


# Venous thromboembolism and major adverse cardiovascular events in patients with hip fractures suffering from SARS-CoV-2 infection: a systematic review

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## Abstract

**Introduction:** Hip fractures represent 1 of the most common injuries in older adults. They are associated with increased perioperative morbidity and mortality. Additionally, current research suggests that SARS-CoV-2 infection may worsen the prognosis of the hip fracture patients who undergo hip fixation. The aims of the present study were: (1) to determine the rate of specific adverse events including VTE (venous thromboembolism) and major adverse cardiovascular events (MACEs) in patients with hip fracture and concomitant SARS-CoV-2 infection undergoing surgery; and (2) to examine if the aforementioned population is at increased risk for VTE and MACEs, when compared to SARS-CoV-2 free patients with hip fracture.

**Methods:** PubMed, EMBASE, Cochrane, Web of Science, Google scholar and medRxiv were searched from March 2020 to January 2021 for English language studies with patients suffering from hip fractures and SARS-CoV-2 -CoV-2. 2 researchers were involved in the data extraction and the quality assessment of the studies respectively.

**Results:** The literature search yielded a total of 1256 articles of which 14 were included in the systematic review and 7 in the meta-analysis respectively. The estimated pooled rate for VTE and MACE were 4.3% and 6.3% respectively. Patients with hip fracture and concomitant SARS-CoV-2 infection who undergo surgery are at increased risk for VTE, when compared to SARS-CoV-2 free patients (odds ratio 2.8 [95% CI, 1.1–7.1]). These patients are also at increased risk for MACE postoperatively as indicated by the odds ratio 2.4 (95% CI, 1.0–5.8). The quality of the studies was moderate.

**Conclusions:** Although there is a lack of high-quality data it seems that patients with hip fractures and concomitant SARS-CoV-2 infection are facing a 2.8 and 2.4 times increased risk for VTE and MACE.

## Keywords

COVID-19, hip fractures, myocardial infraction, SARS-CoV-2, stroke, venous thromboembolism

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## Introduction

Hip fracture is quite prevalent in older adults with a reported incidence up to 15%.<sup>1</sup> Several factors, such as osteoporosis, vitamin D deficiency and systemic comorbidities not only they predispose the elderly to fragility hip fractures, but they also make them more prone to increased perioperative morbidity and mortality.<sup>1</sup> Early surgical management seems mandatory in terms of enhanced recovery and rehabilitation. However, hip fracture patients still represent a challenge for the perioperative team as the

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reported postoperative mortality can reach 10 to 15% at 30 days and 35% at 12 months respectively.<sup>2</sup>

On the other hand, perioperative SARS-CoV-2 infection expose the surgical population to increased risk of morbidity and mortality.<sup>1,3,4</sup> Common complications include venous thromboembolism (VTE) and major adverse cardiovascular events (MACE). Hence, it is suggested that, whenever possible, elective surgery should be delayed for at least 7 weeks following SARS-CoV-2 infection.<sup>4</sup> As the SARS-CoV-2 pandemic is multiplying, there is increasing probability that the 2 entities (COVID-19 and hip fracture) will co-exist in the same patient.<sup>1</sup> Moreover, even in areas with low community SARS-CoV-2 infection rates, the surgical population is at risk of nosocomial SARS-CoV-2 infection due to increased circulation of the virus in the hospital. Thus, higher rates of postoperative complications and deaths are anticipated.<sup>5</sup>

The hip fracture and the SARS-CoV-2 infection are well-recognised major risk factors for a pro-inflammatory over-activation and hyper-coagulability cascade which may lead to devastating outcome in patients suffering from both pathologies. While the increased mortality is well described in the literature,<sup>1</sup> little is known about the complications after hip fractures in patients with co-existing SARS-CoV-2 disease. Hence, the aims of the present study were: (1) to determine the rate of specific thromboembolic-related adverse events, also known as venous thromboembolism (VTE), and the rate of major adverse cardiovascular events (MACE) in patients with hip fracture and concomitant and SARS-CoV-2 infection (primary outcome); and (2) to examine if patients suffering from hip fractures and SARS-CoV-2 infection are at increased risk for VTE and MACEs, when compared to patients without SARS-CoV-2 (secondary outcome).

## Patients and methods

### Study design and registration

The objectives, methodology and inclusion criteria for enrolment were prespecified in a standardised protocol.<sup>6</sup> The manuscript was prepared according to the Standard Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (PRISMA).<sup>7</sup> Additionally, because all studies were observational, the MOOSE guidelines were followed during the preparation of the manuscript.<sup>8</sup> The search strategy, study selection, bias assessment and data extraction were defined *a priori* and the protocol was registered in the PROSPERO register (International Prospective Register of Systematic Reviews) with number CRD42020221789.<sup>9</sup>

### Search strategy

An electronic search of the English-language literature was conducted from March 2020 to May 2021 using the

PubMed/MEDLINE, EMBASE, Cochrane, Web of Science, Google scholar and medRxiv databases. Search terms included (SARS-CoV-2 OR Coronavirus) AND (hip fracture). Related articles suggested by the PubMed search engine and reviews on the subject were searched for additional relevant articles. Comparable search strategies were implemented on EMBASE, Cochrane, Web of Science, Google scholar and medRxiv databases.

### Definitions

Under the term VTE, pulmonary embolism (PE) and deep venous thromboembolism (DVT) were included. In addition, under the term MACE, stroke, acute myocardial infarction (MI), hospitalisation for heart failure and cardiovascular death (CVD) were included.

### Eligibility criteria

We focused on studies involving patients with hip fractures suffering from SARS-CoV-2 infection and reporting on adverse events including VTE and MACE. Our search was limited to adult patients undergoing surgery due to hip fracture, and English language. Studies not reporting the outcomes of interest or including <5 patients were excluded. Other exclusion criteria were review articles, animal studies, studies in non-English language, abstracts from scientific meetings. Studies from preprint repositories were allowed (medRxiv). Studies not reporting the primary outcomes or not involving hip fractures were also eliminated. Manual search in the references of the included studies was also performed to find additional studies. 2 reviewers (AK, MN) performed the literature research according to Cochrane recommendations on 21 May 2021.<sup>6</sup> Independently, the aforementioned reviewers evaluated the eligibility of studies for inclusion in this review, in an unblinded standardised manner. In the case of disagreement, all issues were discussed with the 2 senior review authors (EA and MH). Before starting the statistical analysis, a new search was done to identify any new studies.

### Data extraction

Each study was described by the name of the primary author and year of publication. 2 reviewers (AK, MN) extracted the following data from each study: (1) study design; (2) number of patients in the SARS-CoV-2 group; (3) number of patients in the control group; (4) rate of DVT in the SARS-CoV-2 group; (5) rate of DVT in the control group; (6) rate of PE in the SARS-CoV-2 group; (7) rate of PE in the control group; (8) rate of VTE events (DVT and PE) in the SARS-CoV-2 group; (9) rate of VTE events (DVT and PE) in the control group; (10) rate of nonfatal stroke in the SARS-CoV-2 group; (11) rate of nonfatal stroke in the control group; (12) rate of nonfatal

myocardial infarction in the SARS-CoV-2 group; (13) rate of nonfatal myocardial infarction in the control group; (14) rate of hospitalisation for heart failure in the SARS-CoV-2 group; (15) rate of hospitalisation for heart failure in the control group; (16) rate of cardiovascular death in the SARS-CoV-2 group; (17) rate of cardiovascular death in the control group; (18) rate of MACE events in the SARS-CoV-2 group; and (19) rate of MACE events in the control group respectively. No contact with the authors was made for missing data.

### Quality evaluation

The reporting quality of the gathered observational studies was assessed independently by 2 reviewers (AK and FA) using ROBINS-I (“Risk of Bias in Non-randomised Studies - of Interventions”) tool.<sup>10</sup> In case of any disagreement the issues were resolved by 2 senior review authors (EA and MH). Traffic light and summary plot were created for the included studies. In addition, the NHI/NHLBI quality assessment were also applied. This 9-item tool is specifically designed for case series studies.<sup>11</sup>

### Data synthesis and statistical analysis

Our data were summarised graphically using the VOS-Viewer in a key word strength occurrence network.<sup>12</sup> The available evidences were summarised in a systematic review according to the available evidences. In every case a narrative review was realised. In addition, a quantitative analysis was conducted in the presence of numeric data. The meta-analysis estimates were reported in absolute and relative estimates along with the 95% confidence intervals (CIs). Statistical analysis was performed with the Open Meta-Analyst software.<sup>13</sup> The Der Simonian-Laird method was employed to compute the pooled effect sizes in terms of the expected high level of heterogeneity among studies. Heterogeneity was assessed with the  $I^2$  statistic. Random effects model was used and pooled rates with 95% CI were estimated at first, including all studies. In addition, for case control studies the odds ratio (OR) for the outcomes VTE and MACE were calculated and depicted in forest plots. Statistical significance was set to  $p < 0.05$ .

## Results

### Literature search results

In total 1256 articles were obtained through the database search. The data were represented in a key word strength occurrence network with the use of VOS viewer (Figures 1 and 2). After removing duplicates, a total of 776 were screened for eligibility based on title and abstract. After application of inclusion and exclusion criteria 731 records

were excluded (reviews, not in English, not human, not SARS-CoV-2, not hip fracture) and 45 full-text articles were assessed for eligibility. Full text screening resulted in the exclusion of 32 records (absence of outcomes of interest, less than 5 patients). Additionally, 1 article was found through references list. The final systematic review therefore yielded a total of 14 studies (Figure 3).<sup>14–27</sup>

### Study characteristics

The 14 studies included in the systematic review reported data from 1320 patients in total (345 patients with SARS-CoV-2 infection, 974 in the control group). The total number of patients that were included in the meta-analysis is 774 (140 patients with SARS-CoV-2 infection, 634 in the control group). 5 of the included studies were multicentre, while half of the studies were case series and half of them were case control series enabling direct estimation of the odds ratio of outcomes among patient with and without SARS-CoV-2 infection respectively (Table 1). Follow-up ranged from 1 to 3 months.

### Risk of bias and quality of overall evidence

Overall, there were no randomised controlled studies available to be included in this systematic review, hence the risk of bias was considered to be elevated. Moreover, according to the Cochrane tool for non-randomised studies - of interventions (ROBINS-I) 2 studies suffered from selection bias, 4 from classification bias and 2 from bias due to deviation from indented intervention (Figures 4 and 5). From the 7 case control studies, only 2 were unaffected by all kinds of bias. In summary, 6 studies had serious risk of bias, 1 study had moderate and 7 had low risk. With regard to NHI/NHLBI tool for case series the score of the studies ranged from 3 to 8 out of 9 (Table 2).

### VTE

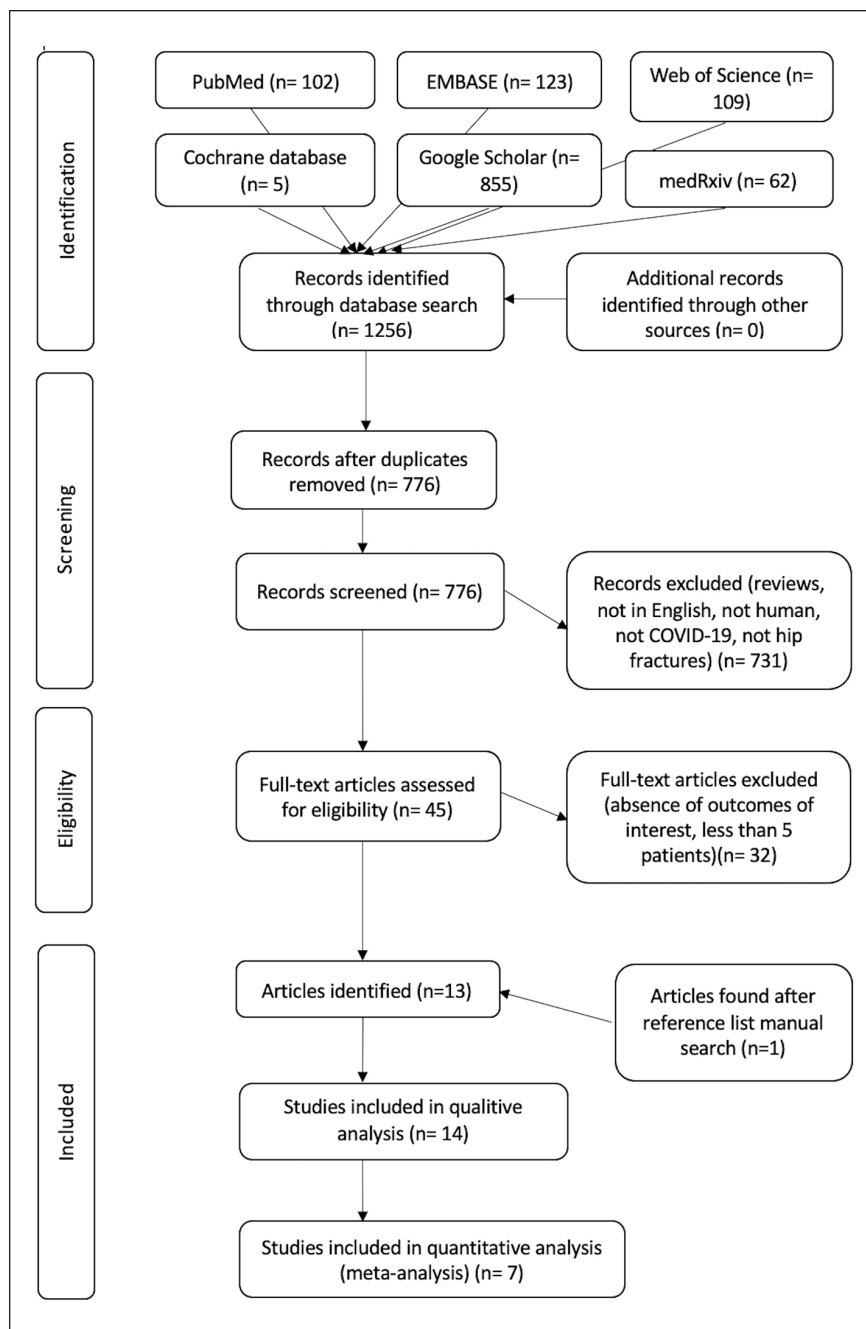
Combining all 14 studies, VTE ranged from 0% to 13.4% in SARS-CoV-2 group with a pooled summary rate of 5.7% (95% CI, 3.2–8.2). In addition, the estimated pool rates of DVT and PE in the same group were 4.3% (95% CI, 1.1–7.5) and 3.7% (95% CI, 0.6–6.7) respectively. In 7 studies, the control group was available, and the calculated odds ratio of suffering a VTE event among patients with and without SARS-CoV-2 was 2.8 (95% CI, 1.1–7.1) ( $p=0.03$ ) (Figure 6).

### MACE

Synthesising data from all 14 studies MACE rate was computed at 6.3% in SARS-CoV-2 group (95% CI, 2.8–9.7). The estimated pool rate for stroke, MI, CVD was approximated at 2.5% (95% CI, 0.2–4.9) for stroke, 2.5% (95% CI, 0.8–4.3) for MI, and for CVD 5.7% (95% CI,







**Figure 3.** Preferred reporting system for systematic reviews and meta-analyses (PRISMA) flowchart showing that a total of 45 relevant records, 14 studies fulfilled our eligibility criteria.

0.4–11) respectively (Figure 7). In the sub-analysis of the case-control studies the estimated odds ratio for MACE was 2.4 among patients with and without SARS-CoV-2 (95% CI, 1.0–5.8) ( $p=0.05$ ).

## Discussion

### Summary of evidences

Based on the results of our study the estimated rate of VTE and MACE in patients undergoing surgery due to hip

fractures, who are suffering from a concomitant SARS-CoV-2 infection is rather high. Moreover, the aforementioned group is at increased risk of VTE and MACE when compared to hip fracture patients without SARS-CoV-2 infection. To the best of our knowledge this is the first systematic review and meta-analysis regarding the impact of SARS-CoV-2 infection in the incidence of VTE and MACE postoperatively in patients undergoing hip fixation. In the present study we found that there is a medium body of mostly low-quality data supporting that patients who undergo surgery due to hip fracture and suffer from

Table 1. Summary of basic characteristics of eligible studies.

First author year	Publication Study design	Number of patients in the COVID-19 Group	Number of patients in the Control Group	Rate of DVT in the COVID-19 Group	Rate of DVT in the Control Group	Rate of PE in the COVID-19 Group	Rate of PE in the Control Group	Rate of VTE events (DVT and PE) in the COVID-19 Group	Rate of VTE events (DVT and PE) in the Control Group	Rate of stroke in the COVID-19 Group	Rate of stroke in the Control Group	Rate of nonfatal myocardial infarction in the COVID-19 Group	Rate of nonfatal myocardial infarction in the Control Group	Rate of hospitalisation for heart failure in the COVID-19 Group	Rate of hospitalisation for heart failure in the Control Group	Rate of cardiovascular death in the COVID-19 Group	Rate of cardiovascular death in the Control Group	Rate of MACE events in the COVID-19 Group	Rate of MACE events in the Control Group
Cheung et al. <sup>14</sup> 2020	Retrospective case series	10	NA	10% (1/10)	NA	0%	0%	10%	NA	0%	NA	0%	NA	NA	NA	0%	NA	0%	NA
De et al. <sup>15</sup> 2020	Multicentre retrospective case series	34	NA	0% (0/14)	NA	0% (0/14)	NA	0% (0/14)	NA	0% (0/14)	NA	7.1% (1/14)	NA	0% (0/14)	NA	0% (0/14)	NA	7.1% (1/14)	NA
Ego et al. <sup>16</sup> 2020	Multicentre retrospective case series	17	107	NA	NA	11.8% (2/17)	2.8% (3/107)	11.8% (2/17)	2.8% (3/107)	1.9% (2/107)	11.8% (2/17)	2.8% (3/107)	NA	NA	NA	11.8% (2/17)	0% (0/107)	23.5% (4/17)	4.7% (5/107)
Fadulemola et al. <sup>17</sup> 2020	Retrospective case control	20	55	0% (0/20)	0% (0/55)	0% (0/20)	0% (0/55)	0% (0/20)	0% (0/55)	0% (0/20)	0% (0/55)	1.8% (1/55)	0% (0/20)	0% (0/55)	0% (0/20)	0% (0/55)	0% (0/55)	0% (0/20)	1.8% (1/55)
Giorgi et al. <sup>18</sup> 2020	Retrospective case control	17	48	0% (0/17)	0% (0/48)	NA	NA	0% (0/17)	0% (0/48)	NA	NA	0% (0/17)	0% (0/48)	NA	NA	0% (0/17)	4.2% (2/48)	0% (0/17)	4.2% (2/48)
Avil et al. <sup>19</sup> 2020	Retrospective case series	30	NA	6.6% (2/30)	NA	NA	NA	6.6% (2/30)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	6.6% (2/30)
Kayani et al. <sup>20</sup> 2020	Multicentre retrospective case control	82	340	NA	NA	NA	NA	13.4% (11/82)	NA	NA	NA	2.4% (2/82)	NA	NA	NA	NA	NA	2.4% (2/82)	NA
Konda et al. <sup>21</sup> 2020	Multicentre retrospective case control	31	288	NA	NA	NA	NA	6.5% (2/31)	2.1% (6/288)	0% (0/31)	1% (3/288)	6.5% (2/31)	2.4% (7/288)	NA	NA	6.5% (2/31)	3.8% (11/288)	12.9% (4/31)	7.2% (21/288)
Lakhani et al. <sup>22</sup> 2020	Retrospective case series	19	NA	5.2% (1/19)	NA	0%	0%	5.2% (1/19)	NA	0%	NA	NA	NA	NA	NA	0%	NA	31.5% (6/19)	NA
LeBrun et al. <sup>23</sup> 2020	Multicentre retrospective case control	9	50	0% (0/9)	2% (1/50)	NA	NA	0% (0/9)	2% (1/50)	NA	NA	0% (0/9)	2% (1/50)	NA	NA	44% (4/9)	NA	44% (4/9)	NA
Morelli et al. <sup>24</sup> 2020	Retrospective case series	10 0206	NA	0%	NA	0%	NA	0%	NA	0%	NA	0%	NA	NA	NA	0%	NA	0%	NA
Muse et al. <sup>25</sup> 2020	Retrospective case series	5	NA	0% (0/5)	NA	0% (0/5)	NA	0% (0/5)	NA	0% (0/5)	NA	0% (0/5)	NA	NA	NA	0% (0/5)	NA	0% (0/5)	NA
Perazzo et al. <sup>26</sup> 2020	Retrospective case series	16	NA	0% (0/16)	NA	6.2% (1/16)	NA	6.2% (1/16)	NA	6.2% (1/16)	NA	0% (0/16)	NA	NA	NA	12.5% (2/16)	NA	18.8% (3/16)	NA
Ward et al. <sup>27</sup> 2020	Retrospective case control	46	86	4.3% (2/46)	3.5% (3/86)	4.3% (2/46)	3.5% (3/86)	4.3% (2/46)	3.5% (3/86)	2.2% (1/46)	0% (0/86)	0% (0/46)	0% (0/86)	NA	NA	NA	NA	2.2% (1/46)	0% (0/86)

DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism; NA, not applicable.

Study	Risk of bias domains							Overall
	D1	D2	D3	D4	D5	D6	D7	
Agar et al.	+	+	+	+	+	+	+	+
Cheung et al.	+	X	+	+	+	+	-	X
De et al.	+	+	+	+	+	+	+	+
Egol et al.	+	+	+	X	+	+	+	X
Fadulelmola et al.	+	+	X	+	+	+	+	+
Giorgi et al.	+	+	+	+	+	+	+	+
Kayani et al.	+	+	+	+	+	+	+	+
Konda et al.	+	X	+	X	+	+	+	X
Lakhani et al.	+	+	+	+	+	-	+	-
LeBrun et al.	+	+	X	+	+	+	+	X
Morelli et al.	+	+	X	+	+	+	+	X
Muse et al.	+	+	+	+	+	+	+	+
Perazzo et al.	+	+	+	+	+	+	+	+
Ward et al.	+	+	X	+	+	+	+	X

Domains:  
 D1: Bias due to confounding.  
 D2: Bias due to selection of participants.  
 D3: Bias in classification of interventions.  
 D4: Bias due to deviations from intended interventions.  
 D5: Bias due to missing data.  
 D6: Bias in measurement of outcomes.  
 D7: Bias in selection of the reported result.

Judgement  
 X Serious  
 - Moderate  
 + Low

Figure 4. Study assessment according to ROBINS-I (“Risk of bias in non-randomised studies - of interventions”) tool.

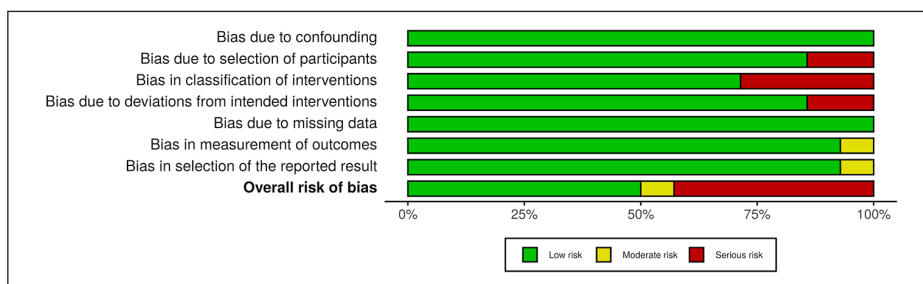


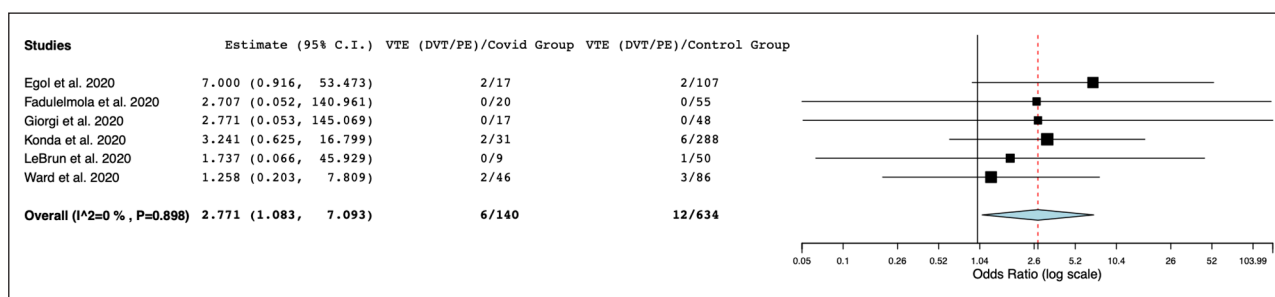
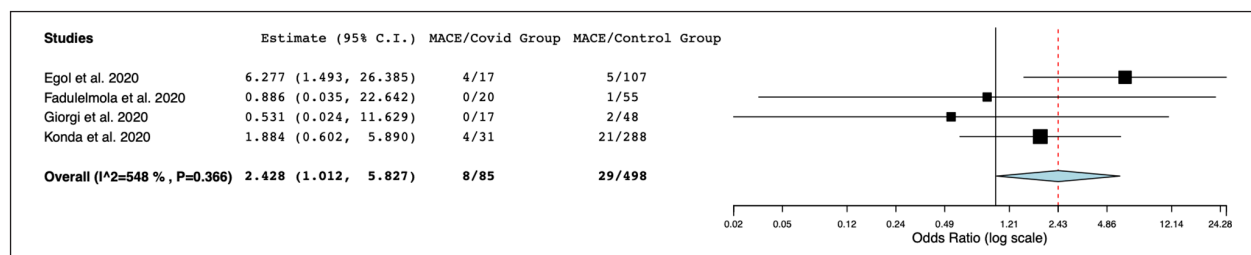
Figure 5. Summary plot of bias assessment of the included studies.

SARS-CoV-2 infection are at increased risk for VTE, including PE and DVT, when compared to SARS-CoV-2 free patients. Moreover, there is a small body of medium

to low quality data indicating that hip fracture patients with SARS-CoV-2 infection who undergo surgery are at increased risk for MACE postoperatively. The risk of

**Table 2.** Quality assessment of the studies according to NHI/NHLBI tool.

First author	Publication year	Study design	NHI/NHLBI tool (max 9)
Cheung et al. <sup>14</sup>	2020	Retrospective case series	7
De et al. <sup>15</sup>	2020	Multicentre retrospective case series	8
Egol et al. <sup>16</sup>	2020	Multicentre retrospective case control	8
Fadulelmola et al. <sup>17</sup>	2020	Retrospective case control	7
Giorgi et al. <sup>18</sup>	2020	Retrospective case control	7
Anil et al. <sup>19</sup>	2020	Retrospective case series	7
Kayani et al. <sup>20</sup>	2020	Multicentre retrospective case control	8
Konda et al. <sup>21</sup>	2020	Multicentre retrospective case control	8
Lakhani et al. <sup>22</sup>	2020	Retrospective case series	4
LeBrun et al. <sup>23</sup>	2020	Multicentre retrospective case control	8
Morelli et al. <sup>24</sup>	2020	Retrospective case series	4
Muse et al. <sup>25</sup>	2020	Retrospective case series	4
Perazzo et al. <sup>26</sup>	2020	Retrospective case series	3
Ward et al. <sup>27</sup>	2020	Retrospective case control	8

**Figure 6.** Estimated pooled results for VTE (DVT/PE) between patients with and without SARS-CoV-2 infection.**Figure 7.** Estimated pooled results for MACE between patients with and without SARS-CoV-2 infection.

CVD was also found to be higher in the aforementioned group of patients. Patients with hip fractures and concomitant COVID-19 have also increased mortality, in addition to elevated risk for adverse events. In a recent meta-analysis, it was found that this group had increased in-hospital and 30-day mortality with odds ratio of 18 and 6 respectively.<sup>1</sup>

The results are in accordance with the current literature. MACE after hip fractures ranges from 2% to 16.4% in patients not infected with SARS-CoV-2 depending on the follow-up and study design.<sup>28,29</sup> We measured a pooled estimate of 6.3% in COVID-19 patients, probably due to short follow-up and the retrospective nature of most studies. Even with this short follow-up and small numbers the

comparative analysis disclosed increased risk in these patients. Regarding VTE events, a recent sub-analysis of 2 randomised trials revealed VTE incidence of 2.5%,<sup>30</sup> which is lower than the pooled estimated rate of this study (5.7%). Again, in the pooled analysis, the odds ratio between COVID-19 and non-COVID-19 patients was 2.8 favouring the non-COVID-19 patients, which experienced statistically less VTE events.

### Clinical implications

It seems that the increased risk of morbidity and mortality in hip fracture who undergo surgical fixation and suffer from SARS-CoV-2 infection could be explained by the



“three hit” model/theory.<sup>1,4,16,31</sup> Hip fracture (first hit) is associated with an acute inflammatory over-activation and subsequent hypercoagulability, which are responsible for the high risk of pulmonary and cardiovascular complications, such as PE, DVT, stroke, MI and CVD in hip fracture patients and further amplified by the patients’ comorbidities.<sup>1,4,16</sup> Furthermore, SARS-CoV-2 infection (second hit) generates a 2-phase inflammatory cascade, “the cytokine storm”, which is responsible for the high mortality rate in the subset of the infected patients.<sup>16,31</sup> Moreover, SARS-CoV-2 infection is a prothrombotic state with both venous and arterial thrombosis. The thrombotic profile of SARS-CoV-2 infection is multifactorial and could be interpreted as that of the Behcet syndrome.<sup>31</sup> It seems that there is a constant interaction between the CRS and the hypercoagulability in SARS-CoV-2 infection and the ongoing pulmonary inflammation further enhances the infection-related thrombosis. Even if vaccination can ameliorate the severity of COVID-19, still many countries are behind an acceptable vaccination rate due to vaccine unavailability or people’s scepticism. New variants emerge contributing to new waves of the disease. So, many geriatric patients with hip fractures are even now diagnosed with SARS-CoV-2 and are susceptible to VTE and MACEs.

Hip fracture surgery (third hit) with the associated neuroendocrine perioperative response further attenuates the CRS and the hypercoagulability caused by the SARS-CoV-2 infection.<sup>32</sup> It has been shown that thromboprophylaxis may reduce the VTE occurrence and improve the overall survival in patients suffering from SARS-CoV-2 pneumonia. However, despite the administration of anticoagulants, even in high therapeutic dose, the thrombotic complications were still high. Other reasons that contributed to increased VTE events and MACE might be the suboptimal peri-operative care, rehabilitation and nursing of these patients due to pandemic constraints and limited hospital resources.

It should be highlighted that COVID-19 patients with any history of cardiovascular disease or a high burden of cardiovascular risk factors are more vulnerable to develop complications from COVID-19 and are at increased risk of poor prognosis.<sup>33,34</sup> The estimated rate of MACE in patients suffering from SARS-CoV-2 infection is 23%,<sup>34</sup> while patients with a known history of cardiovascular disease are at increased risk of MACE due to SARS-CoV-2 infection (OR=6.0 (95% CI. 4.3–8.4),  $p < 0.001$ ).<sup>33</sup> Moreover, the population of people who sustain a hip fracture is already facing an appreciable background mortality rate, including MACE besides the SARS-CoV-2 infection. Older age, especially >80 years old and low left ventricular ejection fraction, <50%, are the most important predictors for cardiovascular complications following hip fracture surgery,<sup>35,36</sup> while a recent meta-analysis reports that any pre-existing cardiovascular disease may significantly increase the risk of mortality after hip fracture surgery.<sup>37</sup>

On the other hand, older age and pre-existing cardiovascular diseases are recognised poor prognostic markers for hospitalised patients with SARS-CoV-2 infection.<sup>34</sup> Hence, even before surgery patients with hip fractures suffering from SARS-CoV-2 are at increased risk for MACE. Lastly, as proposed by the European Society of Cardiology and the European Society of Anaesthesiology the estimated surgical risk for hip fracture surgery is classified as intermediate. Thus, the 30-day risk of CVD and MI, taking into account only the surgical intervention regarding the hip fracture fixation without considering the patient’s comorbidity, is 1 to 5% risk of,<sup>38</sup> which means that hip fixation could further amplify the increased cardiovascular risk of the aforementioned patients.

Moving on, as it is well-known optimal hip fracture management requires performing surgery within 24 to 48 hours in terms of enhanced prognosis and improved survival.<sup>37,39</sup> On the other hand, for the elective and semi-elective surgeries in patients suffering from COVID-19 infection delaying surgery up to 7 weeks it is suggested, in an attempt to reduce the perioperative mortality.<sup>4</sup> However, in patients with hip fracture and a concomitant COVID-19 infection delaying surgery does not seem feasible. Instead, several proposed risk stratification tools such as the modified Score for Trauma Triage in the Geriatric and Middle-Aged (STTMGA<sub>COVID</sub>) can prove quite useful. The implementation of these stratification tools could support the decision to postpone the surgery until the improvement or the remission of the symptoms from the SARS-CoV-2 infection,<sup>25</sup> as it seems that delayed surgery improves function and reduces major complications when compared to conservative treatment with no surgery at all.<sup>40</sup> Hence, the perioperative team should always briefly inform the patients and their families about the significantly increased risks of mortality and morbidity in patients with hip fracture and a concomitant COVID-19 infection. A multidisciplinary experts’ approach, including infection control measures and adequate monitoring, follow-up and rehabilitation seems mandatory for the optimal perioperative management of these patients.

### Strengths and limitations

Our study contains an extensive search strategy and was conducted according to the PRISMA guidelines.<sup>15</sup> Moreover, search strategy, selection of studies, data extraction and quality assessment were performed by different reviewers independently and were double-checked in terms of transparency and accuracy.

The limitations were acknowledged, such as the inclusion of retrospective studies that lacked randomisation and blinding. The quality assessment of the included studies showed varying quality. There were no randomised studies to be included in our study. Moreover, there was a large heterogeneity between the included studies. However, in

an attempt to present a complete overview of a prevalent and high-clinical importance issue we included all the available studies in our analysis. Hence, it seems that further, high-quality studies with a large body of evidence are required to elucidate more definitive results regarding the impact of SARS-CoV-2 infection in patients with hip fractures who undergo surgery.

## Conclusion

This review suggests that there is a high rate of VTE and MACE in patients with hip fractures and concomitant SARS-CoV-2 infection. Although there is a lack of high-quality data it seems that patients with hip fractures and concomitant SARS-CoV-2 infection are at increased risk for VTE and MACE in comparison to non-infected patients. The acute inflammatory over-activation and hyper-coagulability that emerge from the injury and amplify due to the SARS-CoV-2 infection might be responsible for the observed poor outcomes. The perioperative team should inform briefly the patients' and their families about the significantly increased risks of mortality and morbidity. A multidisciplinary experts' approach, including infection control measures and adequate monitoring, follow-up and rehabilitation seems mandatory for the optimal perioperative management of patients with hip fractures and concomitant SARS-CoV-2 infection in order to improve the overall outcome.


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