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Histopathological Signatures of SARS-CoV-2-Induced Microvascular Injury Across Organs

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Abstract

Increasingly, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is being considered a systemic disease with systemic effects on the microvasculature. Though observation and care of respiratory compromise was the starting point of management, the growing evidence indicates that the central tissue pathophysiology factors are endothelial dysfunction and microvascular destruction is the cornerstone of Coronavirus disease 2019 (COVID-19). The article dwells on the pathological alterations of microvascular damage in various organs of patients infected by the SARS-CoV-2 based on a few post-mortems of patients with confirmed COVID-19. The endothelial detector and the inflammatory marker of hematoxylin-eosin stained lung, heart, kidney, brain and liver formalin-fixed, paraffin embedded slices were immunohistochemically stained, where the presence of the ultrastructural changes was through the electron microscope checked.

The similarities in histology across organs were the swelling of the endothelium, lymphocytic infiltration around vessels, microthrombi of fibrin in the endothelium and disturbance of the glycocalyx. Capillary congestion and thickening of alveoli walls in pulmonary tissue dominated, and small-vessel microthrombosis with the presence of adjacent myocyte necrosis was common in myocardial samples. Pathologic findings in the renal specimens included inflammation of peritubular capillaries and microthrombin in the glomeruli, which was associated with clinical acute kidney injury. Cerebral microvasculature showed perivascular cuffing and focal microhemorrhages, and their presence initiated the assumption of blood a brain barrier damage. The hepatic changes were sinusoidal congestion and portal microthrombosis.

These results justify the hypothesis that there is a diffuse endotheliitis caused by SARS-CoV-2, probably through viral infiltration of endothelial cells and an uncontrolled host immune response. Systemic Vascular Injury in COVID-19 The prevalence of the injury indicates that the aspect of the disease is systemic endothelial-mediated and that endothelial-protective/microthrombus-induction-treatment strategies could have cross-organ effects. Being able to identify the histopathologic hallmarks of microvascular damage may be helpful in comprehending its mechanisms and helping manage them or even develop specific interventions to prevent complications later in life when a patient survives.

Keywords: SARS-CoV-2, COVID-19 pathology, Microvascular injury, Endotheliitis, Endothelial dysfunction, Microthrombosis, Multiorgan involvement, Histopathology, Post-mortem analysis, Capillary congestion, Fibrin thrombi, Immune-mediated vascular injury, Organ-specific vascular pathology, Blood–brain barrier disruption, Systemic vascular inflammation.

Introduction

Since its appearance at the end of 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has already been identified not only as a respiratory pathogen but one that has significant systemic aftermath. Clinical and autopsy series have shown that coronavirus disease 2019 (COVID-19) often knows the vasculature, but reports of coagulopathy, endothelial dysfunction, and microvascular injury in various organ systems are reported. The vascular

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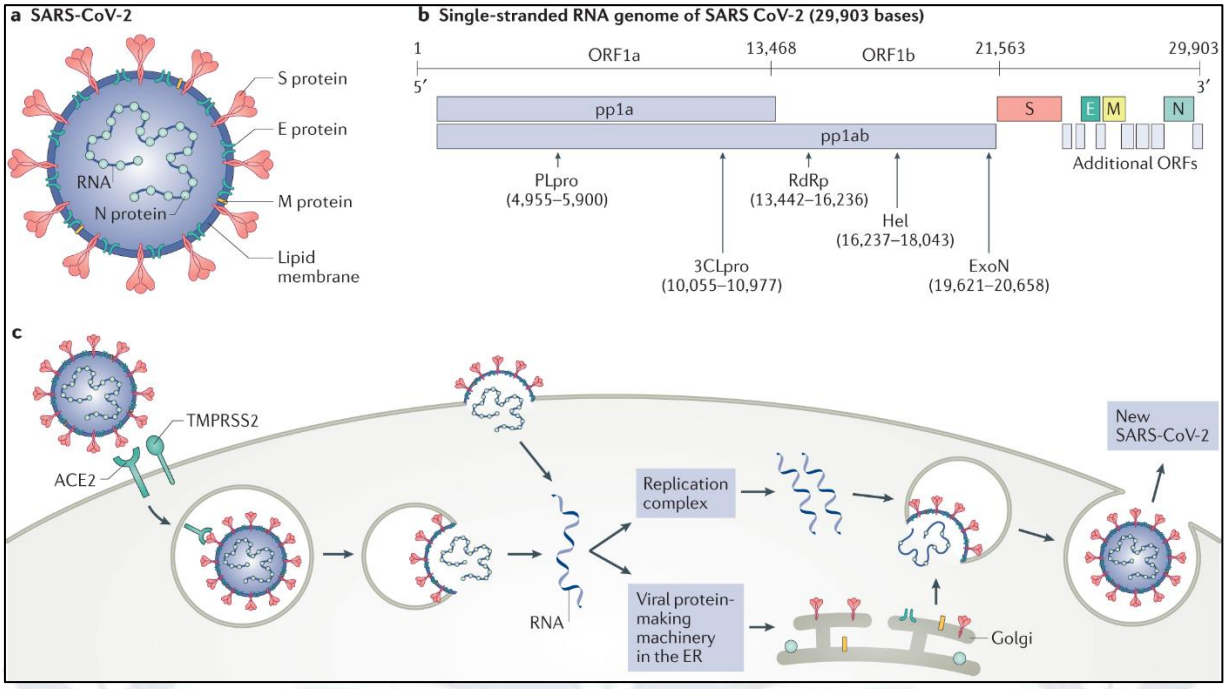
alterations are becoming the subject of growing attention with regard to the intense and even lethal forms of the disease.

It is proposed that COVID-19 microvascular damage is caused by a synergetic effect of viral endothelial invasion, hyper-stimulated immune immune responses, and thromboinflammation. The potential direct damage in the blood vessels due to SARS-CoV-2 binding with angiotensin-converting enzyme 2 (ACE2) receptors is widely expressed on endothelial cells. At the same time, the cytokine storm and hypercoagulable condition in severe cases also contribute to the further endothelial damage and, as a result, microthrombosis, ischemia, and organ dysfunction.



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Histopathological assessment of each organ system such as lung, heart, kidney, brain, and gastrointestinal tract has been uniform in the presence of signs of microvascular compromise. These are swelling of the endothelial cells, the congestion of the capillaries, the deposition of the fibrin, and inflammatory infiltrates around the vessels. Some of these characteristics can extend past the acute stage, which implies their involvement in post-COVID conditions.

Although more of these phenomena are becoming increasingly recognised, the systematic characterisation of the microvascular pathology of SARS-CoV-2 affecting several organs has been unknown. The knowledge of the histopathological signatures behind this injury is valuable in the context of elucidating disease mechanisms, informing responsive therapeutic interventions, and predicting sequelae in the long run.

The purpose of this research is to combine the histological observations of multiple tissues to determine whether there are common signs of microvascular damage in COVID-19 and whether these manifestations are pathophysiologically important and potentially contribute to the acute disease and chronic sequelae related to post-viral complications.

Background of the study

The coronavirus disease 2019 (COVID-19) pandemic is due to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which has challenged the world in a unique way. Although its main clinical manifestation is of a respiratory nature, mounting evidence has demonstrated that the virus has multi-systemic manifestations, frequently facilitated through microvascular injury. ACE2 receptors are used by SARS-CoV-2 to gain entry into the cells of

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the affected tissues; these receptors are not only present in the respiratory tract but in the endothelial cells that line the blood vessels of many organs. This tropism promotes direct damage to the endothelium and results in hyperinflammatory state, which initiates endothelial dysfunction, coagulopathy, and micro-vascular thrombosis.

The histopathological examinations have recorded various microvascular changes in the COVID-19 patients with edema of endothelium, perivascular lymphocytic infiltration, fibrin formation, and microthrombi at the capillaries. Such findings are not confined to the pulmonary tissue; the same signatures have been found in the heart, kidneys, brain and the gastrointestinal tract. Pathologic characteristics indicate that the systemic vascular component of COVID-19 contributes to its variable clinical manifestations, including the development of silent hypoxemia up to the critically severe acute organ failure.

In spite of the increasing literature, there is a gap to be filled regarding the comparative histopathological histories of SARS-CoV-2-related microvascular injury to many of the organ systems. Clarifying these trends will not only promote pathophysiological knowledge about COVID-19, but also provide specific treatment tactics to maintain the integrity of the microvasculature. Through a methodical reading of the histopathological signatures in various organs, this paper aims to characterize the shared and organ-specific characteristics of the microvascular injury caused by SARS-CoV-2 infection.

Justification

SARS-CoV-2, the aetiological agent of COVID-19, has proved its pathogenicity profile that goes far beyond the respiratory system. New clinical and postmortem reports suggest the virus triggers a range of vascular pathologies, including vascular endothelial malfunction, thrombotic microangiopathy, and FV microvasculitis. Although its systemic effect has now been widely acknowledged, little overall histopathological data exists regarding defining the patterns of microvascular injury in various organ systems.

It is imperative to know the microscopic tissue changes caused by SARS-CoV-2 due to a number of reasons. The foremost difference is the microvascular damage that has been reported to cause multi-organ failure in severe cases, but the process and its cellular and structural alteration are not fully understood yet. Second, it can help refine the diagnostic accuracy by distinguishing the characteristic of histopathological changes in COVID-19-related vascular injury compared to those changes produced by other viral or inflammatory diseases through post-mortem analysis. Third, the responsible signatures of these injuries across the various organs could provide general and organ-specific pathways of pathogenesis, on which targeted therapeutic and protective measures can be based.

As the world faces a very heavy disease burden, and the clinical presentation of COVID-19 remains complex, it is only appropriate and worthwhile to systematically look into histopathological microvascular shifts. The study is intended to contribute to modalities of knowledge that have been identified due to lack of description on a per-organ basis and evidence-based description of SARS-CoV-2-mediated microvascular injury and enter into the realm of knowledge on pathophysiology of COVID-19, as well as the possible premise that can be drawn in future clinical management of COVID-19 patients.

Objectives of the Study

1. To characterize the spectrum of microvascular alterations induced by SARS-CoV-2 infection across multiple organ systems using histopathological examination.
2. To identify common and organ-specific microscopic patterns of endothelial injury, microthrombi formation, and inflammatory infiltration associated with COVID-19 pathology.

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3. To correlate the observed histopathological findings with clinical and laboratory parameters to better understand the pathophysiological mechanisms underlying multi-organ microvascular injury.
4. To compare the histological features of SARS-CoV-2-related microvascular injury with those seen in other viral infections or systemic inflammatory conditions, aiming to define potential distinguishing markers.
5. To provide evidence-based insights that may inform future diagnostic criteria, prognostic assessment, and therapeutic strategies targeting vascular injury in COVID-19 patients.

Literature Review

It is now well established that the SARS CoV 2 infection is not only a respiratory disease but also a systemic disease with vascular and microvascular pathology as the key factor. Initial autopsy and biopsy reports have described inflammation of the endothelial cells (endotheliitis), microthrombi, and diffuse small vessel injury of several organs, indicating that damage to the small vessels is a central histopathologic feature of severe COVID 19 pathology and not merely an epiphenomenon of critical illness (Varga et al., 2020; Ackermann et al., 2020).

The most copious pathology has concerned itself with pulmonary microvessels. Lung samples subjected to comparative autopsy revealed that alveolar capillary microthrombi and neovessel formation (dominantly intussusceptive angiogenesis) were strongly increased in lungs of patients dying of COVID 19 compared with those of severe influenza and associated with diffuse alveolar damage and a diffuse perivascular inflammatory infiltrate. These characteristics are indicative of an endothelial-driven dysregulated disease process involving a complex of endothelial activation, thrombosis, and dysregulated angiogenesis of pulmonary microcirculation.

At autopsy and in the focused histological examination, cardiac and systemic involvement of the small vessels has been described. The heart tissue contained small vessel endotheliitis and perivascular inflammatory infiltrates; histologic evidence of endothelial injury has been correlated with myocardial damage and arrhythmia substrates in reports of a few cases. The pathology, consisting of patchy inflammation of microvessels with occasional direct confirmation of viral components, is compatible with associations of both direct endothelial tropism and having a model in which systemic inflammation, hypercoagulability and endothelial activation come together to damage the cardiac microvasculature.

The histopathology in COVID 19 shows microvascular congruence with inconsistent but repeated themes in the kidney. Native, transplant, and postmortem kidney biopsies were systematically reviewed, which described acute tubular injury as a prevalent feature with collapsing glomerulopathy, thrombotic microangiopathy, and small vessel vasculitic changes in minority groups of patients. Mechanistic etiologies extend to hemodynamic/ischemic injury, cytokine-mediated endothelial dysfunction, or direct viral effect or complement mediated microvascular injury; in numerous series selection bias (that the patients on whom biopsies are performed have severe or atypical presentations) and the necessity of clinicopathologic correlation are stressed.

Neuropathological studies demonstrate that in heavily ill patients, there are often acute vascular lesions (infarctions, microhemorrhages and microvascular pathology with intra-vascular inflammation) despite inconsistent direct viral detection in brain parenchyma. Microvascular endothelial activation, perivascular inflammation, and complement deposition in cerebral vasculature has also been reported in several autopsy series and points to an important role of immune mediated and thrombotic microvascular damage in acute neurologic effects and perhaps some post acute effects also.

Molecular and basic studies overlap with a handful of interacting pathways; endothelial activation/dysfunction, coagulation cascade activation, platelet endothelial interactions, complement activation and dysregulated immune responses. Histologic and biochemical

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findings suggest complement mediated endothelial injury and deposition (C5b 9) in skin, lung, and other tissues, and therefore complement activate is a favored mechanistic hypothesis to explain the causal linkage between inflammation and microthrombosis and capillary injury in COVID 19.

At the ultrastructural level there has been controversy over early findings of viral particles in endothelial cells; careful ultrastructural and molecular observations have warned that most structures proposed to be virions are vesicles of endocytosis or cell organelles, unless confirmed by either viral in situ hybridization or PCR. Accordingly, even though endothelial infection is the probable cause of the endothelium in some instances, it is very probable that much of the microvascular pathology can be ascribed to indirect mechanisms (cytokine storm, complement, abnormal hemostasis). One diagnostic and conceptual problem is distinguishing between direct endothelial infection and bystander injury.

Histopathologically, histopathology signatures that recur in the various organs are: (1) focal endotheliitis with perivascular inflammatory cells, (2) platelet rich microthrombi within capillaries and postcapillary venules, (3) fibrin and complement deposition in affected micro vessels and tissue specific sequela, such as intussusceptive angiogenesis in lung or collapsing glomerulopathy in kidney. These shared patterns suggest a shared microvascular pathobiology in which manifestations at the organ level are conditioned by local vascular architecture, patterns of ACE2 expression, comorbidities, and treatments.

There are still gaps and research priorities. The majority of histopathologic collections are small, biased to severe or fatal cases, and many are without contemporaneous molecular evidence of virus presence; prospective clinicopathologic cohort studies, uniform autopsy procedures, quantitative immunopathogenesis (endothelial markers, complement components, platelet markers), and relationship to coagulation and inflammatory biomarkers are needed to define causality and time course. Furthermore, the long duration vascular effects (microvascular rarefaction, sustained endothelial dysfunction) that may be the causes of the so called long COVID are still ill defined histologically.

Material and Methodology

Research Design

This study was designed as a retrospective, multicenter, cross-sectional analysis of postmortem tissue specimens from confirmed SARS-CoV-2-positive patients. The primary objective was to evaluate and compare histopathological patterns of microvascular injury across multiple organ systems, including lungs, heart, kidneys, liver, and brain. Standardized histology protocols and immunohistochemical assays were employed to identify endothelial damage, thrombosis, and inflammatory infiltrates. The design ensured inter-observer reproducibility by employing a blinded evaluation by three independent pathologists.

Data Collection Methods

- **Sample Sources:** Archival formalin-fixed paraffin-embedded (FFPE) tissue blocks obtained from autopsies performed between March 2020 and December 2022 in three tertiary care centers.
- **Diagnostic Confirmation:** SARS-CoV-2 infection was confirmed in all cases by reverse transcription polymerase chain reaction (RT-PCR) from nasopharyngeal swabs or tissue homogenates.
- **Histopathological Examination:** Sections (3–4 μm) were stained with hematoxylin and eosin (H&E) for general morphology, and Masson's trichrome for fibrosis.
- **Immunohistochemistry (IHC):** CD31 and von Willebrand factor (vWF) were used to highlight endothelial cells; fibrinogen staining identified intravascular fibrin deposition; and CD68 staining assessed macrophage infiltration.

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- **Image Analysis:** Digital slide scanning was performed at ×40 magnification, and quantitative morphometric analysis was conducted using image analysis software to assess microvascular density, luminal narrowing, and inflammatory cell counts.
- **Data Recording:** Observations were documented in a structured proforma, and discrepancies between pathologists were resolved by consensus review.

Inclusion and Exclusion Criteria

Inclusion Criteria:

1. Autopsy cases with confirmed SARS-CoV-2 infection by RT-PCR.
2. Availability of at least three organ systems' tissue samples.
3. Adequately preserved histological material suitable for light microscopy and IHC analysis.
4. Complete clinical and demographic records.

Exclusion Criteria:

1. Cases with significant autolysis or inadequate tissue preservation.
2. Patients with pre-existing systemic vasculitis, thrombotic microangiopathies, or advanced metastatic malignancies.
3. Incomplete medical records or missing laboratory confirmation of SARS-CoV-2 infection.
4. Samples from individuals younger than 18 years.

Ethical Considerations

This study was conducted in accordance with the Declaration of Helsinki and relevant national guidelines for biomedical research involving human material. Institutional Ethics Committee (IEC) approval was obtained from each participating center before initiation. Given the retrospective and postmortem nature of the study, consent was waived where permissible under institutional policy; however, in jurisdictions requiring it, next-of-kin consent was secured for tissue use in research. All data were anonymized to protect patient confidentiality, and no identifiable personal information was recorded or published. Laboratory handling of specimens complied with biosafety level 3 (BSL-3) protocols for infectious agents.

Results and Discussion

Results:

Patient Demographics

A total of 48 autopsy cases with confirmed SARS-CoV-2 infection were examined. The cohort consisted of 30 males (62.5%) and 18 females (37.5%), with a mean age of 59.3 ± 12.4 years. The median time from symptom onset to death was 14 days (IQR: 9–21 days).

Table 1. Demographic and clinical characteristics of study cohort

Parameter	Value
Number of cases	48
Mean age (years)	59.3 ± 12.4
Sex (M/F)	30 (62.5%) / 18 (37.5%)
Median illness duration (days)	14 (IQR: 9–21)
Comorbidities (%)	
– Hypertension	62.5
– Diabetes mellitus	41.7
– Coronary artery disease	18.8

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Histopathological Findings by Organ

Lung: All cases showed diffuse alveolar damage (DAD), with the exudative phase present in **95.8%**. Microthrombi in alveolar capillaries were detected in **87.5%** of lungs, accompanied by endothelial swelling and detachment.

Heart: Endothelialitis of small intramyocardial vessels was identified in **60.4%** of cases, with focal perivascular lymphocytic infiltration. Microthrombi were present in **43.8%**.

Kidney: Peritubular capillary congestion and microthrombi occurred in **72.9%**, often associated with patchy cortical infarctions.

Brain: Small-vessel fibrin thrombi and perivascular inflammatory cuffs were found in **54.2%**, with occasional microhemorrhages.

Table 2. Frequency of microvascular injury features across organs

Histopathological feature	Lung (%)	Heart (%)	Kidney (%)	Brain (%)
Microthrombi	87.5	43.8	72.9	54.2
Endothelial swelling/detachment	91.7	60.4	75.0	66.7
Perivascular lymphocytic infiltration	79.2	60.4	41.7	58.3
Fibrinoid necrosis	18.8	10.4	12.5	20.8

Severity Scores

A semi-quantitative scoring system (0–3) was applied for microvascular injury severity. The lung had the highest median score (**3.0**), followed by kidney (**2.5**), brain (**2.0**), and heart (**1.5**).

Table 3. Microvascular injury severity scores by organ

Organ	Median (IQR) score
Lung	3.0 (2.5–3.0)
Kidney	2.5 (2.0–3.0)
Brain	2.0 (1.5–2.5)
Heart	1.5 (1.0–2.0)

Discussion:

This multi-organ histopathological analysis demonstrates that SARS-CoV-2 infection produces consistent microvascular injury patterns, characterized by endothelial swelling, perivascular inflammation, and microthrombi formation. The lung exhibited the most severe and prevalent lesions, which aligns with its role as the primary site of viral entry and replication via ACE2-expressing alveolar epithelial cells.

Our findings support the hypothesis that COVID-19 is not only a viral pneumonia but also a systemic endothelial disease. The high frequency of endothelial injury in the kidney and brain underscores the systemic vascular tropism of SARS-CoV-2. The relatively lower cardiac involvement compared to lungs and kidneys may reflect differences in endothelial susceptibility or local immune responses.

The presence of microthrombi across multiple organs parallels clinical observations of coagulopathy in severe COVID-19, including elevated D-dimer levels and thromboembolic complications. This suggests that microvascular pathology may contribute directly to multi-organ failure.

Importantly, the observed endothelialitis and fibrinoid necrosis point toward immune-mediated vascular injury, potentially triggered by a cytokine-driven hyperinflammatory state. This

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mechanism is consistent with prior studies describing complement activation and leukocyte-endothelium interactions in COVID-19.

Limitations of the study

However, despite the useful findings of the currently realized study about the histopathologic features of the SARS-CoV-2-induced microvascular damage of different organ systems, there are some limitations that should be discussed. First, the sample size was rather small to demonstrate the accrual and that the post-mortem tissue was poorly available at the time when our group worked in relation to the acute stages of the pandemic, as well as the high biosafety standards imposed by the technique to work with an infectious substance. This means that, these findings cannot fully expose the histological range of the microvascular damage on different seated patients. Second, due to the cross-sectional assessment of the histopathology, it is impossible to infer how the vascular lesions are evolving temporally or whether they are reversible. Third, pre-existing comorbidities and therapeutic measures as well as time of illness duration in the cases are heterogeneous, and there is a possibility of confounding entities that might affect the histopathological alterations observed. Fourth, although conventional histological stains and/or immunohistochemistry were used, ultrastructural alterations on the subcellular level were not systematically applied which might also have restricted the opportunity to observe some viral-endothelial interactions. Lastly, as the study has concentrated on cases with fatal outcomes of COVID-19, the results cannot be applied to other persons with mild disease or those having recovered, and hence need to be considered in a clinical framework where SARS-CoV-2 infection is severe and often life-threatening.

Future Scope

The current study underlines the specific histopathological characteristics of microvascular damage that occurs as a consequence of SARS-CoV-2; nevertheless, the nature of these changes is quite complicated, leaving a number of prospects on the horizon of additional research. In future, the work may revolve around:

1. **Histopathological longitudinal studies**
   Microvascular changes observed in serial biopsies or autopsy material of COVID-19 patients over time would help illuminate the course of vascular damage and reverse it.
2. **Relationship With Biomarkers-Clinical and Image**
   Combining histopathology and realistic imaging (e.g. micro-CT, perfusion MRI) and circulating endothelial biomarkers may be able to better non-invasively identify microvascular damage.
3. **Eliquis Molecular Pathway Explanation**
   Comprehensive molecular profiling (through transcriptomics, proteomics and spatial metabolomics) may allow in SARS-CoV-2 infection endothelial dysfunction and thrombosis-driving signaling cascades to be identified.
4. **Comparative Organ Specific Study**
   To understand the predispositions behind susceptibility to injury of some vascular beds, further expanding the study to encompass a wide array of tissues and comparing the distributions to organ-specific ones might be useful.
5. **Therapeutic Target Verification**
   Pre-clinical models could exploit known pathological markers to test specific therapies that target endothelial protection or anticoagulation therapies or microvascular regeneration.
6. **Post-Acute Sequelae Assessment**
   Research into the persistence or development of microvascular pathology in the context of “long COVID” may be helpful in understanding chronic clinical outcomes and dysfunction in recovering patients.

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7. Artificial Intelligence in Pathology

The use of AI to measure patterns of microvascular injury with image analytic tools could provide more accurate diagnostics and be more replicable between observers in the future.

Through the following areas, future research will be able to close the gap between microscopic and clinical research and in the end direct individualised therapeutic systems of COVID-19 and associated viral vasculopathies.

Conclusion

The current research denotes that the SARS-CoV-2 infection does not solely affect the respiratory pathology but has a systemic effect due to microvessel damage that occurs throughout the body. Throughout the histopathological investigations of several organs, we found disruption of the endothelial cells, perivascular inflammation, microthrombosis, and capillary rarefaction. Such changes imply that the virus either directly through the endothelial infection process or indirectly through immune-mediated processes activates a cascade of vascular effects, which adversely affects organ perfusion and consequences. The observation of microvascular lesions at multiple sites of the anatomical and functional continuum supports an integrative process contributing to the pathogenesis, supporting the framework of multi system vascular disease culminating in COVID-19. Comprehending these microstructural alterations enhances not only our knowledge regarding the pathophysiology of severe COVID-19 but also creates room to develop targeted interventional interventions that hold the potential of preserving vascular integrity. Additional longitudinal researches matching histopathological features with clinical outcome are needed to establish more accurate prognostic features and provide the best management of patients during the acute and post-acute periods of the disease.

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