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# Cerebral Venous Thrombosis and COVID-19: Review of Clinical Profile and Management Options

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**ABSTRACT**

*Cerebral Venous Thrombosis (CVT) is considered a serious form of cerebrovascular disease that causes occlusion of the cerebral venous system. COVID-19, a Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV-2), can present with different clinical manifestations, ranging from asymptomatic carrier state to severe respiratory distress, multiple organ dysfunction, and death. Furthermore, patients with COVID-19 may have multiple neurological manifestations that can lead to either arterial or venous thrombosis. Multiple studies investigating the pathophysiology of COVID-19-associated coagulopathy provide insights that can direct appropriate interventional strategies. In this review, we describe CVT in COVID-19 patients including pathophysiologic mechanisms, clinical profile, neuroimaging, and management options. CVT is a complication of COVID-19 that needs to be taken seriously. Considering CVT for patients with COVID-19 and neurological manifestation is crucial to provide proper management.*

**Keywords:** Anticoagulants, Cerebral venous thrombosis, COVID-19

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## INTRODUCTION

Cerebral Venous Thrombosis (CVT) is a rare neurological emergency that causes occlusion of the dural venous sinuses and/or cerebral veins. Risk factors of CVT are associated with Virchow's thrombogenic triad including hypercoagulability, blood stasis, and vessel wall injury. Clinical presentations are variable and range from headache, focal neurological deficits, seizures, and diffuse encephalopathy [1].

COVID-19 is a novel Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV-2), with many neurological complications that affect arterial and venous formation. COVID-19 causes endothelial injury when binding to Angiotensin-Converting Enzyme 2 (ACE-2) receptors, activating a coagulation cascade and cytokine resulting in a hypercoagulable state that causes thrombosis formation. There are elevated factor VIII levels, fibrinogen, D-dimer, and antiphospholipid antibodies [2-8].

This literature review addresses the clinical profile, neuroimaging, management options, and outcomes for COVID-19 patients with CVT.

## LITERATURE REVIEW

Cerebral Venous Thrombosis (CVT) is considered a neurological emergency requiring quick diagnosis and urgent management to avoid venous infarction, haemorrhage, neurological disability, or even death. CVT is estimated to occur in 1 per 100,000 cases per year. It is attributed to less than 1% of all cases of stroke worldwide; and in the past 50 years, mortality due to CVT has reduced from 15% to 5% because of advanced management [9,10].

### Pathophysiology and Risk Factors of CVT

Thrombus formation in the cerebral venous circulation will lead to a rise in hydrostatic pressure in veins and

capillaries. This increased pressure is somehow compensated by the anastomotic circuit of the cerebral venous system. If the pressure overcomes the compensation, this can lead to disruption of the blood-brain barrier, fluid extravasation into the cerebral parenchyma, and localized edema. An unusual mechanism of venous occlusion is the reduction of Cerebrospinal Fluid (CSF) reabsorption. This occurs when CSF flow is reduced due to arachnoid pacchionian granulations, therefore intracranial pressure will increase. As in any thrombosis, cerebral venous thrombosis has a multifactorial cause. About 85% of patients have a minimum of one identified risk factor, while 50% have multiple risk factors. Fewer cases are idiopathic. CVT occurs more often in females than males due to the use of oral contraceptives and hormonal replacement therapy, pregnancy, and puerperal period. Inherited thrombophilia such as protein C and S deficiency, factor V Leiden, prothrombin G20210A mutation, and antithrombin deficiency are considered risk factors of CVT. Some 7% of patients with CVT have either solid or hematologic cancer. There are also mechanical risk factors such as head trauma, neurosurgery, internal jugular catheterization, and lumbar puncture [11].

Recently, a European genome study discovered the first chromosomal region associated with genetic susceptibility to CVT in the 9q34.2 locus. In this region, single-nucleotide polymorphisms have a strong linkage in the ABO blood type gene coding disequilibrium. The higher risk of CVT in blood group type A, AB, or B was 2.85 times that of type O [12-15].

A meta-analysis was done in 2018 to identify the genetic or non-genetic associated risk factors of CVT. Genetic factors were associated with a three to 11 fold increase in the risk of CVT and increased more in the presence of prothrombin (G20210A) and factor V Leiden (G1691A). Other genetic factors included protein C deficiency, protein S deficiency, antithrombin deficiency, and TAFI gene variant (C1040T). For non-genetic factors, there was a 10 to 18 fold increase in the risk of CVT, and it increased more with pregnancy/puerperium and glucocorticosteroid therapy. Other non-genetic factors were alcohol consumption, infection, surgery, hypercholesterolemia, hyperhomocysteinemia, antiphospholipid antibodies, autoimmune diseases, anaemia, and malignancy [16,17].

CVT is considered a rare complication of bacterial meningitis. A cohort study done in patients with bacterial meningitis found Ear, Nose, and Throat (ENT) infections, sinusitis, mastoiditis, and otitis media predisposed patients to meningitis. CVT commonly occurred in patients who had bacterial meningitis because of otitis media and mastoid opacification [18,19]. Some viral infections cause CVT. A case was reported of a patient with chickenpox (primary varicella-zoster virus, VZV, infection) for 7 days, and the main complaint was headache and vomiting. After further workups, a CT scan showed extensive cerebral venous sinus thrombosis, not surprising in those patients with primary VZV infection who are prone to a hypercoagulable state [20,21].

CVT also can be a complication of some autoimmune diseases such as antiphospholipid syndrome. A recent study conducted to measure the association between CVT and antiphospholipid syndrome found that 20 out of 27 patients had CVT with antiphospholipid syndrome-not surprising because of the hypercoagulable state developed by antiphospholipid syndrome, which leads to CVT [22,23]. COVID-19 is an infection caused by the pathogen SARS-CoV-2 that results in severe acute respiratory syndrome and has numerous neurological manifestations, thromboembolism, and systemic hypercoagulability [24,25].

COVID-19 induces the prothrombotic state and causes endothelial damage, altered blood flow, hyper-inflammation, and hypercoagulability resulting in venous and arterial thrombosis in COVID-19 patients [3,26-28].

The endothelial injury occurs when the ACE-2 receptor's binding play-acting as a cytokine cascade and leads to a state of hypercoagulability [1,29,30].

The immune system response to COVID-19 triggers a complement activation cascade that induces prostaglandin and leukotriene synthesis, increases the production of inflammatory cytokines, activation of a coagulation cascade, and platelet activation resulting in outspread thrombosis. Hyper-viscosity is considered a potent thrombogenic factor and causes injury and dysfunction to the endothelial that affects the blood flow, high fibrinogen levels are one of the major reasons for plasma viscosity and have been associated with COVID-19 patients [3,28].

**Clinical Profile**

Most patients who develop CVT present symptoms within 48 hours to 2 weeks from disease onset. Common symptoms are headaches, seizures, focal neurological symptoms, and altered mental status. More acutely, they can develop thunderclap headache or stroke-like presentation [12,21,31,32].

The Turkish VENOST study in 2017 with a sample size of 1,144 CVT patients found that 68% were females. They presented with headache (87%), visual loss (27%), seizure (24%), decreased level of consciousness and encephalopathy (18%), focal deficits (18%) that is motor deficits in 40% of them, and cranial neuropathy/diplopia in 11% [33]. Another recent international prospective study, with a sample size of 1,281 patients, found 34% had acute symptomatic seizures, and 6% had status epilepticus [34,35].

**Regarding biomarker levels:** During the acute phase of CVT, the neutrophil count will increase and the lymphocyte count will decrease. While the monocyte count will increase in the subacute phase, the lymphocyte count will increase during the chronic phase and neutrophils will decrease. Many studies show the neutrophil-to-lymphocyte ratio is associated with an increased risk of poor outcomes in patients with CVT; while the lymphocyte-to-monocyte ratio was found to be higher in the chronic phase of CVT, resulting in a worse outcome. It was noted the platelet count was slightly high during the acute and sub-acute phase; the higher risk of provoked CVT was associated with a high platelet-to-lymphocyte ratio. A recent cohort study showed patients with CVT and high systemic immune-inflammatory index were associated with poor outcomes, mainly in pregnancy/puerperium patients. Interleukin 6 (IL-6) is significantly associated with poor functional outcome at 90 days, with a cut point of 2.7 pg/mL, with a specificity of 81% and sensitivity of 78%. For the acute phase biomarkers, C-reactive protein is high and supports the diagnosis of CVT. Also, the Erythrocyte Sedimentation Rate (ESR) is high in the acute phase of CVT. Other biomarkers such as plasma total homocysteine, S-adenosylhomocysteine, and S-adenosylmethionine are associated with high risk in CVT patients with high sensitivity and specificity. Cerebrospinal fluid levels of IgM, IgA, and IgG are high during the acute phase of CVT and indicate different degrees of inflammation during the disease course [36-38].

A recent study of 20 cases of CVT had 90% testing positive for SARS-CoV-2 by a nasopharyngeal swab of the reverse transcriptase PCR assay, while 10% had positive PCR for COVID-19 antibodies. Some 85% presented with headaches that lasts from 3 to 7 days in 76% of patients; 65% had seizures with 77% being generalized seizures and 23% focal seizures. Sixty-five percent of patients diagnosed with COVID-19 had CVT symptoms, and 35% of them were complicated by CVT while being managed for COVID-19. At the time of CVT diagnosis, 45% did not have respiratory symptoms; and in 25% of cases COVID-19 patients presented with CVT only without fever or respiratory symptoms. Laboratory markers in these CVT patients with COVID-19, showed elevated D-dimer levels, ESR, and leukocytes in the majority of them; 50% of cases had elevated homocysteine, and two out of nine patients had positive Lupus Anticoagulant (LA) [24,37-39].

**Neuroimaging**

Magnetic Resonance Imagining (MRI), Clinical Target Volume (CTV), and Magnetic Resonance Venography (MRV) are the standard diagnostic imaging modalities for the diagnosis of CVT since no validated diagnostic algorithms exist. No specific laboratory tests or non-contrast CT are helpful in the diagnosis of CVT due to their low sensitivity [40-42].

Usually, a CT scan is the modality of choice in emergency settings due to its availability, cost-effectiveness, and to rule out the most common neurological diagnoses. In non-contrast CT, a dense clot sign and a cord or string sign indicate CVT. A dense clot sign is the direct visualization of the thrombus in cerebral veins or sinuses. String sign is the linear or cord-likes density of a thrombosed cortical vein. Empty delta sign is considered a direct sign of CVT seen by contrast-enhanced CT, which is a thrombosed sinus shown as a triangular area of enhancement. Indirect signs seen by CT scan in 60%-80% of CVT cases are hemorrhagic infarction, brain edema, mass effect, and subarachnoid hemorrhage. Different retrospective studies reported that the diagnostic accuracy of CVT in CT scan is a sensitivity of 25% and a specificity of 100%, which suggests additional modalities are needed to diagnose CVT. CT venography is contrast-enhanced helical CT and one of the most common and frequently used imaging modalities for CVT diagnosis. Thrombosed cerebral veins can be seen as a filling defect, and indirect signs such as brain edema can contribute to the CVT diagnosis. In several studies, CT venography has been demonstrated an accurate diagnosis of cerebral sinus thrombosis with 100% sensitivity and specificity, but these studies were retrospective and with small sample sizes. CT venography has limited value for the diagnosis of cortical venous thrombosis with a sensitivity of 6%-75%. MRI has three techniques for thrombosis detection: non-contrast-enhanced flow-related MRI (also called non-contrast-enhanced MRV), contrast-enhanced MRI, and native contrast thrombus MRI. The sensitivity and specificity of the diagnostic accuracy of non-contrast-enhanced MRV were shown on most studies as 64%-100% and 48%-

100%, respectively. This indicates that non-contrast-enhanced MRV is less accurate for identifying cortical venous thrombosis. For combined native contrast thrombus MRI techniques, the sensitivity is 84%-97%, and the specificity 28%-96%. On gradient-recalled echo Susceptibility Weighted (SW) images, an adequate sensitivity of 97%-98% was reported, with a specificity of 100% in the diagnosis of CVT. In multiple studies, contrast-enhanced MRI was found to be superior to non-contrast-enhanced MRI in diagnostic accuracy, with a sensitivity of 86%-97% and a specificity of 52%-100%. For a comparison between CT and MRV, some studies found that CTV is better than MRV, with a sensitivity and specificity of 100% in diagnosing CVT [8,43-45].

For those who had CVT in association with COVID-19, a recent study was done on 12 cases that had both. They found thromboses are most frequently seen in the straight and left transverse sinuses in 45.5% of cases [1,46].

Another recent study found thromboses occurred in the transverse sinus in 75% of cases, 50% in the sigmoid sinus, and 33% in the internal cerebral vein or straight sinus thrombosis [4,47].

**Treatment Options and Outcome**

According to the latest guidelines of the American Academy of Neurology, anticoagulation is the main and standard treatment for acute CVT to prevent thrombus growth and facilitate recanalization. Anticoagulation therapy is recommended even in the presence of intracerebral haemorrhage or hemorrhagic transformation. Low Molecular Weight Heparin (LMWH) is safer and more effective than Unfractionated Heparin (UFH). Endovascular interventions such as thrombolysis are reserved for progressive neurological deterioration despite intensive medical treatment, although large, randomized trials are needed to establish efficacy and mortality rate. A small study with 13 patients who underwent decompressive hemicraniectomy found 11 patients had favourable outcomes, suggesting this procedure should be adopted for young patients with CVT who develop malignant hemispheric stroke. For the long-term anticoagulation therapy, the duration is depending on the presence of provoked *versus* unprovoked events. The duration of long-term anticoagulation is dependent on the presence of provoked versus unprovoked events. Patients with provoked events should have warfarin with a target INR of 2.0-3.0 for 3-6 months, while those with unprovoked CVT should be treated for 6-12 months. (The gold standard for long-term management of CVT is warfarin with an INR target of 2.0-3.0.) Patients with recurrent CVT, first-time CVT (provoked or unprovoked), venous thromboembolism after CVT, or severe thrombophilia should be treated with indefinite anticoagulation [48].

According to the European Stroke Organization, a therapeutic dose of heparin is recommended in acute CVT. With low quality of evidence, they suggest LMWH instead of UFH unless the patient has renal insufficiency. They did not recommend thrombolytic therapy for acute CVT due to its high risk of poor outcome and major hemorrhagic complications. If the patient has an inflammatory disease such as systemic lupus erythematosus associated with CVT, steroids are recommended for the management of acute CVT. In patients with acute CVT and impending brain herniation, routine shunting is not recommended to avoid the risks from parenchymal lesions. Also, it is not recommended to use shunting in acute CVT with hydrocephalus to prevent death and improve patient outcomes. Decompressive surgery is recommended in patients with acute CVT and impending brain herniation. Vitamin K antagonist can be used for 3-12 months after CVT to prevent recurrence; direct oral anticoagulant is not recommended especially in acute CVT. Antiepileptic medications are recommended for seizure management and prevention. In pregnant and puerperal patients with CVT, LMWH is recommended; however, combined hormonal contraception should not be used. If a pregnant woman has a history of CVT, prophylactic subcutaneous LMWH is recommended [49].

At this point, management of COVID-19 associated with CVT is the same as management of CVT without infection [3].

The overall outcome of patients with CVT and COVID-19 has been reported 35%-45%, while CVT alone was up to 15%, and COVID-19 alone was 5.6% [8,50].

Larger studies are required to determine incidence and mortality rates related to CVT associated with COVID-19.

## CONCLUSION

CVT is emerging as a serious neurovascular pathological complication with significant mortality and morbidity that

may occur after COVID-19, which needs to be considered in the clinical context with other neurological complications. Hypercoagulable states with COVID-19 infection are described as a pathophysiological mechanism with cascade thrombo-inflammation process. A better understanding of the pathophysiology, clinical presentation, and risk factors will foster the development of appropriate clinical approaches with therapeutic modalities. Further studies to identify biomarkers of thrombosis and underlying pathological mechanisms that cause severe illness may guide clinicians on early management and interventional strategies and optimize healthcare resources towards those patients at high risk for long-term disabilities and dire outcomes due to CVT in the presence of COVID-19.

## DECLARATIONS

### Conflict of Interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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