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#### **ABOUT COVER**

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SYSTEMATIC REVIEWS

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

Jennifer J Ferraro, Allie Reynolds, Sylvia Edoigiawerie, Michelle Y Seu, Sydney R Horen, Amir Aminzada, Alireza Hamidian Jahromi

Jennifer J Ferraro, Michelle Y Seu, Sydney R Horen, Amir Aminzada, Division of Plastic and Specialty type: Medical laboratory Reconstructive Surgery, Department of Surgery, Rush University Medical Center, Chicago, IL technology 60612, United States Provenance and peer review: Allie Reynolds, Sylvia Edoigiawerie, Medical School, University of Chicago, Chicago, IL 60637, Invited article; Externally peer United States reviewed. Alireza Hamidian Jahromi, Department of Surgery, Temple University Hospital, Philadelphia, Peer-review model: Single blind PA 19140, United States Peer-review report's scientific Corresponding author: Alireza Hamidian Jahromi, MD, Assistant Professor, Doctor, quality classification Department of Surgery, Temple University Hospital, 3401 N. Broad Street, Parkinson Pavilion, Grade A (Excellent): 0 Suite 400, Philadelphia, PA 19140, United States. alirezahamidian@yahoo.com Grade B (Very good): B Grade C (Good): C, C Grade D (Fair): 0 Abstract Grade E (Poor): 0 BACKGROUND P-Reviewer: Al-Ani RM, Iraq; Du Several unique clinical features of severe acute respiratory syndrome coronavirus BB, China 2 (SARS-CoV-2), the cause of coronavirus disease 2019 (COVID-19) infection, have

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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 metaanalysis 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 using the key words "COVID-19" AND "surgery" AND "thromboembolism" AND "complication". 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. Titles and abstracts were screened by two authors and full-text articles were assessed for eligibility and inclusion. Finally, results were further refined to focus on articles that focused on surgical interventions that were necessitated by COVID-19 thrombotic complications.

#### **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

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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 considerable elevation in Ddimer and fibrin split products, with little to no associated change in activated partial thromboplastin time and prothrombin time<sup>[2]</sup>.



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. 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).

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Table 1 Synopsis of reviewed st	udies on coronavirus disease 2019 thromb	boembolisms necessitating surgical intervention
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Ref.	Location	Study design	No. of patients	Age (yr)	Sex: Males, females (%)	Comorbidities	Thromboprophylaxis	Thromboembolic complication(s)	Surgical intervention(s)	Outcome
Adekiigbe <i>et al</i> [43], 2020	NY, United States	Case report	1	47	Male	DM	Yes	Cutaneous vasculitic lesions and gangrene of all toes, bilateral DVT	Bilateral transmetatarsal amputations of all 10 toes	Discharged home
Ali Nasir <i>et al</i> [20], 2021	Pakistan	Case report	1	64	Male	T2DM, HTN	No	Acute LLI	Above knee amputation	Discharged home
Balanescu <i>et</i> al[33], 2021	MI, United States	Case series	4	20-77 (median 52)	Male (50)	Obesity (50%)	Unknown	PE	Mechanical thrombectomy (100%)	Discharged home (100%)
Bilge <i>et al</i> [21], 2021	Turkey	Case report	1	73	Male	HTN	No	Upper extremity arterial thromboembolism	Left upper extremity arteriotomy and arterial thrombectomy. Repeat thrombectomy 12 h later. Amputation at the level of the forearm 13 d later. Stump revision with amputation 22 d later	Discharged home
Bozzani <i>et al</i> [ <mark>22</mark> ], 2020	Italy	Case series	6	71 (49- 83)	4 males (66)	3 PAD, other unknown	Unknown	Acute LLI	Urgent revascularization procedures (embolectomy in 3 cases, and hybrid open/endo procedures in other 3)	1 rethrombosed day 5, died 30 d later of MOF. 1 rethrombosed day 5, repeat embolectomy, above knee amputation. 4 discharged home. 23 discharged home in good condition
Cheung <i>et al</i> [55], 2020	NY, United States	Case report	1	55	Male	HTN	No	SMA thrombosis, bowel ischemia	Emergency exploratory laparotomy and SMA thrombectomy, necrotic small bowel resection	Discharged home
Dao et al <mark>[56]</mark> , 2021	CA, United States	Case report	1	61	Male	HTN	Yes	Free floating descending aortic thrombus	Percutaneous vacuum assisted aortic thrombectomy	Discharged home
Dinoto <i>et al</i> [23], 2021	Italy	Case report	1	78	Male	DM, obesity, prior remote endovascular surgery for large popliteal aneurysm	No	Acute LLI. Thrombosis of left femoral-popliteal stent	Mechanical thrombectomy	Discharged home
Galastri <i>et al</i> [ <mark>34</mark> ], 2020	Brazil	Case report	1	57	Male	DM, obesity, HTN	Yes	Massive PE	Catheter directed thrombolysis	Discharged home
Gutierrez <i>et al</i> [39], 2022	NY, United States	Case report	1	53	Male	HTN, remote smoking, DM	Yes	Due to phlegmasia cerulean dolens	Fasciotomy and mechanical thrombectomy	Discharged PAD 70
Hwabejire et	MA,	Case series	20	$58 \pm 7$	13 males	Obesity (60%)	85% (17) received	Acute bowel ischemia	Laparotomy with resection of bowel	50% overall mortality rate: (1)

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al <mark>[19</mark> ], 2021	United States				(65)		preoperative anticoagu- lation			100% mortality in patients $\ge 65$ yr; (2) 33% mortality < 65 yr; and (3) 40% (8) developed
Jamshidi <i>et al</i> [ <mark>40]</mark> , 2021	CA, United States	Case report	1	51	Male	Tricuspid atresia status post Fontan and extrac- ardiac Shunt	Yes	Bilateral lower extremity DVT, phlegmasia cerulea dolens of the left lower extremity	Catheter directed mechanical thrombectomy (PAD 13), left below knee amputation (PAD 41)	Discharged to rehabilitation facility PAD 50
Khanna <i>et al</i> [ <mark>32]</mark> , 2021	PA, United States	Case report	1	67	Female	HTN	No	Acute stroke from bilateral anterior circulation large vessel occlusion	Bilateral simultaneous mechanical thrombectomy	Full neurologic recovery
Nascimbene <i>et al</i> [35], 2021	TX, United States	Case report	1	44	Male	Patent foramen ovale, T2DM, HTN, dyslip- idemia, obesity	No	Massive PE with a large right atrial thrombus	Percutaneous right and left atrium embolectomy	Discharged home
Naudin <i>et al</i> [ <mark>24</mark> ], 2021	France	Case report	1	56	Male	T2DM, HTN, obesity	No	Acute aortoiliac thrombus and LLI	Aortoiliac and lower limb artery mechanical thrombectomy and left lower limb fasciotomies, subsequent left below knee amputation	Extubated but still in ICU 6 wk post operatively
Szeles <i>et al</i> [ <mark>25</mark> ], 2021	NY, United States	Case report	1	67	Male	DM, hyperlipidemia, HTN	No	Acute LLI and aortic mural thrombosis	Emergency bilateral aortoliliac and distal embelectomies, followed by transmetatarsal amputation of the right foot and below knee amputation of the left limb	
Topcu <i>et al</i> [ <mark>26</mark> ], 2021	Turkey	Single center cross sectional study	3	62 (58- 70)	3 (100)	1 ex-smoker	Yes (100%)	Acute LLI	3 emergency surgical thrombectomy	1 minor amputation (33.3%); 1 death (33.3%); 1 bilateral major amputation (33.3%)
Traina <i>et al</i> [ <mark>18</mark> ], 2021	Italy	Case report	1	80	Male	CVD, prior endovascular aortic repair in 2019 for abdominal aneurysm repair, and dyslipidemia	No	Bowel ischemia with aorto-enteric fistula formation	Laparotomy with resection of necrotic small bowel (occult COVID- 19, diagnosed on histologic examination of resected small bowel)	Discharged home
Vyas <i>et al</i> [ <mark>36</mark> ], 2020	NY, United States	Case report	1	32	Male	None	No	Large saddle pulmonary embolus	Bilateral percutaneous pulmonary artery mechanical thrombectomy	Discharged home 3 d post procedure
Yang <i>et al</i> [ <b>17</b> ], 2021	Germany	Cohort study	20	69 (62- 72)	15 males (75)	65% (13) obese	25% (5)	Colonic ischemia	12 (60%) underwent (sub)total colectomy, 7 (35%) right hemicolectomy, 1 (5%) ileocecal resection	9 (45%) surgical complications, 10 (50%) required revision surgery, 9 (45%) mortality
Zivkovic <i>et al</i> [57], 2021	Serbia	Case report	1	44	Female	None	No	Ascending aorta floating thrombus with acute right arm ischemia	Surgical thrombus extraction through open sternotomy and bypass surgery	Discharged POD 6

Madani <i>et al</i> [27], 2021	CA, United States	Cases report	1	40	Male	HTN, T2DM	Yes	Acute LLI	Right lower extremity above knee amputation	Discharged 41 d after admission
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DM: Diabetes mellitus; DVT: Deep venous thrombosis; HTN: Hypertension; LLI: Lower limb ischemia; PE: Pulmonary emboli; MOF: Multi organ failure; SMA: Superior mesenteric artery; PAD: Peripheral artery disease; ICU: Intensive care unit; CVD: Cardiovascular disease; COVID-19: Coronavirus disease 2019; POD: Post op day.

#### 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 thrombosis.

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) hospit-alized patients and ICU patients with COVID-19 (1.3% and 6.2%, respectively)[37,38]. Interestingly, our study included two cases of phlegmasia cerulean 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

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Figure 1 Search strategy for our systematic review to find the currently published medical literature describing surgical interventions necessitated by coronavirus disease 2019 thrombotic complications. COVID-19: Coronavirus disease 2019.

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 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

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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 molecularweight 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 onethird 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 metaanalysis 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



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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 was performed using an algorithmic approach to review all the currently available articles in the 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 literature search 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 relevant were excluded. 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, abstracts, and 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 reviewed and 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.

#### FOOTNOTES

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