

# Early mortality outcomes of patients with fragility hip fracture and concurrent SARS-CoV-2 infection

A SYSTEMATIC REVIEW AND META-ANALYSIS

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## Aims

Hip fracture is a common condition of the older, frailer person. This population is also at risk from SARS-CoV-2 infection. It is important to understand the impact of coexistent hip fracture and SARS-CoV-2 for informed decision-making at patient and service levels.

## Methods

We undertook a systematic review and meta-analysis of observational studies of older (> 60 years) people with fragility hip fractures and outcomes with and without SARS-CoV-2 infection during the first wave of the COVID-19 pandemic. The primary outcome was early (30-day or in-hospital) mortality. Secondary outcomes included length of hospital stay and key clinical characteristics known to be associated with outcomes after hip fracture.

## Results

A total of 14 cohort and five case series studies were included (692 SARS-CoV-2 positive, 2,585 SARS-CoV-2 negative). SARS-CoV-2 infection was associated with an overall risk ratio (RR) for early mortality of 4.42 (95% confidence interval (CI) 3.42 to 5.82). Early mortality was 34% (95% CI 30% to 38%) and 9% (95% CI 8% to 10%) in the infected and noninfected groups respectively. Length of stay was increased in SARS-CoV-2 infected patients (mean difference (MD) 5.2 days (3.2 to 7.2)). Age (MD 1.6 years (0.3 to 2.9)); female sex (RR 0.83 (95% CI 0.65 to 1.05)); admission from home (RR 0.51 (95% CI 0.26 to 1.00)); presence of dementia (RR 1.13 (95% CI 0.94 to 1.43)); and intracapsular fracture (RR 0.89 (95% CI 0.71 to 1.11)) were not associated with SARS-CoV-2 infection. There were statistically, but not clinically, significantly greater Nottingham Hip Fracture Scores in infected compared with non-infected patients (MD 0.7 (0.4 to 0.9)).

## Conclusion

SARS-CoV-2 infection is associated with worse outcomes after hip fracture. This is not explained by differences in patient characteristics. These data can be used to support informed decision-making and may help track the impact of widespread adoption of system-level and therapeutic changes in management of the COVID-19 pandemic.

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## Introduction

People who sustain hip fractures are also those likely to be at greatest risk from SARS-COV-2 infection due to their age and comorbidities.<sup>1</sup> Delays to hip fracture surgery are associated with an increased risk of death<sup>2,3</sup> and the response to the COVID-19 pandemic at organizational and clinical levels

may have impacted our ability to provide timely surgery. Patients, families, clinicians, and service providers need objective data on the impact of COVID-19 to inform clinical and service delivery decision-making. The pandemic is likely to continue for the foreseeable future and this study also aims to provide an insight into how hip fracture outcomes for

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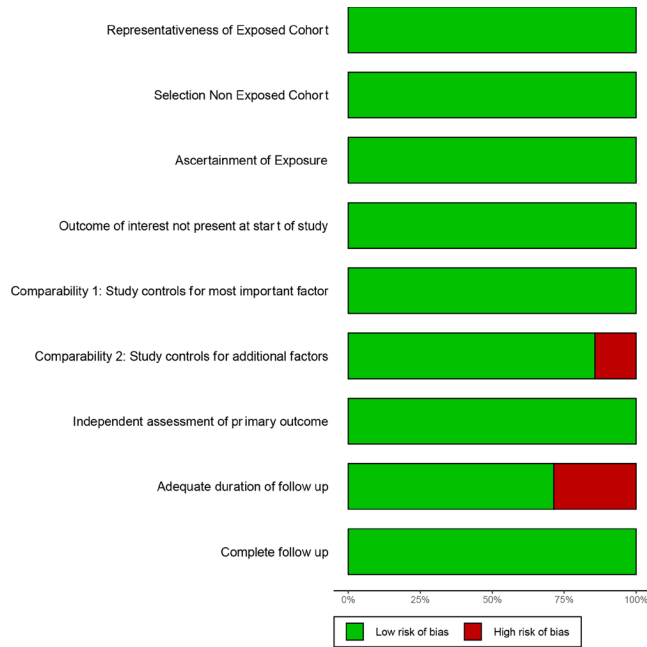


Fig. 1

Summary of risk of bias assessments for all included studies, using the Newcastle-Ottawa Scale.<sup>10</sup>

people with and without confirmed SARS-CoV-2 infection are being affected by the pandemic.

Our primary objective was to determine the association between SARS-CoV-2 infection and mortality after hip fracture. Secondary objectives were to describe the clinical characteristics of people with hip fracture with and without SARS-CoV-2 infection, and to investigate the association of infection with other outcomes.

## Methods

We included any full text articles considering our specified population including randomized controlled trials, cohort studies, and case-control and case series studies. Previous systematic reviews were included, and the incorporated studies used if they met inclusion criteria. To be included, articles had to have been published in English or provide a link to an English translation. Articles must also have been published between 1 December 2019 and 23 November 2020, and searches were rerun at the time of final manuscript preparation.

Studies were included for assessment of our primary outcome only if complete data on mortality were available and studies were only included for description of the 'hip fracture - SARS-CoV-2' population if they contained adequate data on patient characteristics. We excluded individual case reports, conference abstracts, editorials, and opinion pieces. We excluded studies without an English translation, or those studies published outside the specified time frame.

**Population.** We included adult patients (over 60 years of age) admitted with any fragility hip fracture, with a

concurrent diagnosis of SARS-CoV-2 infection either at admission or during the index admission. We included patients with a fragility hip fracture as part of a polytrauma, provided there was no associated head injury. We did not impose any limitations on sex, ethnicity, or nationality. We also did not impose any limitations on comorbidities or functional status, including dementia or care home residency.

**Exposure and comparisons.** Patients were included whether SARS-CoV-2 infection was diagnosed pre- or post-admission. We included patients managed conservatively and with any form of surgical intervention. If an included study also contained a group of patients with fragility-related hip fractures without a diagnosis of SARS-CoV-2 (including patients who tested negative and those who were not tested) these patients were used as controls for comparisons (provided they were sufficiently matched for age and demographics). Contemporaneous and previous year controls were allowed.

**Outcomes.** Our primary outcome was early patient mortality, combining hospital inpatient mortality and 30-day mortality as a single outcome. Secondary outcomes included a priori were: hospital length of stay (days); admission to intensive care unit (ICU) (proportion); whether surgical fixation was performed (proportion); time to surgical fixation (hours); reoperation rates (proportion); and discharge destination if reported (proportion). We also reported outcomes on respiratory and cardiovascular complications including but not limited to: supplemental oxygen therapy requirement; respiratory arrest; myocardial infarction; and venous thromboembolism.

**Search strategy.** This systematic review was conducted and reported in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines<sup>4</sup> and registered on PROSPERO. Using the Healthcare Database Advanced Search (property of National Institute for Health and Care Excellence (NICE)), we conducted a Boolean search on PubMed (1946 to 2020), MEDLINE (1946 to 2020), Embase (1974 to 2020), and CINAHL (1981 to 2020) for various terms referring to "COVID-19" and "hip fracture". Exploded Medical Subject Headings terms were used on MEDLINE and Embase. To increase our scope, a separate search was also conducted using SCOPUS (1966 to 2020), Google Scholar, and the Cochrane Library. Backwards and forwards citation searches were also conducted using the references of included studies.

**Data collection and analysis.** Two reviewers (HA, EM) independently assessed the eligibility of articles based on our inclusion criteria by screening titles and abstracts. Selected articles were then subjected to a full-text read and excluded based on our criteria. Disagreements were resolved via discussion with an independent third reviewer (IKM). Data were recorded in comma-separated value data tables. All study data were double checked

	Representativeness of Exposed Cohort	Selection Non Exposed Cohort	Ascertainment of Exposure	Outcome of interest not present at start of study	Comparability 1: Study controls for most important factor	Comparability 2: Study controls for additional factors	Independent assessment of primary outcome	Adequate duration of follow up	Complete follow up
Arafa	+	+	+	+	+	+	+	+	+
Clement Hall	+	+	+	+	+	+	+	+	+
Egol Konda	+	+	+	+	+	+	+	+	+
Fadulemola	+	+	+	+	+	+	+	+	+
Kayani	+	+	+	+	+	+	+	+	+
LeBrun	+	+	+	+	+	+	-	+	+
Macey	+	+	+	+	+	+	+	+	+
Maniscalco	+	+	+	+	-	+	-	+	+
Munoz Vives	+	+	+	+	-	+	-	+	+
Narang	+	+	+	+	+	+	+	+	+
Rasidovic	+	+	+	+	+	+	+	+	+
Sobti	+	+	+	+	+	+	-	+	+
Thakrar	+	+	+	+	+	+	+	+	+
Ward	+	+	+	+	+	+	+	+	+

Fig. 2

Risk of bias for individual studies, using the Newcastle-Ottawa scale.<sup>10</sup>

by at least two of the investigators. In addition to participant outcomes, data were extracted on the number of SARS-CoV-2 positive hip fracture patients, the number SARS-CoV-2 negative hip fracture control patients, and patient characteristics (where available). This included sex, age, presence of dementia, comorbidities, source

of admission, Nottingham Hip Fracture Score (NHFS),<sup>5-7</sup> Charlson Comorbidity Index (CCI),<sup>5</sup> and American Society of Anesthesiologists (ASA) physical status.<sup>8</sup> Standard deviations (SDs) were estimated from interquartile ranges (IQRs) using the approach recommended by Wan et

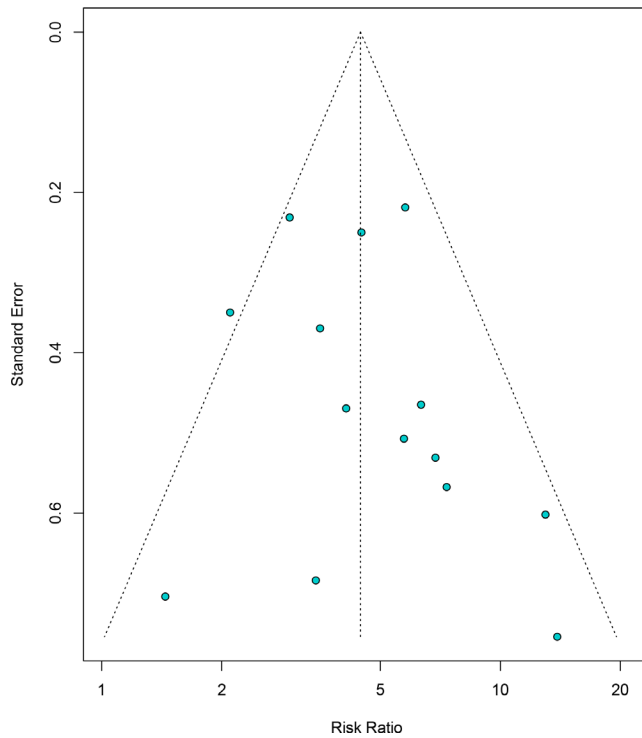


Fig. 3

Funnel plot of included studies for risk of mortality associated with SARS-CoV-2 and hip fracture.

al.<sup>9</sup> Risk of bias assessments were performed using the Newcastle-Ottawa scale.<sup>10</sup>

**Statistical analysis.** Analysis and data presentation were performed using R and the meta package (R Foundation for Statistical Computing, Austria). Where appropriate, meta-analysis was performed using Mantel-Haenszel risk ratios (RRs) with 95% confidence intervals (CIs). A DerSimonian random effects model was used as we anticipated high levels of heterogeneity. We estimated publication bias for the primary outcome using funnel plots. Sensitivity analyses are reported with data restricted to larger studies ( $\geq 30$  included participants in the non-SARS-CoV-2 group or  $\geq 10$  deaths in the SARS-CoV-2 group).

## Results

A total of 16 studies describing 14 cohorts (564 SARS-CoV-2 positive, 22,585 SARS-CoV-2 negative) were included.<sup>11–26</sup> Of these, 11 studies originated from the UK,<sup>11,13–15,17,20–22,24–26</sup> three from the USA,<sup>12,16,23</sup> and one each from Italy<sup>18</sup> and Spain.<sup>19</sup> The report from Clement et al<sup>24</sup> is an expansion of the data reported by Hall et al.<sup>14</sup> Only mortality data from Clement et al<sup>24</sup> are included; all other data are from Hall et al.<sup>14</sup> The reports from Egol et al<sup>12</sup> and Konda et al<sup>23</sup> describing the same cohort and data have been combined. In addition, we encountered five case series articles.<sup>27–31</sup>

All observational studies reported similar patient demographics, with the exception of the patient population for Kayani et al,<sup>15</sup> which contained younger, fitter patients with a greater proportion of intracapsular fractures. Analyses were repeated with this study excluded. Of the observational studies, 11 directly compared positive and negative SARS-CoV-2 cases<sup>11–16,18–20,23–26</sup> while three studies compared positive cases during the pandemic period with matched patients from 2019 or the pre-pandemic period.<sup>17,21,22</sup>

Two studies did not report the diagnosis method of COVID-19.<sup>11,21</sup> All other studies reported using polymerase chain reaction (PCR) but no details of cycle count thresholds were provided. Most studies gave little (e.g. ‘clinically indicated’) or no detail on the indications for, or symptoms in, those tested.<sup>11–14,17–26</sup> Kayani et al<sup>15</sup> reported that 73 of 82 SARS-CoV-2 cases were symptomatic; 54/82 had respiratory symptoms or fever. LeBrun et al<sup>16</sup> reported that 4/9 SARS-CoV-2 cases were hypoxic. Hall et al<sup>14</sup> reported that seven of 27 SARS-CoV-2 positive patients had symptoms ‘suggestive of COVID-19 at admission’, and the remainder became swab positive (presumably based on testing after clinical suspicion) later during admission. The proportions of the cohort study populations tested was reported in seven studies (median 0.56 (IQR 0.44 to 0.7)).<sup>11,16,17,19,21,22,25</sup> There was one recently published systematic review that identified six studies up to July 2020.<sup>32</sup>

**Risk of bias assessment.** The observational cohort studies were generally at low risk of bias for the primary outcome (Figures 1 and 2) and length of stay and patient characteristics where reported. The case series were at higher risk of bias for representativeness of the cohort and a lack of control for confounding factors. There was no evidence of publication bias for mortality outcomes assessed by funnel plot (Figure 3).

**Early mortality.** A total of 14 cohorts from 16 studies were included reporting early mortality. Ten reported 30-day mortality. Of the others, mortality was reported as inpatient in one,<sup>16</sup> a minimum of ten days (mean 15 days) in another,<sup>19</sup> and unclear in two studies.<sup>18,21</sup> Ten cohorts (442 patients) were from the UK, two from the USA (40 patients), and one each from Spain (23 patients) and Italy (32 patients). Four case series reported early mortality at seven days,<sup>27</sup> 14 to 39 days,<sup>30</sup> 30 days,<sup>29</sup> and unclear in one.<sup>31</sup> The overall RR for early mortality was 4.42 (95% CI 3.42 to 5.82) (Figure 4). This result was qualitatively unaffected by inclusion of larger studies only (RR 5.4 (95% CI 3.4 to 8.58) or limiting outcomes to 30-day mortality (RR 3.91 (95% CI 3.01 to 5.09)). The absolute risk of early mortality was 34% (95% CI 30% to 38%) for patients with confirmed SARS-CoV-2 compared with 9% (8% to 10%) in contemporaneous patients without confirmed infection (Figure 5).

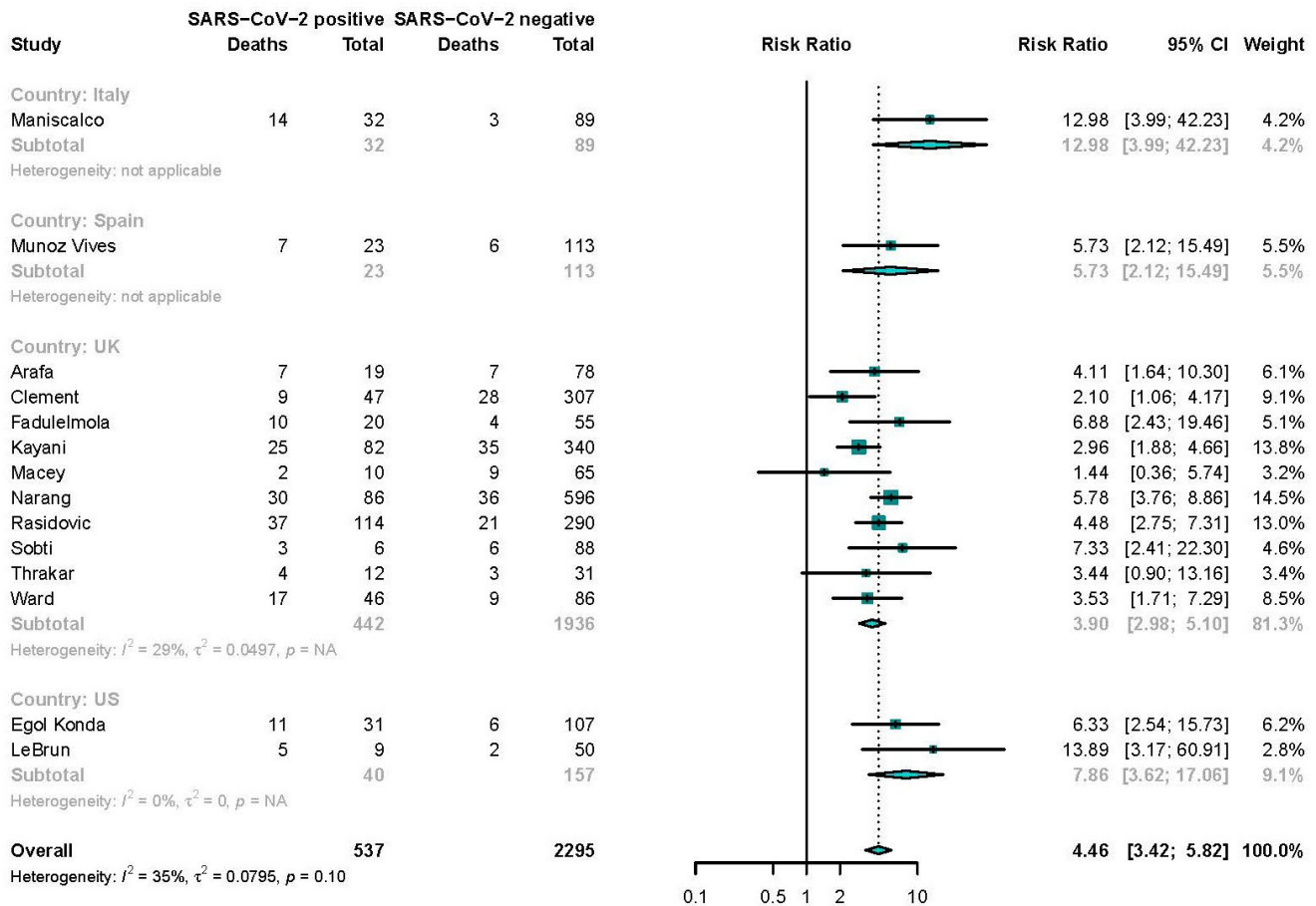


Fig. 4

Risk ratio for early mortality associated with SARS-CoV-2 infection in older people with fragility hip fracture. CI, confidence interval.

Six studies reported mortality outcomes for noninfected patients during the pandemic and equivalent cohorts from 2019.<sup>11,12,17,18,21,22</sup> The relative risk of early mortality in the SARS-CoV-2 negative 2020 cohorts ( $n = 458$ ) compared to 2019 ( $n = 572$ ) was 1.09 (95% CI 0.69 to 1.73).

Two studies reported data for patients with a diagnosis of SARS-CoV-2 at or shortly after admission compared with those with a later ( $\geq$  seven days) diagnosis.<sup>14,29</sup> Mortality at 30 days was not significantly different in either study (RR 1.18 (0.62 to 2.22)<sup>29</sup> and 3/6 vs 6/21).<sup>14</sup>

**Characteristics of patients with and without confirmed SARS-CoV-2 infection.** Eight cohorts<sup>11,12,14–16,20,23,25,26</sup> reported data for age. Patients with confirmed SARS-CoV-2 infection were significantly older than those without (mean difference 1.6 years (0.3 to 2.9)) (Figure 6).

Nine cohorts<sup>11–16,20,23,25,26</sup> reported data on sex distributions (1,533 female, 789 male). Female sex was not associated with confirmed SARS-CoV-2 diagnosis (RR 0.83 (95% CI 0.65 to 1.05)). Exclusion of smaller studies did not change this lack of association (RR 1.04 (0.65 to 1.66)).

Seven studies<sup>13–16,20,25,26</sup> reported data on source of admission distributions (1,386 home, 428 not home). Admission from home was not associated with confirmed SARS-CoV-2 diagnosis (RR 0.51 (95% CI 0.26 to 1.00)). Exclusion of the study by Kayani et al<sup>15</sup> resulted in a significant association between source of admission and SARS-CoV-2 diagnosis (RR 0.74 (95% CI 0.58 to 0.93)). Exclusion of smaller studies did not change this lack of association (RR 0.43 (95% CI 0.16 to 1.17)).

Six cohorts<sup>12,14–16,23,25,26</sup> reported data on presence of dementia (or cognitive dysfunction). A diagnosis of dementia was not associated with confirmed SARS-CoV-2 diagnosis (RR 1.13 (95% CI 0.94 to 1.43)). Exclusion of smaller studies did not change this lack of association (RR 1.14 (95% CI 0.92 to 1.41)).

Data for global markers of frailty or comorbidity were reported adequately by eight studies: NHFS by five,<sup>11,14,20,25,26</sup> CCI by two,<sup>12,13,23</sup> and ASA by three.<sup>15,25,26</sup> NHFS were greater in patients with SARS-CoV-2 infection (MD 0.7 (0.4 to 0.9)) (Figure 7). CCI scores were not significantly different between patients with and without SARS-CoV-2 infection in the studies that reported them.

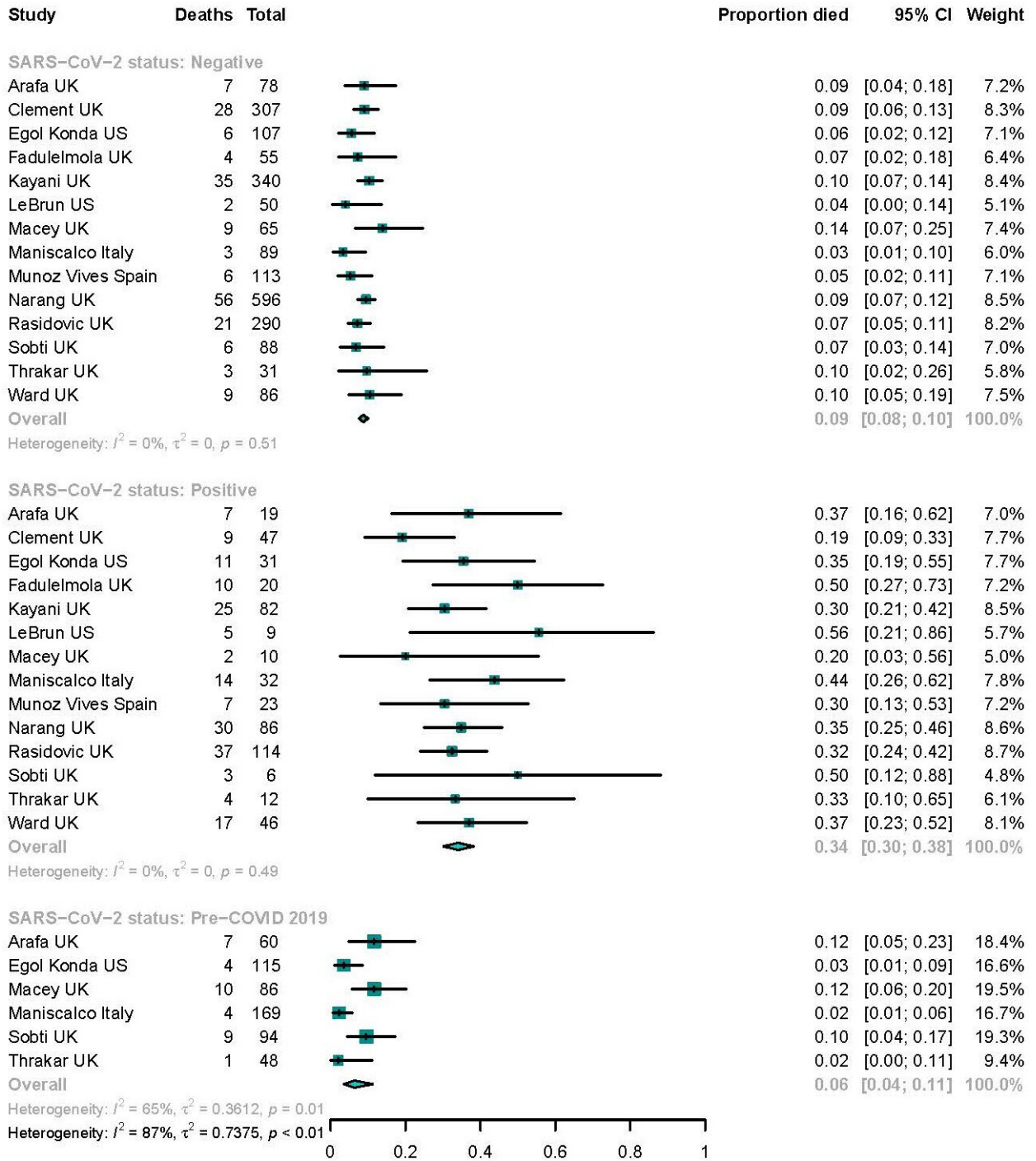


Fig. 5

Absolute risk for early mortality associated with SARS-CoV-2 infection in older people with fragility hip fracture. CI, confidence interval.

Mean ASA grades were not different between groups (MD 0.2 (-0.1 to 0.4)).

The distribution of fracture types was reported from nine cohorts<sup>11-16,20,23,25,26</sup> and was not associated with risk of infection (intracapsular fracture RR 0.89 (95% CI 0.71 to 1.11)).

**Risk factors for mortality in patients with confirmed SARS-CoV-2 infection.** Four studies provided data on risk factors associated with mortality in the presence of confirmed SARS-CoV-2 infection.<sup>15,25,28,29</sup> Multiple comorbidities were identified as a significant risk factor in two studies,<sup>15,25</sup> and increasing age was identified as a risk factor only in one study.<sup>28</sup> Male sex was associated with mortality by two studies<sup>25</sup> but not the other two.<sup>15,29</sup>

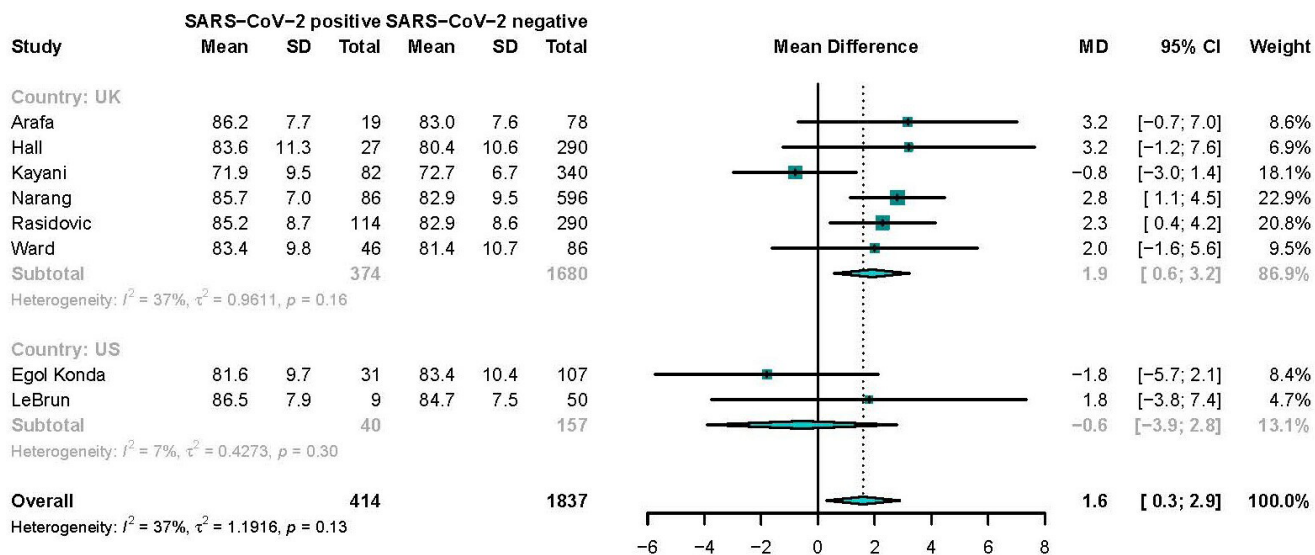


Fig. 6

Mean difference in age between SARS-CoV-2 positive and negative patients with hip fracture. CI, confidence interval.

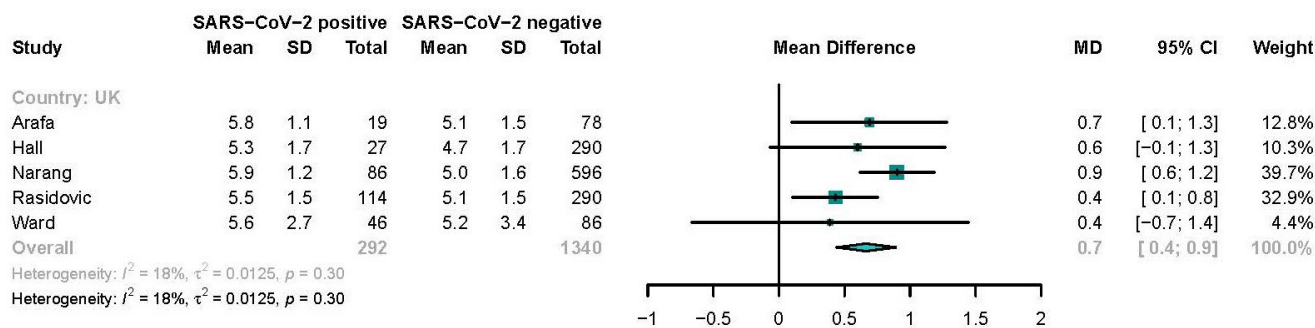


Fig. 7

Mean difference in Nottingham Hip Fracture Score between SARS-CoV-2 positive and negative patients with hip fracture. CI, confidence interval.

Causes of death were generally not reported. Arafa et al<sup>11</sup> described seven out of seven SARS-CoV-2 positive deaths as COVID-19 pneumonitis; Konda et al<sup>23</sup> and Fadulemola et al<sup>13</sup> found that seven out of 11 and seven out of ten deaths were associated with pneumonia or COVID-19 pneumonia respectively; and Thrakar et al<sup>22</sup> and Ward et al<sup>26</sup> reported four out of seven and 14 out of 17 with COVID-19 as a contributory cause, respectively.

Details of included and excluded studies and all secondary analyses are available from the corresponding author (Supplementary Material).

## Discussion

Around one in three older people with hip fracture and infection with SARS-CoV-2 died within 30 days at the time of the 'first wave' of the pandemic, compared with around one in ten without known infection. This was despite clinically minimal differences in important characteristics.

All of the included studies were of good quality as assessed by the Newcastle-Ottawa ratings. Almost all of the data reported are from 'Western' healthcare systems, so we cannot draw conclusions about other systems or populations. The association between SARS-CoV-2 infection and outcome is robust to the exclusion of smaller studies. All of the studies reported data from around the time of peak infection in their respective country. There is a risk of confirmation bias as sicker patients were more likely to be tested, particularly in the early phase of the pandemic. However, qualitatively, the high 30-day mortality appears consistent regardless of testing strategy. Where reported, most patients with positive tests had symptoms, or the testing was 'clinically indicated'. We suggest that as second and third waves of COVID-19 appear around the world, it is important that clinicians collect and report data on hip fracture outcomes.

It is unlikely that false positive results were a particular issue given that testing was clinically driven, rather

than screening for all. There will be number of unknown SARS-CoV-2 infections either due to false negative test results, or lack of any testing. However, the mortality in the 'negative' groups is broadly the same as previous years, suggesting either that the rate of SARS-CoV-2 infection was low or that asymptomatic SARS-CoV-2 infection is not associated with marked increases in mortality.

We suggest that these data are important for several reasons. First, they provide information to support clinical decision-making and communication. At the start of the pandemic, NHS guidance on management of hip fractures stated that "most people with coronavirus will survive, even those with frailty."<sup>33</sup> This, and other similar statements, now have data to support them. Clinicians and those responsible for service delivery can use these data to continue to provide patient-centred hip fracture services. SARS-CoV-2 is not a contraindication to surgery after hip fracture, even if the outcomes are worse. Honest communication with patients and their loved ones remains as important as ever.

Second, they provide indirect evidence of the additional impact of symptomatic SARS-CoV-2 infection. There have been questions asked about whether people are dying with, rather than of, COVID-19. We would argue that the three- to four-fold increase in 30-day mortality between patients with and without SARS-CoV-2 infection during the first wave, in the absence of clinically important difference in other predictors of outcome, is strongly supportive of the causative role of infection in death. The difference in NHFS, while statistically significant, is not sufficient to explain the increased mortality. Where reported, the presenting symptoms and cause of death are clearly ascribed to complications from COVID-19.

Third, most of the data reported here, though not all, have used the England, Wales, and Northern Ireland (National Hip Fracture Database) or Scottish (Scottish Hip Fracture Audit) databases as existing frameworks for rapid, robust data collection. Without the existence of these continuous data collection tools, it is unlikely that such high-quality data would have been available so quickly.

Finally, the comparative data between patient outcomes during the pandemic and in comparable cohorts from previous years would suggest that clinicians and services have succeeded in protecting the care of older patients with hip fracture despite the pandemic pressures.

However, this study also raises questions. The impact of nosocomial SARS-CoV-2 infection is not clear. Only two studies reported these data, and even here the distinction between hospital-acquired and initially undiagnosed is not clear.<sup>14,29</sup> The data from the International Multicentre Project Auditing COVID-19 in Trauma & Orthopaedics (IMPACT) studies suggest that outcomes are similar regardless of time of diagnosis. The current data do not

allow distinction between an association of hospital-acquired COVID-19 with those at higher risk of adverse outcome, versus hospital-acquired infection causing a worse outcome. The clinically driven nature of testing would suggest that later-onset COVID-19 was not simply an asymptomatic association, though unfortunately symptoms at postoperative onset were poorly described. It is not known whether outcomes will be different in second or third waves. Widespread vaccination is hoped to reduce the incidence and severity of COVID-19. Patients presenting with hip fracture and SARS-CoV-2 infection in the first wave may have a different risk profile to those presenting later and hospitals are hopefully better able to reduce the risk of nosocomial infection.

Mortality after hip fracture is significantly worse in the presence of SARS-CoV-2 infection, but the majority of patients will survive to 30 days. These outcomes after hip fracture are not readily explained by differences in patient characteristics. Future studies should ideally report the symptoms and signs present when a laboratory diagnosis is made, alongside the timing, to better inform understanding of the impact of infection in this vulnerable group. More data are needed to understand, and ideally prevent, the impact of hospital-acquired SARS-CoV-2 in this vulnerable patient population.

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## Supplementary material



Figures for supplementary analyses not reported in main paper.

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