Original Research Article

Effect of COVID-19 Infection to Incidence of Thromboembolic Phenomenon in Hip and Knee Fracture or Arthroplasty Surgery Patients: A Systematic Review

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ABSTRACT

Introduction: COVID-19 is now recognized as an inflammatory disease with an increase in pro-coagulation factors. Orthopaedic procedures are also associated with high incidence of thromboembolism. This systematic review aims to give some perspective and consideration for orthopaedic surgeon when facing orthopaedic surgery patient with COVID-19.

Methods: A systematic literature search was done in PubMed, Cochrane central database, MedRvix, and PubMed Central up until 10th November 2020 using the following keywords: (COVID-19 OR SARS-CoV-2) AND (hip fracture OR femoral fracture OR TKA OR THA).

Results: Combination of soft tissue trauma, limited mobility, and pro-coagulation state of COVID-19 can overwhelm patient's biologic reserve and causing endothelial dysfunction, which creates fibrin deposition and thrombus. These findings reflected in D-dimer and C-reactive protein increase in COVID-19 patients. This group of patients usually experienced delay from injury to hospital admission and delay from admission to surgery time. Any delay can increase thromboembolic incidence due to limited mobilization. To reduce thromboembolism in this group of patients, some hospitals have implemented modification of the clinical pathway for trauma patients, perioperative thrombosis prophylaxis, and avoid surgical treatment with high risk of thromboembolism.

Conclusion: From limited data, it appears that COVID-19 infection may increase thromboembolic incidence in orthopaedic surgery patients. In facing orthopaedic surgery patients with COVID-19 infection, the risk/benefit and the chance of thromboembolic phenomenon should be evaluated carefully for perioperative treatment.

Keywords: COVID-19, SARS-CoV-2, Thromboembolism, Orthopaedic surgery, Complication
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INTRODUCTION

COVID-19 is an infectious disease by SARS-CoV-2 virus. COVID-19 has a wide range of clinical manifestations from mostly asymptomatic or mild to rapidly progressive and life-threatening conditions.[1] In severe cases of COVID-19, Cytokine release syndrome developed, which predisposed patients to thromboembolic disease.[2] Cytokine release will affect endothelial tissue and active platelet aggregation, creating a pro-coagulation state.[3] Pro-coagulation state of COVID-19 infection also mirrored in elevated D-dimer level of patients with SARS-CoV-2 Virus infection.[4]

A similar condition of pro-coagulation also occurs in traumatic patients and surgery patients, especially orthopaedic patients. Several factors contribute to this increase in pro-coagulation. Use of tourniquet, immobilization, and bed rest will cause venous blood stasis, and according to Virchow's triad will increase thrombi formation.[5] Surgical manipulation of the extremity will damage the vascular endothelial lining, trauma will increase thromboplastin agents.[6] Moreover, use of bone cement of polymethylmethacrylate (PMNA) also induces hypercoagulability.[6] From the available data, orthopedic cases such as trauma, fracture, and arthroplasty are found to be associated with higher thromboembolism events compared to medical cases.[6] Incidence of deep vein thrombosis (DVT) ranges from 40-60% in major orthopaedic surgery.[7]

Thromboembolism phenomenon complication can increase morbidity and mortality in orthopaedic surgery patients.[8] Patient with thromboembolism shows a high level of mortality with 6% of DVT patients and 12% of pulmonary embolism patients died in one month after diagnosis.[9] From an economic burden standpoint, the cost of venous thromboembolism (VTE) is substantial. Additionally, a complication from VTE such as post-thrombotic syndrome and heparin-induced thrombocytopenia also increase the cost.[10]

There were cases of COVID-19 patients who need orthopedic surgery.[11,12] The researchers hypothesize that a combination of COVID-19 infection and orthopedic surgery will increase the incidence of the thromboembolism phenomenon. There are still limited studies that try to look for the effects of both COVID-19 and orthopaedic surgery associated with thromboembolism events. Because of this reason, this systematic review aims to explore the effect of both COVID-19 infection and hip and knee fracture or arthroplasty in the incidence of thromboembolism events, the underlying reasons, and the method of thromboembolism events prevention in this group of patients. PRISMA 2020 guidelines were used to structure this systematic review.[13]

METHODS

In this systematic review, PRISMA guidelines were used to structure the research.[13]

2.1 Eligibility Criteria

In this research, we aim to find out if COVID-19 infection will affect thromboembolism phenomenon in hip or knee fracture or arthroplasty surgery compared to hip or knee fracture or arthroplasty surgery in patients without COVID-19. We included a research article that stated the diagnosis status of COVID-19 and the type of thromboembolism phenomenon in the lower extremity orthopaedic surgery procedure. We did not include abstracts only publications, review articles, commentaries, grey articles, and letters. Positive COVID 19 was defined as a positive oropharyngeal or nasopharyngeal swab test with real-time reverse transcription-polymerase chain reaction (RT-PCR) for SARS-CoV-2 before, during, or after hospitalization. The type of thromboembolism phenomenon that we were looking for was venous thromboembolism (VTE) and pulmonary thromboembolism (PTE) that happened perioperatively. Researcher excluded articles which do not use RT-PCR for COVID-19 diagnosis.

2.2 Search Strategy and Study Selection

We performed a systematic literature search in PubMed, Cochrane central database, MedRvix, and PubMed Central (PMC) up until 10th November 2020 using the following keyword: (COVID-19 OR SARS-CoV-2) AND (hip fracture OR femoral fracture OR TKA OR THA). We searched for research papers only in English language as the authors capability. Orthopaedic cases mentioned in the keyword represent the majority of thromboembolism event causes.[9] We excluded thromboembolism events associated with bone cancer to focus our result on trauma cases, as cancer has a different pathophysiology pathway to induce thrombosis compared to trauma.[14] After the removal of the duplicate article, two authors independently screened the titles and abstracts of the remaining articles based on the inclusion and exclusion criteria. Selected

articles will be checked for an additional research article, which is included in the relevant article, that might be missed from the literature search. There was no article focusing on single-blinded or double blinded process because some of this journal related to case report and systematic review.

2.3 Data Collection Process

After removal of duplicate article and checking for relevance to inclusion and exclusion criteria, 2 authors checked for any bias of the article and then decided whether the article would be included in the research. Disagreement between the authors was solved by consensus or by a third person. From all the included articles we listed the title, authors, year of publication, study design, number of subjects, age, sex, hypertension, diabetes mellitus, cardiovascular diseases, location of the fracture, percentage of thromboembolic events, COVID-19 status, and mortality. Unavailable data from selected articles would be marked with an X in Table 3. Articles that passed the inclusion and exclusion criteria but had some missing data were still included in the study to have a thorough discussion about the aim of the study.

RESULTS

The search result, which simplified into *Figure.1*, yielded a total of 677 articles, of which 537 articles came from PMC, 73 from PubMed, 33 from MedRvix, and 34 from the Cochrane central database. After screening duplicates and excluding irrelevant articles based on the title, 42 articles were examined for full-text availability and data associated with the aim of the study. After a full-text assessment, 13 articles were included for analysis.

3.1 Characteristics of Studies

The 13 articles included in the study consisting of 3 case series, 1 case report, 4 systematic reviews, 4 cohort studies, and 1 observational study. From the search for additional articles related to the aim of the study, we did not find any additional research articles. Each primary study was then grouped into positive and negative COVID-19. The suspect group was a group of patients with the clinical characteristic of COVID-19 but no data of RT-PCR.[14] Data of patients' characteristics were noted and elaborated in table 1. Data of patient's comorbidity, location of surgery, thromboembolism incidence, and mortality were included in table 3.

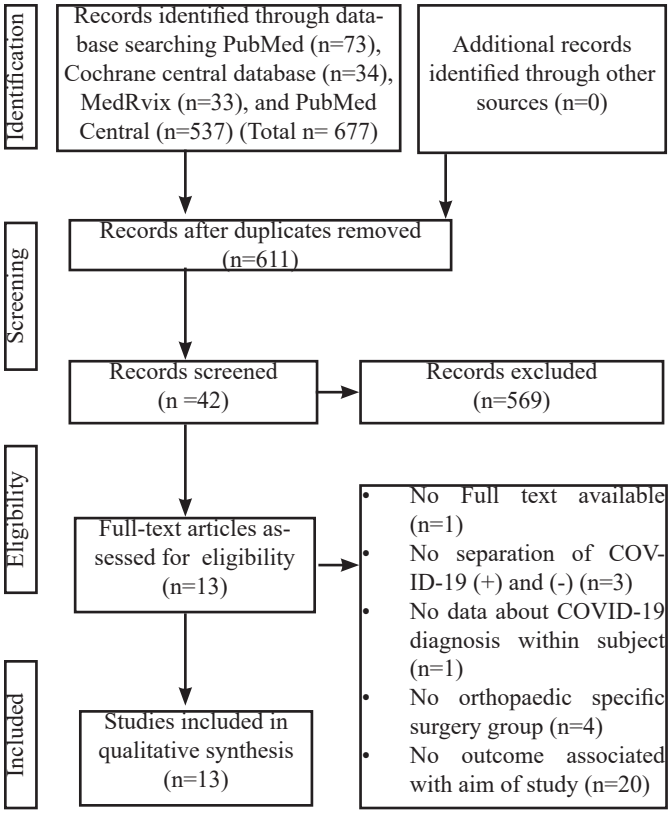

Figure 1. PRISMA diagram.

3.2 Risk of Bias Analysis

Analysis of individual research article was done according to the study design. The National Institute of Health (NIH) quality assessment tool was used for risk of bias analysis of case reports and case series studies.[15] The results of the case series risk of bias analysis are shown in Table 2. The Risk of Bias in Non-randomized Studies (ROBINS-I) was used for Cohort study.[16] The results of cohort study bias analysis are shown in Fig. 2.

3.3 Thromboembolism Incidence in COVID-19 and Orthopaedic Surgery Patients

There are limited cohort studies that mentioned the thromboembolism incidence in COVID-19 and Orthopaedic surgery patients. A retrospective multicenter cohort study documented 82 cases of hip and femur Fracture with COVID-19, which found 11 (13.4%) cases of thromboembolism postoperatively.[11] In this study, the use of thromboembolic prophylaxis and patients' comorbidity was not mentioned. Another prospective cohort study by Egol *et al*. found 2 VTE incidence out of 17 patients (11.8%) in hip and femur fracture and COVID-19 posi-

Table 1. List of Studies Included in the Review

Title	Authors	Publication Year	Study Design	Subject Number	COVID-19 Infection	Age	Sex	
							male (%)	female (%)
Early outcomes after hip fracture surgery in COVID-19 patients in New York City	Cheung et al.	2020	retrospective cohort study	10	+	67-90	2 (20)	8 (80)
Increased Mortality and Major Complications in Hip Fracture Care During the COVID-19 Pandemic: A New York City Perspective	Egol et al.	2020	prospective cohort study	17	+	82.4 +- 9.6	12 (70.6)	5 (29.4)
				12	Suspect	80.6 +- 9.9	2 (28.6)	10 (71.4)
				107	-	83.4 +- 10.4	34 (31.8)	73 (68.2)
Characteristics and early prognosis of covid-19 infection in fracture patients	Mi et al.	2020	case series	10	+	34-87	2 (20)	8 (80)
COVID-19: not a contraindication for surgery in patients with proximal femur fragility fractures.	Morelli et al.	2020	case series	10	+	72-98	2 (20)	8 (80)
Delayed surgery versus nonoperative treatment for hip fractures in post-COVID-19 arena: a retrospective study of 145 patients.	Mi et al.	2020	retrospective observational study	108	-	65-79	38 (35.1)	70 (64.8)
Fractures in Patients With COVID-19 Infection: Early Prognosis and Management. A Case Series of 20 Patients in a Single Institution in Lombardy, Northern Italy.	Jannelli et al.	2020	case series	20	+	82.06 (59-95)	4 (20)	16 (80)
Hip Fracture Outcomes During the COVID-19 Pandemic: Early Results From New York.	LeBrun et al.	2020	Multicenter retrospective cohort study	50	-	84.7	12 (24)	38 (76)
				9	+	86.5	3 (33.3)	6 (66.6)
The effects of COVID-19 on perioperative morbidity and mortality in patients with hip fractures.	Kayani et al.	2020	retrospective multicenter cohort study	82	+	71.9	31 (33.7)	51 (62.1)
Timing and Tips for Total Hip Arthroplasty in a Critically Ill Patient With Coronavirus Disease 2019 and a Femoral Neck Fracture.	Kaidi et al.	2020	case report	1	+	67	1 (100)	0 (0)
Coronavirus disease 2019 (COVID-19) markedly increased mortality in patients with hip fracture - A systematic review and meta-analysis.	Lim et al.	2020	systematic review					
COVID-19. An update for orthopedic surgeons	Abdelnasser et al.	2020	systematic review					
Fracture management during COVID-19 pandemic: A systematic review.	Kumar et al.	2020	systematic review					
Inflammatory and Coagulative Considerations for the Management of Orthopaedic Trauma Patients With COVID-19: A Review of the Current Evidence and Our Surgical Experience.	Puzzitiello et al.	2020	systematic review					

(+): Positive RT-PCR of SARS-CoV-2, (-): Negative RT-PCR of SARS-CoV-2, (-): Data not available

Table 2. Case Report & Case Series Risk of Bias Analysis

Major Components	Mi et al. 2020	Morelli et al. 2020	Jannelli et al. 2020	Kaidi et al. 2020
1. Was the study question or objective clearly stated?	Yes	Yes	Yes	Yes
2. Was the study population clearly and fully described, including a case definition?	Yes	Yes	Yes	Yes
3. Were the cases consecutive?	Cannot Determine	No	Yes	Not Applicable
4. Were the subjects comparable?	Yes	No	No	Not Applicable
5. Was the intervention clearly described?	Yes	Yes	Yes	Yes
6. Were the outcome measures clearly defined, valid, reliable, and implemented consistently across all study participants?	Yes	Yes	Yes	Yes
7. Was the length of follow-up adequate?	Yes	Yes	Yes	Yes
8. Were the statistical methods well-described?	Yes	No	Yes	Not Applicable
9. Were the results well-described?	Yes	No	Yes	No
Quality Rating	**Good**	**Fair**	**Good**	**Fair**

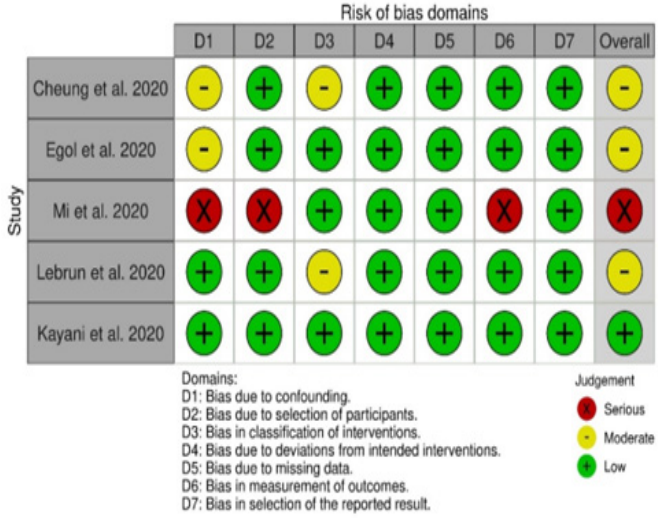

Figure 2. ROBINS-I Analysis for Cohort Studies

tive group. In the same study, VTE incidence was found in 3/107 (2.8%) of the COVID-19 negative group.[12] In this study, all patients with hip fractures received prophylactic level of low-molecular-weight heparin during admission until 1-month post-injury.[12] If compared to pre-pandemic era, the incidence of thromboembolic events were 2.8% in Total Knee Arthroplasty (TKA) from 2.1% pre-pandemic event, 1.9% in Total Hip Arthroplasty (THA) from 0.3% pre-pandemic event, 1.1%[17,18] in hip fracture surgery from 0.45% pre-pandemic event and 0.64% in simple fracture of lower extremities from 0.1% pre-pandemic event.[19] In this study, patients were given anticoagulant or antiplatelet agents and/or mechanical prophylaxis.[17] In another study, VTE incidence was 1.17% in the minor trauma group (ISS≤15) and 6.8% in the major trauma group (ISS>15).[20]

From the literature, most of the studies excluded patients less than 18 years of age at the time of injury, open fracture, periprosthetic fracture, and revision fracture surgery.[11] We only found one article that compares thromboembolism incidence in fracture patients with COVID-19 positive or negative. Comparing the results of the different articles cannot be performed because different articles have different inclusion and exclusion criteria and different data collection methods.

DISCUSSION

4.1 Pro-thromboembolism Factor in COVID-19 and Surgery Patients

4.1.1 Pathology of COVID-19 and Surgery Patients

In the two-hit concept introduced by Moore and Moore to explain the pathway for post-traumatic complication development, "first hit" is the physiological response to injury, and the second hit is the subsequent intervention or any ongoing physiologic disturbance.[21] From this principle, a damage control orthopedic in polytrauma patient is used to minimize the second hit and decrease any complication incidence.[22] COVID-19 infection can be a part of the "first hit" or elevate the "first hit" effect from trauma inpatient with orthopaedic surgery.[4] This effect be more prominent in patients with severe inflammatory responses associated with COVID-19.[4] COVID-19 infection in itself increases thromboembolic disease through direct and indirect effects.[3] Reports find elevation of Interleukin 2 (IL-2), IL-6, and tumor necrosis factor (TNF)-α in COVID-19 patients, which indicates an increased inflammatory response.[23] Diffuse alveolar damage and endothelial dysfunction can then occur.[24] Endothelial cells dysregulation and platelets & leukocytes activation result in excessive thrombin generation and inhibition of fibrinolysis. Causing fibrin deposition

and predisposing the patient to microangiopathy and microthrombi.[24,25]

The most common observed hemostatic abnormality inpatient with COVID-19 infection is elevated D-dimer level (>1µg/mL).[4,26] C-reactive protein (CRP) was found elevated in 90% of patients but prothrombin times are normal in 70% of patients.[4] In a case series of 10 patients with COVID-19 and hip fracture, it was found uniformly elevated D-dimer, ferritin, and Lactate dehydrogenase (LDH) but normal PT/INR and PTT.[4] One patient with DVT had markedly elevated CRP (194.1 mg/L) and elevated D-dimer, ferritin, and LDH (5.85 ug/mL, 223mg/mL, and 284 U/L, respectively).[4] Another case series by Mi *et al*. demonstrated 10 cases of COVID-19 positive patients with fracture had similar results, with 9 patients had high serum levels of D-dimer and CRP. High D-dimer is postulated to be caused by limited activity which all patients in the case series are in.[4] Another laboratory result that characterized fracture patients with COVID-19 positive are higher neutrophil count.[4]

Even with an asymptomatic patient, COVID-19 infection may amplify the initial inflammatory response to trauma.[27] A descriptive study by Cheung *et al*. reported 10 COVID-19 patients who underwent hip fracture surgery. The all ten patients were asymptomatic on admission and also presented similar laboratory results of elevated D-dimer, ferritin, and LDH on admission.[28] One patient had VTE in addition to respiratory failure and died postoperative at day 19.[28] High level of suspicion of COVID-19 status should be implemented as 4-18% of patients with positive swab assay for SARS-CoV-2 can be asymptomatic.[11,29]Additionally, COVID-19 has an incubation period of ten to 14 days, which in this period, patients are asymptomatic but highly contagious.[29]

4.1.2 VTE in Orthopaedic Trauma and Surgery

The Incidence of thrombosis caused by cast and immobilization is around 17%.[11] Injuries to the pelvis also increase the risk of thrombus. Pathophysiology of thrombus occurrence is caused by the Virchow factor consisting of venous stasis, endothelial injury, and hypercoagulability.[5] Immobilization of lower extremity, especially at the ankle, will decrease muscle pump function and increase venous stasis. Trauma and injury factors to the endothelial tissues are believed to support the occurrence of thrombus in the event of trauma and orthopedic surgical procedures. Recent studies support findings in the form of procoagulant particles and thrombogenic particles as well as a decrease in antithrombin III levels that support clotting.[30] Damaged tissue induces a local and systemic inflammatory response similar to COVID-19 infection, which elevates IL-6 and TNF-α.[27] This combination of soft tissue trauma and pro-coagulation state of COVID-19 that Puzzitiello *et al*. referred to as reaching a "tipping point", where patient's biologic reserve overwhelmed, causing alveolar damage, microvascular injury, interstitial edema, hemodynamic lability, and end-organ failure.[27,31] Damaged endothelium increases thrombus formation. This is supported by the incidence of pulmonary embolus in asymptomatic COVID-19 with relatively low intraoperative embolus burden.[27] Coagulation abnormalities also can be seen by increased D-dimer level, decrease prothrombin time, and international normalized ratio. [27]

4.1.3 Delayed Operation / Prolong Immobilization

One case series study of 43 orthopaedic surgery patients during the COVID pandemic explained a delay from admission to surgery time during the COVID-19 pandemic because of pre-operative screening of COVID-19, which is 2 days of COVID-19 RNA and antibody detection assays.[32] Average waiting time from admission to surgery was 5.3 ± 2.8 days, which is 2 days longer than the pre-COVID era.[32] Additional info from these patients, before arriving at the emergency room, they stayed at home for more than 10 days without anticoagulants. Although there is still not enough information to predict the incidence of thromboembolism in COVID-19 and surgery without prophylaxis, in patients who underwent hip surgery without prophylaxis before the COVID-19 pandemic, thromboembolism incidence was found at 40-60%.[7]

In the same study, they found delayed time from injury to hospital admission by 2.1 days. Delayed seek for hospital help maybe because most trauma patients are afraid to go outside because of local government advice to stay indoors during the pandemic.[32] Patients with trauma to lower extremity would likely be bed-bound or have limited mobility causing an increased chance of thromboembolism.[33]

Patients with severe infection with COVID-19 are also usually evaluated by orthopaedic surgeons to be unfit for surgery[4]. Although this decision would reduce the amount of soft tissue injury from the operation, it would increase immobilization time (> 7 days) and in turn,

could increase thromboembolic incidence.[34] A guide from WHO also recommends treating orthopedic trauma patients with COVID-19 who need surgery immediately because it reduces the risk of thromboembolism due to immobilization.[35]

Thromboembolism also can happen after the orthopaedic operation.[36] In One study, asymptomatic COVID-19 patients undergoing surgery were reported to have significant higher admission to the Intensive Care Unit (ICU) than non-surgical COVID-19 patients (44.1% vs 26.1%).[37] A collection of case studies stated that the presence of co-morbid COVID-19 is the biggest cause of thrombosis. This is due to the hypercoagulation process being exacerbated by the ICU care, which causes patients to be immobilized, subsequently increasing the risk or causing high incidence of venous thrombosis.[38]

As the review stated that the number one contributor of the thromboembolism event is the orthopaedic surgery itself, the COVID-19 disease is the co-factor that worsens the event by increasing the coagulability of the blood.

4.2 Methods to Decrease Thromboembolism Events

4.2.1 Modification of the Clinical Pathway

Since the COVID-19 outbreak, hospitals around the world designed a modification of the clinical pathway for trauma patients.[32] All patients with orthopaedic trauma should be tested for COVID-19.[19,27] Reason for this recommendation is that patients with COVID-19 infection can appear asymptomatic, as Zoe *et al*. found. Baseline inflammatory markers (IL-6, D-dimer, and CRP) can be used to predict disease progression.[27] Screening in patients with COVID-19 who have high risk of thromboembolism can be seen from D-Dimer, fibrinogen, and factor VIII levels.[35] In patients with positive COVID-19 and high-risk fracture, consider doing lower extremity duplex ultrasound to check for pre-existing thrombosis.[27] Vena cava filter is one method that is used as an alternative when anticoagulants are not available or contraindicated in the patients, but it is not recommended for first-line treatment.[39] Concern arising from emergent cases that need operation <24 hours. In these cases, COVID-19 screening with RT-PCR cannot be done. The solution is to treat all trauma and orthopaedic surgery emergent operations as positive COVID-19 until proved otherwise.[40]

4.2.2 Perioperative Thromboembolism Events Prophylaxis

As COVID-19 is associated with increased D-dimer level, experts from the American College of Cardiology support the use of empiric anticoagulation on therapeutic dose for inpatient with COVID-19 infection with highly elevated D-dimer level.[3] Based on the pre-COVID era, American College of Chest Physicians (ACCP) guidelines encourage using anticoagulation therapy for at least 10 to 14 days and up to 35 days in orthopaedic surgery patients to prevent thrombosis.[41] This recommendation was proven to be effective to reduce the incidence of the thromboembolic phenomenon in Egol *et al*. prospective cohort study that includes 138 patients with orthopaedic trauma. They found no difference in the rate of venous thromboembolism in COVID-19 positive with negative control (2 [11.8%] vs 3 [2.8%], p = 0.138). This is due to all patients with hip fracture getting chemical prophylaxis for at least 1 month after injury.[14] A case series reported that, in mild symptomatic COVID-19 cases, the use of the anti-thromboembolic drug in fracture patients may reduce thrombosis incidence although the patients had high D-dimer (>500μL/L) as out of 20 patients, they reported, there was no thromboembolism incidence.[42] This may be due to prophylaxis use on admission or immediate admission to operation time (1-4 days, only 1 case that delayed until 9 days).[42] Another article published administration of low molecular weight heparin (enoxaparin sodium 4000IU twice daily) before surgery.[43] Benefit of heparin use in trauma patients and COVID-19 also extent to reduce mortality of hospitalized patient with COVID 19 by 20%.[44] This is related to reduced microthrombi formation in pulmonary microcirculation and reducing the incidence of respiratory failure.[44] Use of prophylaxis is also recommended for surgery that is delayed up to 24 hours (MWH and UFH have similar efficacy and safety).[35] In patients who unfit for surgery (*eg*. major trauma), enoxaparin (LMWH) can be given until more appropriate time for surgery. The considerations for this procedure depend on age, comorbidities, immobilization and quality of injury of the patient.[35]

In post-operative time, the patient rehabilitation phase starts as soon as possible with a simple exercise.[45] This avoid complication and also preserve muscle strength and flexibility.[19] The patient also should try to maintain an active lifestyle and rapid mobilization.[46] Prophylaxis use is extended in one case report, which used enoxaparin 40mg per day for 28 days after the patient discharged.[36] Unfortunately, the patient developed non-occlusive thrombi in the right femoral and anterior tibial vein and occlusive thrombus in the right popliteal vein at

2 months postoperatively, which added to consideration of prolonged use of DVT prophylaxis from the standard 1 month in COVID-19 patients.[36]

4.2.3 Alteration of treatment method

Patients experiencing long bone fracture treated with intramedullary fixation are at risk for thromboembolism phenomenon.[47]Consider surgical treatment that avoids canal instrumentation and excessive rearming in intramedullary fixation.[27] Cementless technique in total hip arthroplasty (THA) is preferred over cemented THA in patients with decreased pulmonary function to avoid pulmonary emboli.[36] Cemented THA has been documented to have higher rates of cardiopulmonary complication with 5.7 times higher risk of pulmonary embolism.[48] Complication of emboli can be disastrous because patients with COVID-19 already have decreased cardiopulmonary reserve.[36]

Treatment of fracture non-operatively may lower the inflammation from surgical treatment and can be the choice of treatment in some patients.[49] But the non-operative treatment of the hip fracture is not recommended because of the long immobilization time for traction (8-12 weeks). In a retrospective observational study by Mi *et al*., it was reported that there was an increased incidence of deep venous thrombosis in the non-operative therapy group than the delayed surgery group (12/34 vs 13/99, p=0.004).[50] The highest incidence of thrombosis was in patients treated nonoperatively due to long immobilization. It is, therefore, recommended for operative management, or in delayed operative cases could be given antithrombotic first.[51] The Non-operative treatment of hip fracture is also associated with a higher risk of complications, such as pulmonary infection, pressure ulcers, UTI, which consequently leading to high mortality.[52]

4.2.4 Timing of Surgery

Timing of surgery in hip fracture and other lower extremity fractures has been extensively explored but an additional factor of COVID-19 status can alter the surgeon's decision of surgery timing. The optimal timing of surgery in a patient with COVID-19 still needs to be explored. With varying degrees of COVID-19 infection severity, it is difficult to determine the best time of surgery. The decision of surgery time should be individualized, and every patient should undergo medical optimization before surgery. Caution was reported for patients in the 7-10th day of COVID-19 infection when many patients acutely decompensated.[26] This was observed in non-survivor COVID-19 patients with an upward trend of laboratory results from day 4 to 19 of infection.[26] Similar suggestion was also made by a group of Singaporean orthopaedic surgeons to look at single result of inflammatory markers when planning surgery (TNF-α, IL-1, and IL-10).[53] As worsening systemic inflammation associated with surgery complication[54], upward trend of inflammatory markers can be considered to delay orthopaedic surgery.[55] In a hip fracture patient who is not critically ill, the fracture should be definitively fixed within 24 hours.[56,57]

Up to the moment, there are still no guidelines to choose one method of treatment over another in COVID-19 patients with orthopaedic surgery. Careful consideration for risk/benefit in COVID-19 patients with orthopaedic surgery should be evaluated and treatment should be customized on a patient-to-patient basis.

4.3 Limitation of the study

There is still limited long-term studies on complications in COVID-19 and hip and knee fracture or arthroplasty surgery patients. From studies included in this research, not all studies mentioned the severity of infection or inflammation markers of the subjects. This can bias the conclusion as the severity of infection or inflammation can affect the thromboembolism phenomenon.[28] Not all articles reported the type and the extent of the soft tissue injuries severity, which include in the factors that contribute to the thromboembolic phenomenon. There are also limited RCT studies on thromboembolism prophylaxis in COVID-19 and fracture patients.

4.4. Strength of Study

Our study involved the latest journal related to COVID-19, thromboembolism phenomenon and orthopaedic surgery with the population focus on geriatric population, as the common incidence of thromboembolism and the high prevalence of fracture are usually in the geriatric patients. Further research is needed, focusing on the systematic algorithm of patient selection, and better-quality evidence for perioperative treatment to reduce thromboembolism events and, subsequently, reduce the mortality and morbidity in hip and knee fracture or arthroplasty surgery with COVID-19 infection.

CONCLUSION

It appears that COVID-19 infection may increase thromboembolic incidence in hip and knee fracture or arthroplasty patients. The combination of pro-coagulation condition of COVID-19 and orthopaedic surgery, and delayed trauma to surgery time, may contribute to the increasing thromboembolic incidence. To reduce the thromboembolic incidence, the use of thrombosis prophylaxis perioperatively, avoidance of high-risk procedure and optimizing the patient's condition before surgery may be beneficial. In facing orthopaedic surgery patients with COVID-19 infection, the risk/benefit and the chance of thromboembolic phenomenon should be evaluated carefully for perioperative treatment. Further study needs to search for optimal timing of surgery and perioperative medical intervention in fracture patients with COVID-19 to reduce mortality.

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