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Associations between SARS-CoV-2 infections and thrombotic complications necessitating surgical intervention: A systematic review

Ferraro JJ *et al.* COVID-19 and thromboembolic complications

Abstract

BACKGROUND

Several unique clinical features of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the cause of coronavirus disease 2019 (COVID-19) infection, have been identified and characterized. One such feature, mostly among patients with severe COVID-19 infection, has become known as COVID-19-induced coagulopathy. Surgical patients with a history of or active COVID-19 infection bear a significantly higher risk for postoperative thrombotic complications. These patients may require surgical intervention to treat severe thrombotic complications. Few studies have been carried out to better characterize this association. The purpose of this study was to perform a systematic review and meta-analysis of the literature on COVID-19 infections that led to thrombotic complications necessitating surgical intervention. We hypothesized that patients with recent or active COVID-19 infection would have high rates of thromboembolic complications both arterial and venous in origin.

AIM

To perform a systematic review and meta-analysis of the literature on COVID-19 infections that led to thrombotic complications necessitating surgical intervention.

METHODS

The current systematic review implemented an algorithmic approach to review all the currently available English medical literature on surgical interventions necessitated by COVID-19 thrombotic complications using the preferred reporting items for systematic reviews and meta-analysis principles. A comprehensive search of the medical literature in the "PubMed", "Scopus", "Google Scholar" top 100 results, and archives of *Plastic and Reconstructive Surgery* was performed by two authors (Reynolds A and Edoigiawerie S) on January 4, 2022, using the key words "COVID-19" AND "surgery" AND "thromboembolism" AND "complication" as well as associated terms. The search string was generated and the records which were not specific about surgical

interventions or thrombotic complications due to COVID-19 infection were excluded. Foreign language articles were not eligible for inclusion. Articles published prior to 2019 were excluded as being prior to the COVID-19 pandemic and therefore not relevant to complications associated with COVID-19 infection. Titles and abstracts were screened by two authors (Reynolds A and Edoigiawerie S) after which full-text articles were assessed for eligibility and inclusion. On initial and secondary search, papers in review, commentary, or letter format or those without accessible full-text articles were excluded. Finally, results were further refined to focus on articles that featured surgical interventions that were necessitated by COVID-19 thrombotic complications. For completion of the search, the references of the selected publications were additionally screened with the previously mentioned inclusion criteria.

RESULTS

The database search resulted in the final inclusion of 22 retrospective studies, after application of the inclusion/exclusion criteria. Of the included studies, 17 were single case reports, 3 were case series and 2 were cross sectional cohort studies. All studies were retrospective in nature. Twelve of the reported studies were conducted in the United States of America, with the remaining studies originating from Italy, Turkey, Pakistan, France, Serbia, and Germany. All cases reported in our study were laboratory confirmed SARS-CoV-2 positive. A total of 70 cases involving surgical intervention were isolated from the 22 studies included in this review.

CONCLUSION

There is paucity of data describing the relationship between COVID-19 infection and thrombotic complications necessitating the need for surgical intervention. Intestinal ischemia and acute limb ischemia are amongst the most common thrombotic events due to COVID-19 that required operative management. An overall postoperative mortality of 30% was found in those who underwent operative procedures for thrombotic complications, with most deaths occurring in those with bowel ischemia. Physicians

should be aware that despite thromboprophylaxis, severe thrombotic complications can still occur in this patient population, however, surgical intervention results in relatively low mortality apart from cases of ischemic bowel resection.

Key Words: Thromboembolic; COVID-19; SARS-CoV-2; Surgical intervention; Complications; Surgery

Ferraro JJ, Reynolds A, Edoigiawerie S, Seu MY, Horen SR, Aminzada A, Hamidian Jahromi A. Associations between SARS-CoV-2 infections and thrombotic complications necessitating surgical intervention: A systematic review. *World J Methodol* 2022; In press

Core Tip: Surgical patient with a history of or current active infection with severe acute respiratory syndrome coronavirus 2 bear a significantly high risk for postoperative thrombotic complications. These patients may require surgical intervention to treat severe thrombotic complications. In total, 70 cases of thromboembolic complications necessitating surgical intervention have been documented. These patients have an overall mortality rate of 30%. Intestinal ischemia and acute limb ischemia are the most common thrombotic complications that required operative management. Physicians should be aware that severe thrombotic complications can occur in this patient population, however, surgical intervention results in relatively low mortality apart from cases of ischemic bowel resection.

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a pandemic infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)^[1]. Since December 2019, COVID-19 has spread throughout the world and changed the landscape of biomedical research and healthcare in a myriad of ways. Several unique clinical features of the virus have been identified and extensively characterized. One such feature, mostly among patients with severe COVID-19 infection and to some extent in less severe cases, is known as

COVID-19-induced coagulopathy (CIC), which manifests as ³ considerable elevation in D-dimer and fibrin split products, with little to no associated change in activated partial thromboplastin time and prothrombin time^[2].

A large proportion of patients with CIC have been reported to develop venous and arterial thromboembolic complications^[3]. Critically ill patients and patients undergoing surgeries are generally predisposed to thromboembolism due to a combined immobility, systemic inflammation, endothelial dysfunction, and circulatory stasis^[4,5]. The progression of CIC can be insidious, with some cases of pulmonary embolism (PE) identified as the first sign of SARS-CoV-2 infection in patients with no early evidence of virus upon testing with nasopharyngeal swab^[6]. Thrombotic risks posed by CIC cannot be underestimated, as it is not limited to patients within intensive care or other high-dependency settings^[7].

Postoperative thrombotic complications such as venous thromboembolism (VTE) and PE are responsible for significant morbidity and mortality among patients undergoing invasive procedures and surgeries^[8,9]. Approximately 50% of all reported VTEs are provoked by prolonged immobilization, trauma, surgery, or hospitalization within the last 3 mo^[10,11]. Therefore, a surgical patient with a history of or active COVID-19 infection would be at a significantly higher risk for postoperative thrombotic complications than the general population^[12,13]. Traditionally cases of VTE are treated with systemic anticoagulation (*i.e.*, heparin, low molecular weight heparins, direct oral anticoagulants, and vitamin-K antagonists) following a careful evaluation of the risks and benefits. The thrombolysis is reserved for clinically serious and massive PE conditions in an attempt to dissolve the clot more rapidly than with anticoagulation options and reduce the mortality^[14]. Severe cases of thromboembolic complications may require surgical intervention (*i.e.*, mechanical thrombectomy, catheter direct thrombolysis) to reduce the risk of post thrombotic syndrome and venous insufficiencies [in case of deep venous thrombosis (DVT)]^[15] or the risk of pulmonary insufficiencies, hemodynamic instability and or death (in cases of PE)^[14]. Therefore, a patient with previous or active COVID-19 infection may require surgical intervention to

treat severe thrombotic complications. Few studies have characterized this association[المشار1]. The purpose of this study was to perform a systematic review and meta-analysis of the literature on COVID-19 infections that led to thrombotic complications necessitating surgical intervention.

MATERIALS AND METHODS

The current systematic review implemented an algorithmic approach to review all the currently available English medical literature on surgical interventions necessitated by COVID-19 thrombotic complications using the preferred reporting items for systematic reviews and meta-analysis principles (Figure 1). A comprehensive search of the medical literature in the “PubMed”, “Scopus”, “Google Scholar” top 100 results, and archives of *Plastic and Reconstructive Surgery* was performed by two authors (Reynolds A and Edoigiawerie S) on January 4, 2022, using the key words “COVID-19” AND “surgery” AND “thromboembolism” AND “complication” as well as associated terms.

The search string was generated and the records which were not specific about surgical interventions or thrombotic complications due to COVID-19 infection were excluded. Foreign language articles were not eligible for inclusion. Articles published prior to 2019 were excluded as being prior to the COVID-19 pandemic and therefore not relevant to complications associated with COVID-19 infection. Titles and abstracts were screened by two authors (Reynolds A and Edoigiawerie S) after which full-text articles were assessed for eligibility and inclusion. On initial and secondary search, papers in review, commentary, or letter format or those without accessible full-text articles were excluded.

Finally, results were further refined to focus on articles that featured surgical interventions that were necessitated by COVID-19 thrombotic complications. For completion of the search, the references of the selected publications were additionally screened with the priorly mentioned inclusion criteria. We also cited high-quality articles in *Reference Citation Analysis* (<https://www.referencecitationanalysis.com>).

RESULTS

The database search resulted in the final inclusion of 22 retrospective studies, after application of the inclusion/exclusion criteria. Of the included studies, 17 were single case reports, 3 were case series and 2 were cross sectional cohort studies. All studies were retrospective in nature. Twelve of the reported studies were conducted in the United States of America, with the remaining studies originating from Italy, Turkey, Pakistan, France, Serbia, and Germany. All cases reported in our study were laboratory confirmed SARS-CoV-2 positive. A total of 70 cases involving surgical intervention were isolated from the 22 studies included in this review. The 22 studies which were included in the review are listed in detail in (Table 1).

DISCUSSION

Thromboembolic complications are a well-known sequela of COVID-19 infection, and their incidence has been the subject of many recent studies. The predisposition to the development of both venous and arterial thromboembolic complications by COVID-19 has also been well established, with incidences of thromboembolic complications in COVID-19 patients ranging from 7.2% to 40.8%^[16]. The high complication rate poses a public health concern due to the increased morbidity, mortality and high costs associated with their development^[16]. Such complications also pose a significant challenge to physicians treating them, as the need for a surgical intervention must be weighed against the risk of operation in an unstable and high-risk individual while the patient is in an already prothrombotic state. There is a significant gap in the literature describing the relationship between COVID-19 infections and thrombotic events requiring surgical intervention.

Of the 70 COVID-19 patients with thromboembolic complications necessitating surgical intervention found in our study, 85% ($n = 60$) had thrombotic complications considered to be arterial in origin. The most common complication reported was intestinal ischemia at 60% ($n = 42$)^[17-19]. The second most common complication was acute limb ischemia (ALI) at 23% ($n = 16$), which included 14 cases of lower limb

ischemia and 2 cases of upper limb ischemia^[20-27]. ALI is defined as a sudden decrease in arterial perfusion of an extremity that compromises the viability of a limb^[28]. Prior to the COVID-19 pandemic, the incidence of ALI in the general population was found to be 10 to 15 per 100000 cases each year (0.0001%-0.00015%)^[20]. However, one study performed in a New York City hospital found the rate of ALI in the COVID-19 population to be as high as 0.38%^[29]. Treatment of ALI includes endovascular or open surgical revascularization, however 10% to 15% of patients end up undergoing amputation during their hospitalization^[30,31]. Of the 16 cases of ALI in the population being investigated, 8 (50%) of these patients eventually underwent some form of amputation of the affected extremity. In addition to the above cases, our cohort had 1 case of stroke due to bilateral arterial thrombosis of the anterior circulating vessels, which was treated with bilateral simultaneous mechanical thrombectomy^[32].

In contrast to arterial thrombotic events, venous thrombotic events are a more common sequela of COVID-19, with the PE and DVT at an estimated incidence of 13.5% and 11.8% respectively^[16]. In our study, PE accounted for 10% ($n = 7$) of thrombotic events necessitating surgical intervention^[33-36], notably higher than both the reported incidence of PE amongst non-intensive care unit (ICU) hospitalized patients and ICU patients with COVID-19 (1.3% and 6.2%, respectively)^[37,38]. Interestingly, our study included two cases of phlegmasia cerulea dolens (PCD)^[39,40], a rare and life-threatening form of DVT that results in arterial occlusion secondary to compartment syndrome caused by total venous occlusion^[41]. PCD has been reported to have an amputation rate close to 50%, as well as a mortality of up to 40%^[42]. Of the two patients in our study with PCD, only one required amputation. Also included in our cohort was one patient who required bilateral transmetatarsal amputations due to the development of “COVID toes”, thought to be due to either microvascular thrombosis or related to a rare complication of venous thrombosis manifesting as venous gangrene^[43].

Mortality

Several studies have attempted to quantify mortality related to thromboembolic events in COVID-19 patients. One study found that COVID-19 patients with a thromboembolic event had a 40% mortality rate, over twice that of COVID patients without a thrombotic event^[44]. Another study, a meta-analysis of 8271 patients, found that patients with COVID-19 who had thromboembolic events had a pooled mortality rate of 23%, with thromboembolism significantly increasing the odds of mortality by as high as 74%^[45]. Similarly, Gonzalez-Fajardo *et al*^[46] found a mortality rate of 23.58% in their retrospective review of COVID-19 patients with thrombotic events, with a higher mortality seen in patients with peripheral arterial thrombosis and ischemic stroke compared to those with DVT and PE. Our study of COVID-19 patients with thrombotic events needing surgical intervention produced an overall mortality rate of 30% ($n = 21$). Notably, the highest mortality rate was seen in patients with acute intestinal ischemia who underwent bowel resection (45%, $n = 19$ of 42), followed by patients treated for ALI (13%, $n = 2$ of 15). It is unclear at this time if COVID-19 infection^[2,3] significantly complicated the cases of bowel resection, as acute intestinal ischemia has been noted to have a mortality rate as high as 80%, even without the added complexity of COVID-19 infection^[47]. This is partly due to difficulty in diagnosis, importance of early diagnosis, and the rapid deteriorating nature of ischemic intestinal tissue and the patient's condition. It is possible that severe COVID-19 infection delayed the diagnosis of intestinal ischemia in several of the patients included in this study, leading to higher mortality rates. Difficulties in accessing medical and surgical care due the widespread impact of the current COVID-19 pandemic in every aspect of the health care could also be influential although the true nature and depth of such an impact is a matter of speculation.

Comorbidities

In total, 17 of the 70 patients in this review had specific comorbidity data readily available. The most common comorbidities amongst our cohort of patients were hypertension (64%, $n = 11$), diabetes mellitus (53%, $n = 9$), and obesity (35%, $n = 6$), all of

which have previously been associated with a prothrombotic state^[48,49]. Hypertension has been noted to be an independent risk factor for the development of deep vein thrombosis in a large study of over 18000 patients^[50], so it is not surprising that patients with hypertension and COVID-19 infection were at an increased risk of thrombotic complications necessitating surgical intervention. However, a recent study by Xiong *et al*^[51] demonstrated no increase in thrombotic events among COVID-19 patients who were obese or had hypertension. Interestingly, their meta-analysis also found a previous diagnosis of diabetes mellitus to have a protective rather than potentiating effect on thrombotic events in this population. These results have been attributed to the use of medications such as statins and metformin, which have some degree of anti-inflammatory effects. While concomitant medication use was not a variable under investigation in our study, future studies may look at the relationship between medications with anti-inflammatory effects and reduced thrombotic complications of COVID-19.

Thrombotic prophylaxis

Since it became apparent that COVID-19 produces a prothrombotic state, much of the focus on thrombotic complication management has been shifted towards prevention. In May of 2020, the International Society on Thrombosis and Hemostasis published a statement regarding hospitalized COVID-19 patients in the ICU, recommending routine thromboprophylaxis with standard-dose low molecular-weight heparin or unfractionated heparin, unless contraindicated^[52]. Yet our study found that 44% ($n = 31$) of patients who developed thrombotic complications requiring surgical intervention received some type of prophylactic anticoagulant therapy. This finding is consistent with the current literature, as studies have shown a high rate of thromboembolic complications in COVID-19 patients despite the use of prophylactic anticoagulation^[53], with one study estimating this phenomenon to occur in almost one-third of all critically ill COVID-19 patients^[54]. As previously stated, CIC has been reported to be the presenting symptom of some severe COVID-19 infections, making it possible for some

patients in our study to have had thrombotic events prior to their presentation or COVID-19 diagnosis. Additionally, in several of the studies analyzed by this systematic review, dosage information and duration of thromboprophylaxis was not described, therefore it is unclear if some patients were subtherapeutic with their thromboprophylaxis regimen. Further studies to look at the dose and choice of anticoagulant in relation to severe thromboembolic events in the setting of COVID-19 infection is warranted.

Limitations

Our study is one of the first to analyze the relationship between COVID-19 infection and thrombotic complications that required surgical intervention, but there were several limitations. As all the included studies in this review were retrospective in nature, bias cannot be eliminated. Additionally, differences between the studies included in this review may lead to an additional bias, including the reporting of and variation of type and dosage of thromboprophylaxis. The reporting of outcomes and mortality, location of thrombotic events, and the method of surgical management also varied between many of the studies. Finally, our review drew a relatively small sample size, and our search criteria included only those studies in which patients were reported to have surgical intervention for their thrombotic events, and therefore incidence data could not be calculated.

CONCLUSION

There is paucity of data describing the relationship between COVID-19 infection and thrombotic complications necessitating the need for surgical intervention. Intestinal ischemia and ALI are amongst the most common thrombotic events due to COVID-19 that required operative management. An overall postoperative mortality of 30% was found in those who underwent operative procedures for thrombotic complications, with most deaths occurring in those with bowel ischemia. Physicians should be aware that despite thromboprophylaxis, severe thrombotic complications can still occur in this

patient population, however, surgical intervention results in relatively low mortality apart from cases of ischemic bowel resection.

ARTICLE HIGHLIGHTS

Research background

It is well-known that coronavirus disease 2019 (COVID-19) infection is associated with hypercoagulability among affected patients. This has become known as COVID-19 induced coagulopathy (CIC). This study investigated CIC-related thrombotic complications through a systematic review and meta-analysis of the existing literature.

Research motivation

There is paucity of data describing the relationship between COVID-19 infection and thrombotic complications necessitating the need for surgical intervention. Intestinal ischemia and acute limb ischemia (ALI) are amongst the most common thrombotic events due to COVID-19 that required operative management. An overall postoperative mortality of 30% was found in those who underwent operative procedures for thrombotic complications, with most deaths occurring in those with bowel ischemia. Physicians should be aware that despite thromboprophylaxis, severe thrombotic complications can still occur in this patient population, however, surgical intervention results in relatively low mortality apart from cases of ischemic bowel resection.

Research objectives

Main, overarching objective was to conduct a systematic review to find the currently published medical literature describing surgical interventions necessitated by COVID-19 thrombotic complications. We achieved this objective and identified intestinal ischemia and ALI as the most common thrombotic events necessitating surgical intervention.

Research methods

The current systematic review implemented an algorithmic approach to review all the currently available English medical literature on surgical interventions necessitated by COVID-19 thrombotic complications using the preferred reporting items for systematic reviews and meta-analysis principles. A comprehensive search of the medical literature in the “PubMed”, “Scopus”, “Google Scholar” top 100 results, and archives of *Plastic and Reconstructive Surgery* was performed by two authors (Reynolds A and Edoigiawerie S) on January 4, 2022, using the key words “COVID-19” AND “surgery” AND “thromboembolism” AND “complication” as well as associated terms. The search string was generated and the records which were not specific about surgical interventions or thrombotic complications due to COVID-19 infection were excluded. Foreign language articles were not eligible for inclusion. Articles published prior to 2019 were excluded as being prior to the COVID-19 pandemic and therefore not relevant to complications associated with COVID-19 infection. Titles and abstracts were screened by two authors (Reynolds A and Edoigiawerie S) after which full-text articles were assessed for eligibility and inclusion. On initial and secondary search, papers in review, commentary, or letter format or those without accessible full-text articles were excluded. Finally, results were further refined to focus on articles that featured surgical interventions that were necessitated by COVID-19 thrombotic complications. For completion of the search, the references of the selected publications were additionally screened with the previously mentioned inclusion criteria.

Research results

The database search resulted in the final inclusion of 22 retrospective studies, after application of the inclusion/exclusion criteria. Of the included studies, 17 were single case reports, 3 were case series and 2 were cross sectional cohort studies. All studies were retrospective in nature. Twelve of the reported studies were conducted in the United States of America, with the remaining studies originating from Italy, Turkey, Pakistan, France, Serbia, and Germany. All cases reported in our study were laboratory confirmed severe acute respiratory syndrome coronavirus 2 positive. A total of 70 cases

involving surgical intervention were isolated from the 22 studies included in this review.

Research conclusions

Physicians should be aware that despite thromboprophylaxis, severe thrombotic complications can still occur in this patient population, however, surgical intervention results in relatively low mortality apart from cases of ischemic bowel resection.

Research perspectives

Future directions could focus on how to prevent thrombotic complications and mitigate mortality among patients at risk for ALI and bowel ischemia in particular.

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