



Incidence of Superficial Venous Thrombosis Following Covid-19: A Systematic Review

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Abstract

Background: While research on deep venous thrombosis after COVID-19 has been conducted, there hasn't been a thorough evaluation of the literature on superficial venous thrombosis. By gathering information that can be used by doctors to comprehend and foresee such outcomes in case of infection with COVID-19, our study seeks to close that knowledge gap. Even if the outbreak is over, there is still a risk of re-infection with different strains.

Study Design: Systematic review

Methods: Using PRISMA we discovered articles from the years 2020 through 2023. The databases Cochrane Reviews, PubMed/Medline, and the search engine Google Scholar were all searched. With the conjunctions "OR" and "AND," particular keywords like "Superficial vein," "thrombosis," and "COVID-19" were included in the search approach.

Results: Cerebral sinus veins were most frequently impacted in young and healthy patients, but more than half of these had risk factors for thromboembolism. One uncommon ailment that consistently surfaced in searches was Mondor's disease, and there appears to be a link between this condition and COVID-19. Several COVID vaccinations have been observed to increase the risk of thromboembolic events in those who get them.

Conclusion: When treating a patient with COVID-19, we advise emphasizing the history taking for thromboembolism risk factors. If the patient reports symptoms, we also advise using radiographic studies to look for blockage in the superficial veins of the peripheral limbs, particularly the legs. Even when treating a COVID patient who exhibits no specific signs or symptoms, a high level of suspicion is required. Last but not least, more research should be done on Mondor's illness and its connection to COVID-19, as there have already been a few occurrences of the two being linked in the literature.

Introduction

COVID-19, having encompassed most of the globe during the years 2020 onwards, requires no deep introduction. While the majority of those who were infected with the virus experienced no more than mild to moderate respiratory symptoms, a significant number of people also endured severe complications. With the mortality rate increasing gradually, it was clear that intensive and focused efforts were needed to manage patients infected with the virus.

Highlighting one complication, venous thrombosis is frequently encountered due to the infection triggering coagulopathy. This itself is due to inflammatory damage to vessels, resulting in thrombotic events (1). Even following an acute phase, a patient may remain in that state for an extended period, making him/her vulnerable to further thromboembolic episodes. These can involve veins of any system, and the rate at which the risk decreases varies from case to case, with some patients experiencing thrombotic events even years later.

Delving further into the underlying mechanism of thrombosis as a direct result of COVID-19, it should be understood that the pathophysiology is complex. But basically, endothelial cell injury is the starting point (2). The subsequent thrombo-inflammation can be managed with appropriate drugs, but the speed at which this happens overshoots the diagnostic and therapeutic efforts. Enzymes such as angiotensin-converting enzyme 2 (ACE2) have also been discovered to play a key role in the pathogenesis (3). Increased signaling by thrombin receptors on a variety of cell types leads to coagulopathy and inflammation simultaneously, ultimately pushing cells and tissue to undergo necrosis. Modern treatment has been influenced by studies looking at these molecular interactions.

More on coagulation, while there are a host of factors that contribute, endothelial dysfunction forms the basis. This is also why laboratory investigations often show deranged platelets, D-dimers, fibrinogen, and prothrombin time (4). One thing to note is that thrombus formation in the pulmonary microvasculature structure in patients with COVID-19 is an important factor in determining the severity of the clinical picture and the outcome of this disease.

Rationale

While there has been research on deep venous thrombosis following COVID-19, there has not been a systematic review on superficial venous thrombosis. This study aims to fill that gap by compiling data that can be utilized by physicians to understand and anticipate such events in case of infection with COVID-19. Even though the epidemic is gone, the threat of re-infection with variants still exists. By conducting this study, we hope to provide valuable information to the medical community that can help improve patient outcomes and guide future research on this topic.

Objectives

To identify studies that exclusively look at venous thrombosis of any superficial vein following COVID-19 infection.

To systematically review and analyze the data from these studies to better understand the incidence and risk factors for superficial venous thrombosis following COVID-19 infection.

To provide a comprehensive overview of the current state of knowledge on this topic to guide future research and inform clinical practice.

To identify gaps in the current literature and suggest areas for future research.

Methods

This review was carried out according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines(5) (FIGURE 1). The timeframe of articles ranged from 2020-2023. The databases PubMed/Medline, Cochrane Reviews, and Google Scholar were searched. The search strategy involved using specific keywords such as "Superficial vein," "thrombosis," and "COVID-19" in combination with the conjunctions "OR" and "AND." An example search has been illustrated in Table 1.

| # | Query | Search Details | Results | Time |
|---|---|---|---------|----------|
| 1 | COVID[Title/Abstract] | "COVID"[Title/Abstract] | 312442 | 14:36:44 |
| 2 | thrombosis[Title/Abstract] | "thrombosis"[Title/Abstract] | 162901 | 14:37:36 |
| 3 | (((((Superficial vein[Title/Abstract]) OR (Saphenous vein[Title/Abstract])) OR (cephalic vein[Title/Abstract])) OR (basilic vein[Title/Abstract])) OR (external jugular vein[Title/Abstract])) OR (facial vein[Title/Abstract])) | "superficial vein"[Title/Abstract] OR "saphenous vein"[Title/Abstract] OR "cephalic vein"[Title/Abstract] OR "basilic vein"[Title/Abstract] OR "external jugular vein"[Title/Abstract] OR "facial vein"[Title/Abstract] | 19487 | 14:41:53 |
| 4 | venous thromboses[MeSH Terms] | "venous thrombosis"[MeSH Terms] | 59644 | 14:42:13 |
| 5 | (COVID[Title/Abstract]) AND (thrombosis[Title/Abstract]) | "COVID"[Title/Abstract] AND "thrombosis"[Title/Abstract] | 4659 | 14:42:38 |
| 6 | (COVID[Title/Abstract]) AND ((((((Superficial vein[Title/Abstract]) OR (Saphenous vein[Title/Abstract])) OR (cephalic vein[Title/Abstract])) OR (basilic vein[Title/Abstract])) OR (external jugular vein[Title/Abstract])) OR (facial vein[Title/Abstract])) | "COVID"[Title/Abstract] AND ("superficial vein"[Title/Abstract] OR "saphenous vein"[Title/Abstract] OR "cephalic vein"[Title/Abstract] OR "basilic vein"[Title/Abstract] OR "external jugular vein"[Title/Abstract] OR "facial vein"[Title/Abstract]) | 21 | 14:43:08 |
| 7 | (COVID[Title/Abstract]) AND (venous thromboses[MeSH Terms]) | "COVID"[Title/Abstract] AND "venous thrombosis"[MeSH Terms] | 490 | 14:44:28 |

Table 1: Search strategy on PubMed**Eligibility Criteria**

The inclusion criteria for the studies were as follows:

1. Studies covering thrombosis of superficial veins only following COVID-19 infection.
2. Studies having outcomes or findings reporting on the association between COVID-19 and superficial venous thrombosis

The exclusion criteria for the studies were as follows:

1. Systematic reviews or meta-analysis
2. Articles in languages other than English
3. Animal studies

Data Collection

The Zotero web app was used to detect and import all search results into the Zotero Reference Manager desktop application. The titles and abstracts were then reviewed. Data collected was then compiled into tables within LibreOffice Calc.

Data Items

- Author
- Study type
- Country
- Sample size
- Mean Age
- Gender Ratio
- Outcomes
- Veins involved
- Findings

Information Sources

1. PubMed/Medline (2020-2023)
 2. Cochrane reviews (2020-2023)
 3. Google Scholar (2020-2023)
-

Results

Salient findings

1. Most articles were case studies (TABLE 2)
2. Most commonly affected vessels belonged to the central nervous system (cerebral sinus veins)
3. Patients were generally young and healthy
4. More than half had risk factors for thromboembolism
5. Mondor's disease was one rare condition that frequently appeared in search, and there seems to be an association between this condition and COVID-19
6. Several COVID vaccines have been noted to predispose the recipients to thromboembolic events
7. The number of articles that looked at deep veins outnumbered those that looked at superficial veins
8. Most cases involving superficial veins were managed successfully.

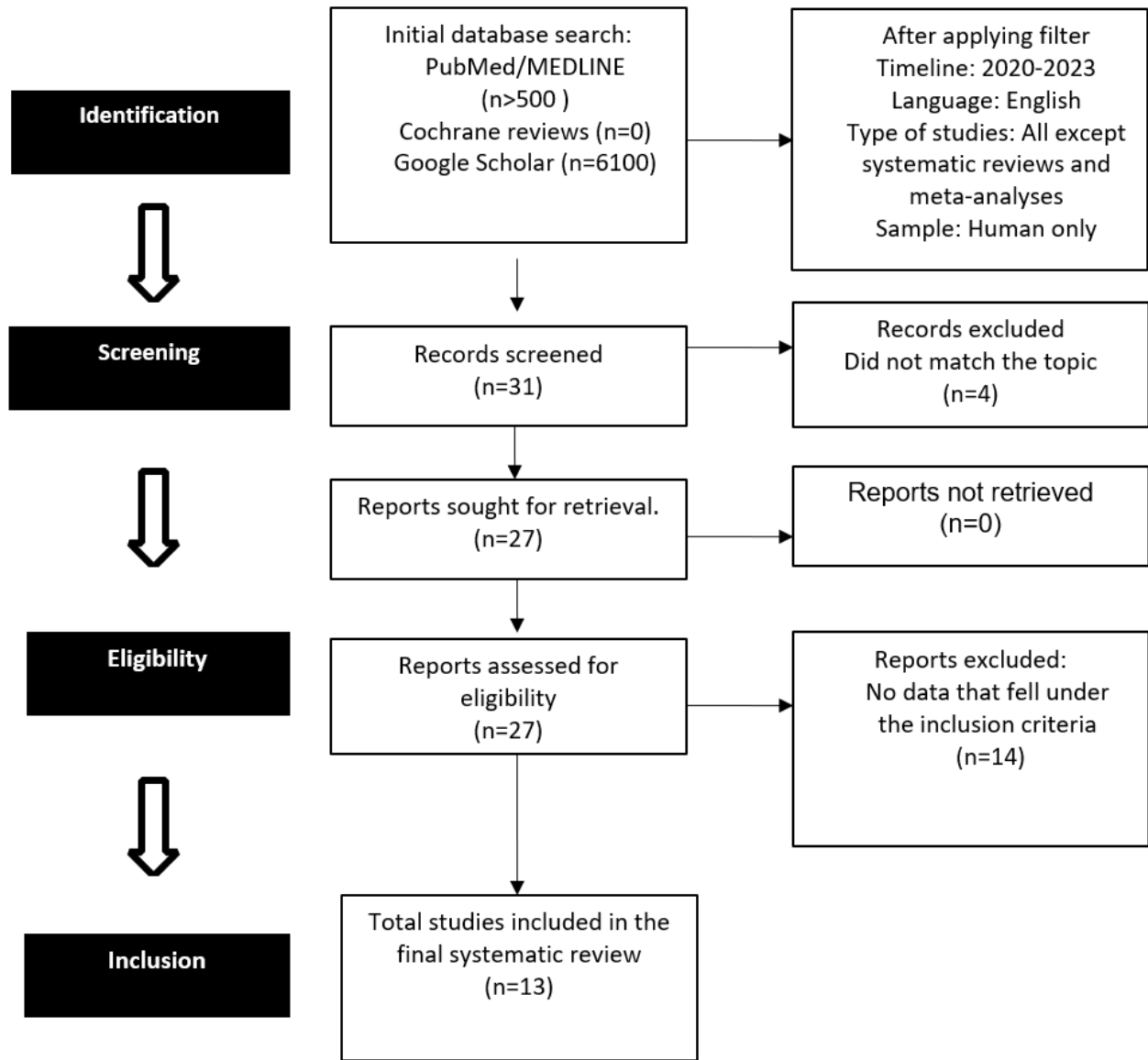


Figure 1: PRISMA Flowchart showing search strategy

| Author | Study Type | Country | Sample Size | Age (mean) | Sex (M/F) | Vessel Involved | Outcomes | Findings |
|--------|-------------|---------|-------------|-------------|-----------|--------------------------------------|--|--|
| (6) | Case Report | China | 1 | 48 | Male | Superior sagittal sinus | Prothrombin time=12.8s INR=1.01 Fibrinogen=289mg/dL D-dimer=0.77µg/mL | Superficial venous thrombosis can occur after a delay from mild COVID-19 infection. |
| (7) | Case Report | Iran | 1 | 40 | Male | Great saphenous vein | D-dimer=0.75µg/mL CRP= 30mg/L ESR= 18mm LDH = 510 | Imaging methods like CT, MRI, and ultrasound should be done in a COVID-19 patient to rule out SVT and DVT so as to prevent pulmonary embolism. |
| (8) | Case Report | Italy | 1 | 28 | Male | Superficial dorsal vein of the penis | Platelets=175,000/mm ³ C-RP= 23.20 mg/dl D-dimer=3.25 g/l Fibrinogen=721 mg/dl | Mondor's disease, while rare, has a higher chance of occurring in COVID-19 due to a prothrombic state |
| (9) | Cohort | France | 2161 | 72 (18-102) | 44% / 56% | Sinus veins of cerebrum | Venous thrombotic events COMIRATY = 31.8% MODERNA = 24.6% AZD1222 = 52.3% | Cerebral venous sinus thrombosis COMIRATY = 0.3% MODERNA = 0.9% AZD1222 = 0.9% |

| | | | | | | | | |
|------|-----------------|---------------|------------------------------------|------|---------------|--|--|--|
| (10) | Case Report | United States | 38 year old woman + 43 mixed group | - | 56% / 44% | Sinus veins of cerebrum | D-dimer level (7.14/mL±12.23 mg/L) Fibrinogen level (4.71±1.93 g/L). | The mean time of diagnosis was 15.6±23.7 days after onset of COVID-19 symptoms 87% had thrombosis of multiple dural sinuses The mortality rate was 39% (13 patients) |
| (11) | Case series | United States | 3 | 34 | 66% / 33% | Sinus veins of the cerebrum: Superior sagittal Straight sinus Transverse sinus | WBC: 16,710 / 9950 / 8840 D-Dimer: 55,000 / 787 / 920 Platelet count: 141,000 / 239,000 / 8600 | Cerebral venous sinus thrombosis can easily occur in previously healthy and young patients. |
| (12) | Case report | Iran | 1 | 57 | Female | Superficial and small saphenous veins | WBC= 2300 × 109/L Platelets= 138 × 103/μL C-RP= 47 mg/L LDH= 655 U/L D-dimer= 1.3 μg/mL | The involvement of the superficial veins was not serious as compared to the deep veins. |
| (13) | Cohort | UK (Scotland) | 8000 | - | Females | Superficial veins of breast (18) and abdomen (2) | Incidence of Mondor's disease (5-fold increase during the same year of COVID) | Mondor's disease may be a more common late manifestation after COVID-19 |
| (14) | Cross-sectional | USA | 41 | 50.1 | 46.3% / 53.7% | Sinus veins of | Involvement of superficial veins | Both superior sagittal and transverse sinus had |

| | | | | | | | | |
|------|-------------|----------|------|--------------------------------------|-------------|----------------------------------|---|---|
| | | | | | | the cerebrum | | the highest frequency of involvement. |
| (15) | Cohort | Portugal | 8547 | 57.3 ± 15.93 | 1:3.2 ratio | Superficial veins | Number of superficial veins involved vs. deep veins involved | 60 patients had superficial vein thrombosis, while only 19 had deep venous thrombosis, but no significant association was noted between COVID |
| (16) | Case report | Turkey | 1 | 33 | Male | Superficial dorsal vein of penis | aPTT= 36.6s PT= 15.1s | Despite anti-thrombotic treatment with rivaroxaban, the patient experienced Mondor's disease during the COVID-19 infection |
| (17) | Case series | Nepal | 2 | 24 year old male, 63 year old female | 1:1 | Superficial veins | PT elevated above the normal range in both cases; other laboratory values were normal | Use of COVISHIELD vaccine has been linked to the development of superficial venous thrombosis |
| (18) | Case series | Africa | 2 | 98-year-old and 64-year-old female | Females | Superficial veins | All laboratory values were within normal ranges | The use of the JANSSEN vaccine was associated with superficial venous thrombosis in one of the cases. |

Table 2: Synthesis of data from the included studies in this review

Discussion

Ours is the first systematic review to exclusively look at cases of superficial venous thrombosis due to COVID-19. Even so, the results of our search have been lukewarm at best. The majority of the articles found were case reports or series. Only a handful were cohort studies. This brings us to the question of why there is such small coverage of this complication of COVID-19. Many factors can be attributed to the dearth of studies. Firstly, during the pandemic, which lasted at its peak for two years, healthcare providers were not aware of what to expect as far as complications were concerned. It takes a good sense of clinical suspicion to determine what is happening to the patient and treat them accordingly. Because the virus was novel, there were limited guidelines on the management initially(19). This, coupled with a lot of pseudo-information regarding the management circulating, and healthcare providers were in disarray. Only the most prominent, notable, and highly discussed complications were given attention, which included respiratory and cardiovascular issues(20). When hypercoagulability was confirmed to occur, and patterns were being observed, only then did physicians start recording the appropriate investigations. Even then, not every case of hypercoagulability was published. Of those that were, the majority mostly focused on the involvement of deep arteries and veins(4). The thrombosis occurring in these vessels was often found in the central nervous system. Thus, any thrombosis that involved superficial vessels as a direct or indirect result of COVID-19 infection was not brought into the limelight.

Several studies reported abnormalities of prothrombin time, d-dimers, fibrinogen levels, and platelet count. This is supported by multiple studies in the literature that report how COVID-19 causes endothelial damage to vessels with subsequent initiation of coagulation(21,22). However, there is a greater incidence of intracerebral hemorrhage as compared to cerebral venous thrombosis. This can perhaps be attributed to the aggressive use of anticoagulants in patients with COVID-19. But what's more interesting is that most of these cases of intracerebral hemorrhage occurred independent of cerebral thrombosis and during the acute phase of COVID-19(23,24). However, one of the included studies in our systematic review reported thrombosis of the superior sagittal sinus in a patient with mild COVID-19 symptoms almost a month after the acute phase of the virus; the patient was also comparatively younger than other patients who experienced non-covid related cerebral thrombosis events(6). While the author did not elucidate the underlying reason for this unique scenario, what's certain is that even a less severe infection can predispose a younger patient to superficial cerebral thrombosis weeks after recovery or discharge from the hospital.

It should be noted that the mortality rate of patients with cerebral venous sinus thrombosis caused by COVID-19 can be significant. This is due to the involvement of other parts of the central nervous system, such as the hippocampus and basal ganglia. Panichpisal et al. noted diffuse involvement of the cerebrum due to multiple sinus veins being involved in their patients. They saw similar findings in 43 others but reported how less than half had risk factors for thrombotic events. Based on these findings, it is essential that early investigations and management are instigated to prevent mortality. Furthermore, a thorough history must be taken to confirm the presence of risk factors, as this would increase the likelihood of thrombotic events, whether in superficial or deep veins.

The fact that cerebral venous sinus thrombosis can happen in previously healthy and young patients should not be taken lightly. A case series reported several young patients with COVID-19 presenting with cerebral venous sinus thrombosis(11). All were below 40 years of age, and while dehydration was blamed as the instigator in two of the cases because all had elevated white blood cell counts, infection was primarily the cause of thrombophlebitis. Other risk factors present in these patients included diabetic ketoacidosis and the use of oral contraceptive pills. What's unusual is that the neurological symptoms were vague or atypical. These included signs such as simple lethargy, headaches, vomiting, and aphasia in one of the patients. Moreover, despite full efforts to treat the patients, all experienced a fatal outcome. This study shows how COVID-induced thrombosis of the cerebral veins can not only present atypically but also how healthy people can fall victim. We reiterate that the risk factors must be given due attention, and these can only be learned from a thorough history.

Similarly, a multicenter, cross-sectional, retrospective study reviewed the clinical and radiological presentation of COVID-19-positive patients diagnosed with Cerebral Venous Sinus Thrombosis(14). Most patients presented with non-specific symptoms such as headache, fever, and gastrointestinal symptoms. D-dimer and inflammatory biomarkers were significantly elevated relative to reference ranges in patients with available laboratory data. The superior sagittal and transverse sinuses were the most common sites for acute cerebral venous thrombosis formation. The median time to onset of focal neurologic deficit from initial COVID-19 diagnosis was three days. However, the median time from the onset of COVID-19 symptoms to radiologic diagnosis of thrombosis was 11 days. While mortality was low in this cohort, the study reinforced how there was an ever-present risk of acute cerebral venous thrombosis in patients positive for COVID-19. Following cerebral venous thrombosis, deep venous thrombosis of the lower limbs is the next most common complication when coagulopathy occurs during a COVID-19 infection. The underlying mechanism is the

same as for cerebral venous thrombosis, that being damage to the endothelial lining to vessels, leading to a cascade of thrombotic events. However, thrombosis of the vessels of the leg carries a high risk for emboli that can migrate to the respiratory system, causing pulmonary embolism, which is fatal. In one of the studies collected, the author noted the patient did not have any such occlusion in his deep veins, but a thrombosis was noted in the distal end of the great saphenous vein(7). While the patient was treated with anti-coagulants, this case showed how superficial vessels were no exception to the effects of COVID-induced coagulopathy. The authors encouraged the use of radiographical investigations to rule out thrombosis of the superficial veins, as even their involvement can lead to pulmonary embolism(25). Thus, we also agree that a protocol be implemented when dealing with patients of COVID-19 that involves regular and prompt use of ultrasound, CT, or MRI to rule out involvement of the veins of the lower limbs.

A unique late manifestation of COVID-19 is Mondor's disease. We found multiple studies that reported the disease. Two studies worth mentioning involve both a man and a group of women(8,13). In the man, the dorsal superficial vein was involved but was treated successfully following anti-coagulants. It is worth noting that there were no other risk factors known that could have led to this rare occurrence. Meanwhile, in Scotland, since the start of the epidemic, a study showed a five-fold increase in the incidence of Mondor's disease in women. Out of the twenty cases, 18 involved the superficial veins of the breast, and 2 involved superficial veins of the abdomen. This increase is statistically significant and points to the association between COVID-19 and Mondor's disease. The underlying mechanism, once again, is how COVID-19 increases the chance of thromboembolic events.

During our literature search, we also sought to discover how vaccination played a part in all this. Knowing how COVID-19 can induce a prothrombotic state, can the state be prevented with timely vaccination? One research that studied this link was heavily limited in its scope(9). The authors looked at only three varieties of vaccines and did not make a direct comparison with the non-vaccinated population. The study merely reports the incidence of both arterial and venous thrombotic events. However, since this was not a randomized control trial, we cannot say for certain what protective effects these vaccines conferred on the patients, if at all. What can be said is how different vaccines showed varying results in the prevention of thrombotic events overall, though it can be argued that this may have been due to the non-homogenous distribution of the sample size and their contrasting baseline characteristics. The authors went further to conclude that it was possible that the vaccines themselves predisposed the patients to a prothrombotic state but stopped short of stating how vaccination was still necessary, and their observations could only amount

to a hypothesis. We agree that while vaccinations against COVID-19 are not without side effects, we cannot pass a verdict on the absoluteness of vaccination against COVID-19 without falling into a scientifically backed discourse, but this falls outside the scope of our topic.

Limitations

1. Because COVID-19 was a novel virus and healthcare providers were initially unaware of its complications, this lack of knowledge likely led to underreporting of certain complications, including superficial venous thrombosis.
2. During the peak of the pandemic, the focus was primarily on managing severe and life-threatening complications of COVID-19, such as respiratory and cardiovascular issues. This could have resulted in less attention being paid to complications involving superficial vessels.
3. When hypercoagulability was confirmed as a complication of COVID-19, most studies focused on deep arteries and veins, often in the central nervous system. This focus could have overshadowed the occurrence of thrombosis in superficial vessels.
4. There might be a publication bias where only cases involving severe complications or novel findings were published. Mild or less severe cases, such as superficial venous thrombosis, might not have been considered significant enough for publication.
5. It's also possible that cases of superficial venous thrombosis were simply not recognized or reported due to a lack of awareness about this specific complication.
6. Of the studies we have included, the majority are case reports which only look at a single patient. The sample size is not enough to deem the findings as significant.

Conclusion

It is clear that there are still a lot of things we simply don't know about the dynamics of the virus and its effects on patients. But from our findings, we can safely deduce that there is indeed an increased incidence of superficial venous thrombosis during an infection with COVID-19. We recommend that history taking for risk factors for thromboembolism be given due emphasis when managing a patient with COVID-19. We also recommend the use of radiographical investigations for finding occlusion in superficial veins of the

peripheral limbs, especially legs, should the patient complain of symptoms. A high degree of suspicion is needed even when managing a COVID-19 patient devoid of any particular sign or symptom. Further studies should be done on Mondor's disease, and its link with COVID-19, as literature has already reported a handful of cases associating the two. Lastly, the authors of this review do not advocate nor reject the use of specific COVID-19 vaccines, but we highly recommend that further workup is done to determine if current COVID-19 vaccines carry a high risk for thromboembolic events.

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