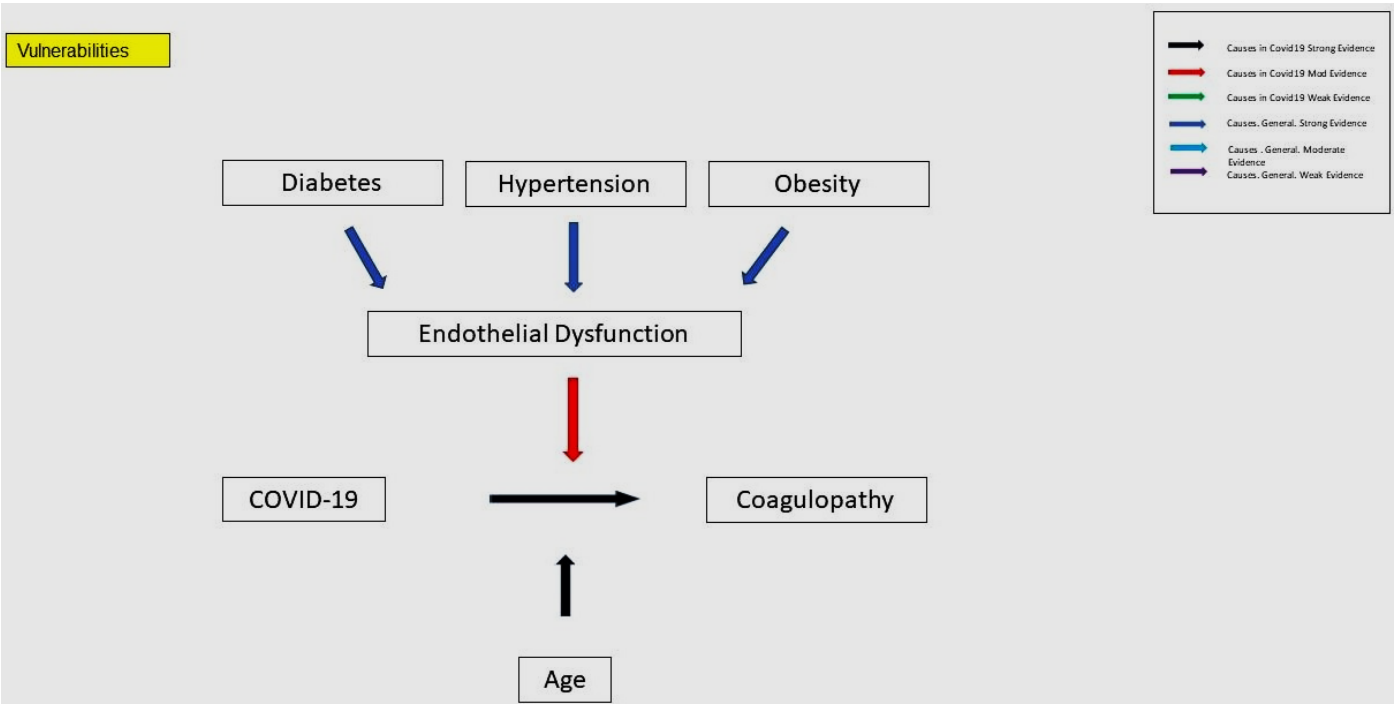

Figure 21. Vulnerability factors in COVID-19