



Postoperative mortality in the COVID-positive hip fracture patient, a systematic review and meta-analysis

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Abstract

Purpose The extent to which concomitant COVID-19 infection increases short-term mortality following hip fracture is not fully understood. A systemic review and meta-analysis of COVID-19 positive hip fracture patients (CPHFPs) undergoing surgery was conducted to explore the association of COVID-19 with short-term mortality.

Methods Review of the literature identified reports of short-term 30-day postoperative mortality in CPHFPs. For studies including a contemporary control group of COVID-19 negative patients, odds ratios of the association between COVID-19 infection and short-term mortality were calculated. Short-term mortality and the association between COVID-19 infection and short-term mortality were meta-analyzed and stratified by hospital screening type using random effects models.

Results Seventeen reports were identified. The short-term mortality in CPHFPs was 34% (95% C.I., 30–39%). Short-term mortality differed slightly across studies that screened all patients, 30% (95% C.I., 22–39%), compared to studies that conditionally screened patients, 36% (95% C.I., 31–42%), ($P=0.22$). The association between COVID-19 infection and short-term mortality produced an odds ratio of 7.16 (95% C.I., 4.99–10.27), and this was lower for studies that screened all patients, 4.08 (95% C.I., 2.31–7.22), compared to studies that conditionally screened patients, 8.32 (95% C.I., 5.68–12.18), ($P=0.04$).

Conclusion CPHFPs have a short-term mortality rate of 34%. The odds ratio of short-term mortality was significantly higher in studies that screened patients conditionally than in studies that screened all hip fracture patients. This suggests mortality prognostication should consider how COVID-19 infection was identified as asymptomatic patients may fare slightly better.

Keywords COVID-19 · SARS-CoV-2 · Hip fracture · Mortality

Introduction

Coronavirus disease 2019 (COVID-19), caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is an international public health emergency. As of December 11, 2020, over 69.6 million cases and approximately 1.58 million deaths have been reported worldwide [1]. Policies to limit its spread have included physical

distancing and lockdown measures. The current literature identifies certain groups at high risk of poor COVID-19 outcomes, but data are lacking for some groups, particularly COVID-positive hip fracture patients (CPHFPs).

Hip fractures are the most common traumatic fracture [2]. In the USA alone, they account for 300,000 annual hospitalizations in patients ≥ 65 [3]. Emerging data shows that during the COVID-19 pandemic, hip fracture incidence has not significantly decreased [4]. This may be attributable to mechanism: 95% of hip fractures result from low-energy traumas mostly occurring in the home [3, 4]. A recent systematic review of 984 hip fracture patients managed during the COVID-19 pandemic revealed a COVID-19 prevalence of 9% [2]. Patients who sustain hip fractures are often elderly with a high comorbidity burden, increasing risk of poor COVID-19 outcomes [5–12]. Overlapping inflammatory responses between orthopedic injury and SARS-CoV-2 infection may also contribute

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to poor outcomes [13–15]. Several studies have shown COVID-positive status in hip fracture patients to be associated with increased 30-day mortality [2, 12]. However, the current literature is limited to a small number of retrospective studies conducted during the early phase of the pandemic. The clinical pathways adopted for patient care among these early studies differed considerably. Some of these differences were a result of necessity secondary to limited availability of diagnostic tests during the health-care crisis created by SARS-CoV-2. Screening capacity in particular varied between medical centers, enabling some to screen all admissions and some to screen only select admissions. Furthermore, it is unknown whether mortality outcomes differed by COVID-19 screening protocol. Given the prevalence and susceptibility of CPHFPs, it is important to understand their surgical outcomes so that providers may more accurately risk stratify and counsel patients and family members. Therefore, the primary aims of this study were to systematically review and meta-analyze: (1) short-term postoperative (30-day) mortality rates in CPHFPs and (2) to explore the association of COVID-positive status with short-term postoperative hip fracture mortality. In both analyses, we explored effects by screening protocol to understand whether the method of patient identification affected mortality prognostication.

Materials and methods

The present systematic review was conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [16].

Search strategy

To identify articles of interest, PubMed, Cochrane Central Database, and EMBASE were searched by two authors independently with “covid AND fracture” with no search filters. Databases were last accessed December 8, 2020. Review of selected article bibliographies was also performed.

Eligibility criteria

Articles included were those that (1) reported on ≥ 10 CPHFPs, (2) reported a primary outcome of mortality, (3) were available in English, and (4) were available in full-text. Articles excluded were those that (1) evaluated non-original data, (2) did not evaluate our target population (e.g., pediatric studies and non-human studies), and (3) evaluated only COVID-negative or COVID-unknown patients.

Quality assessment

Risk of bias assessment for individual articles was performed using the Methodological Index for Non-Randomized Studies (MINORS) criteria [17].

Data extraction

Data extraction on systematic review of qualifying articles was performed by multiple authors and included study design, study location, total number of hip fracture patients (hip fracture as defined by OTA type 31 fracture) [18], operative versus conservative management, COVID-19 screening protocol, COVID-19 screening method, time to surgery, age, follow-up period, clinical presentation, and mortality. We dichotomized COVID-19 screening protocols as either “all patients screened” or “patients screened conditionally.” Regarding clinical presentation, we systematically reviewed for COVID-19 status, time of positive COVID-19 screen (on or after admission), and symptomatology on admission. For the purposes of the present review, patients who recorded only negative COVID-19 screening results for the duration of the study, or who were not tested due to lack of suspicion, were considered COVID-negative. Patients who recorded positive COVID-19 screening results or who were reported to have clinical pictures attributable to COVID-19 alongside absent screening results (presumed positive patients) were considered COVID-positive. We only extracted comparison group data on operatively treated COVID-negative hip fracture patients if treated during the same time period as the study group (CPHFPs). Data reported on historical cohorts, nonoperative COVID-positive or negative hip fractures, or non-hip fractures were ignored. The primary outcome of interest in this review was short-term postoperative mortality.

Analysis

Due to methodological and reporting differences, short-term mortality rates in operatively managed CPHFPs, expressed as a proportion, and associations between COVID-19 status and mortality at the study level, expressed as an odds ratio of mortality, were meta-analyzed using a random effects model. An overall estimate for each outcome and estimates stratified by screening approach were obtained with stratified estimates compared using the Q test. All sub-group analyses were pre-specified. The decision to use a more conservative random effects model was made independent of empirical estimates of heterogeneity which were assessed using I^2 and its 95% confidence interval. Confidence intervals at the 95% level were calculated for all meta-effect estimates. Funnel

plots were used to visually inspect for evidence of publication bias for both short-term mortality rates and the association between COVID-19 positive status and short-term mortality. No adjustment was made for multiple hypothesis testing. An alpha threshold of 0.05 was used to define statistical significance. All analyses were performed using R 3.3.1 (Microsoft, Seattle, WA).

Results

Search results

Our search returned 253 articles on PubMed published from December 2019 to December 2020, one article on Cochrane published in October 2018, and 308 articles on EMBASE all published in 2020. After discarding duplicates, screening for inclusion criteria, and applying exclusion criteria, 19 articles

were selected for qualitative analysis [7–11, 19–32] and 17 for quantitative analysis (Fig. 1) [7–11, 19–29, 31]. Review of selected bibliographies did not yield additional articles. Studies excluded for reporting on < 10 CPHFPs included seven single patient case studies and 15 case series, constituting 63 excluded CPHFPs.

Included articles

Study characteristics are summarized in Table 1. Fourteen retrospective [7, 9–11, 19, 21, 22, 24–28, 30, 32] and four prospective studies [8, 20, 29, 31] were identified. Study design was not specified for one article [23]. Fourteen studies reported data on a contemporary COVID-negative hip fracture group [8–11, 19, 24–32]. All 19 studies combined for a sample size of 3001 hip fracture patients with a mean age of 81.4 (range 41 to 1–101) years [7–11, 19–32]. Six studies reported only on operative patients [10, 21, 24, 27,

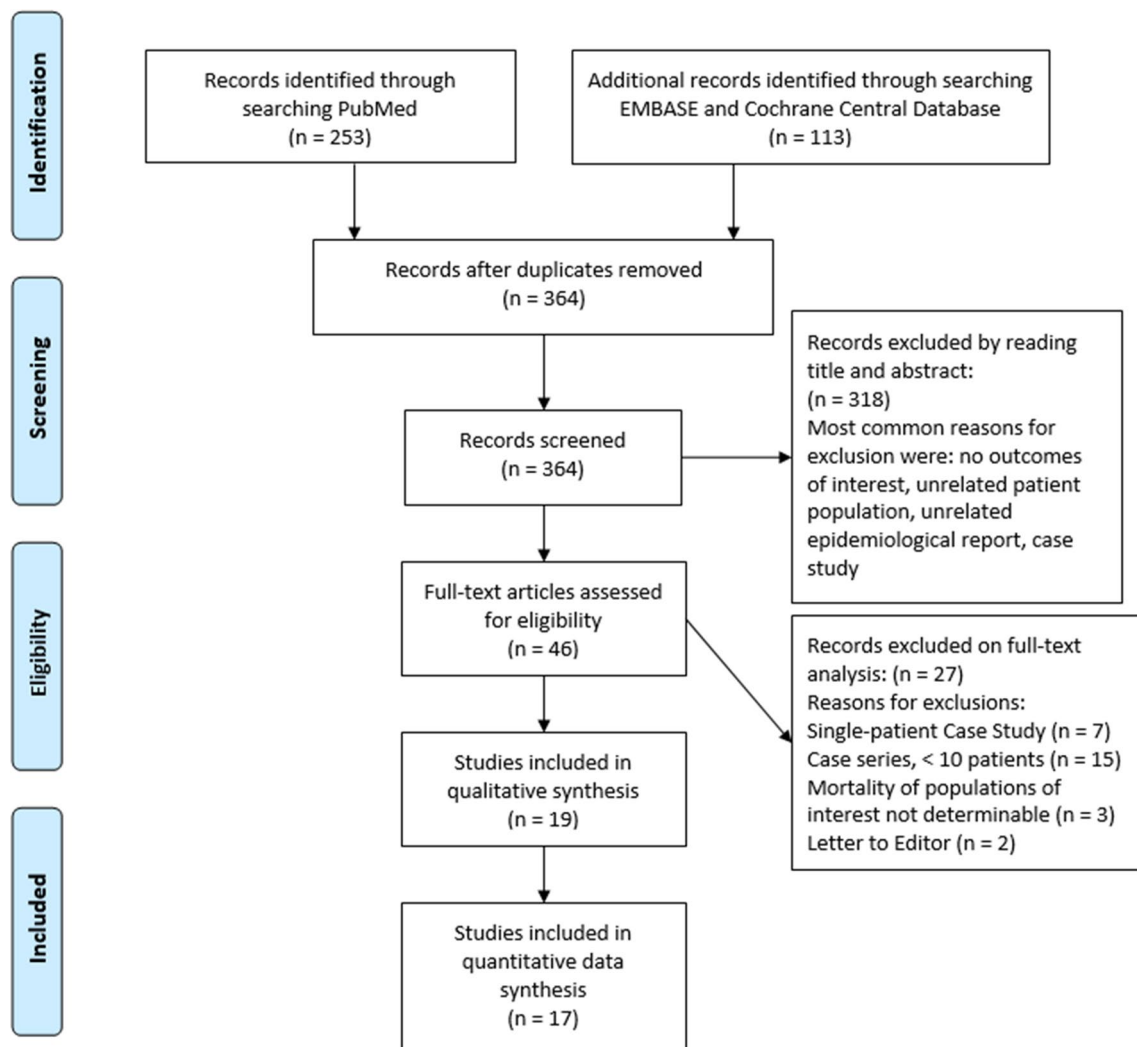


Fig. 1 Prisma flowchart

Table 1 Study characteristics

Study	Location	Design	Total no. of hip fracture patients	Screening protocol	Mean delay to surgery (h)	Age (range) (year)	Follow-up (days)
Arafa et al. [19]	United Kingdom	Retrospective	97	Conditional	28.3	83.7 (60 to 99)	30
Catellani et al. [20]	Italy	Prospective	16	All Patients	Not reported	84.3 (74 to 90)	Inpatient
Cheung et al. [21]	United States	Retrospective	10	All Patients	Not reported	79.9 (67 to 90)	Inpatient
De et al. [22]	United Kingdom	Retrospective	34	Conditional	49.6	85.9	30
Dupley et al. [7]	United Kingdom	Retrospective	64	Conditional	Not reported	83 (46 to 100)	45
Egol et al. [8]	United States	Prospective	138	Conditional	33.6	83	30
Hall et al. [9]	United Kingdom	Retrospective	317	Conditional	Not reported	80.7 (50 to 101)	30 (minimum)
Jannelli et al. [23]	Italy	Not Specified ^a	10	Conditional	Not reported	85.6 (77 to 94)	30
Karayianis et al. [24]	United Kingdom	Retrospective	203	Not Specified	Not reported	81.3 (49 to 99)	30
Kayani et al. [10]	United Kingdom	Retrospective	422	All Patients	Not reported	72.5	30 (minimum)
LeBrun et al. [11]	United States	Retrospective	59	Conditional	22.8	85 (65 to 100)	Inpatient
Macey et al. [25]	United Kingdom	Retrospective	76	Conditional	27	83	30
Mamarelis et al. [26]	United Kingdom	Retrospective	37	All Patients	33.9	80.3 (47 to 99)	30
Maniscalco et al. [27]	Italy	Retrospective	121	Conditional	Not reported	81.8 (41 to 99)	21
Munoz et al. [28]	Spain	Retrospective	136	Conditional	57.6	85.3 (65 to 101)	14
Narang et al. [29]	United Kingdom	Prospective	682	Conditional	Not reported	83.4	30
Rasidovic et al. [30]	United Kingdom	Mixed ^b	404 ^c	Conditional	35.0	83.5	30
Thakrar et al. [31]	United Kingdom	Prospective	43	Conditional	51.2	81.6 (54 to 100)	30
Ward et al. [32]	United Kingdom	Retrospective	132	All Patients	Not reported	82.1 (49 to 100)	30

^aNot specified as retrospective nor prospective

^bMulticenter trial wherein some centers analyzed data retrospectively and some prospectively

^c3/404 patients were missing management data and were excluded from further analysis

29, 31], while the remaining 13 studies reported on both operative and nonoperative patients [7–9, 11, 19, 20, 22, 23, 25, 26, 28, 30, 32]. Five studies reported screening all admitted patients for COVID-19 [10, 20, 21, 26, 32], and 13 studies reported conditional COVID-19 screening [7–9, 11, 19, 22, 23, 25, 27–31]. Screening protocol was not specified for one article [24]. While screening methods for COVID-19 patients varied, all studies employed real-time reverse transcriptase polymerase chain reaction (rRT-PCR) assays of respiratory swabs for some or all COVID-19 screenings [7–11, 19–32]; some studies used imaging and/or clinical judgment instead of (or to supplement) rRT-PCR for diagnosis [8, 11, 19, 20, 23, 24, 26, 27, 30, 32]. Data on time of positive COVID-19 screen and symptomatology on admission were variably reported; thus, it was not summarized herein. The quality of included articles was moderate (see Table, Supplemental Content 1, which contains full MINORS scoring). The average MINORS scores were 9.8 and 18.6 for non-comparative and comparative studies, respectively.

Outcomes

Table 2 summarizes patient mortality for each article stratified by management and COVID-19 status. The meta-effect estimate for short-term mortality in operatively managed CPHFPs ($n=466$) was 34% (95% C.I., 30–39%) (Fig. 2). The I^2 heterogeneity statistic was 0% (95% C.I., 0–46.5%). While there were a limited number of studies within each screening group, the short-term mortality in studies that screened all patients ($n=4$; 113 patients) was 30% (95% C.I., 22%–39%) compared to 36% (95% C.I., 31–42%) in studies that screened patients conditionally ($n=12$; 332 patients), though this difference was not statistically significant ($P=0.22$).

For studies that reported both COVID-positive and negative patients, the meta-effect estimate for the association between COVID-19 positive status and short-term mortality in operatively managed hip fracture patients was an odds ratio of 7.16 (95% C.I., 4.99–10.27) (Fig. 3). The I^2 heterogeneity statistic was 13% (95% C.I., 0–54%). The

Table 2 Mortality by management and COVID-19 status

Study	Operative cohort					Nonoperative cohort		
	Total	COVID+	COVID+ Mortality (%)	COVID-	COVID- Mortality (%)	Total	COVID+	COVID-
Arafa et al. [19]	94	17	29.41%	77	7.79%	3	2	1
Catellani et al. [20]	13	13	30.77%	0		3	3	0
Cheung et al. [21]	10	10	10.00%	0		0	0	0
De et al. [22]	33	33	39.39%	0		1	1	0
Dupley et al. [7]	58	58	44.83%	0		6	6	0
Egol et al. [8]	134	27	33.33%	107	5.61%	4	4	0
Hall et al. [9]	303	25	28.00%	278	6.83%	14	2	12
Jannelli et al. [23]	8	8	25.00%	0		2	2	0
Karayiannis et al. [24]	203	21	19.05%	182	1.65%	0	0	0
Kayani et al. [10]	422	82	30.49%	340	10.29%	0	0	0
LeBrun et al. [11]	57	8	50.00%	49	2.04%	2	2	0
Macey et al. [25]	73	10	20.00%	63	^a	3	0	3
Mamarelis et al. [26]	31	8	37.50%	23	4.35%	6	3	3
Maniscalco et al. [27]	121	32	43.75%	89	3.37%	0	0	0
Munoz et al. [28]	124	15	13.33%	109	2.75%	12	8	4
Narang et al. [29]	682	86	34.88%	596	6.04%	0	0	0
Rasidovic et al. [30]	391	109	^a	282	^a	10	5	5
Thakrar et al. [31]	43	13	38.46%	30	6.67%	0	0	0
Ward et al. [32]	127	45	^a	82	^a	5	1	4
Totals	2927	620		2307		71	39	32

COVID-19 Coronavirus Disease of 2019

^aGroup-specific mortality unspecified

Fig. 2 Forest plot showing postoperative CPHFP mortality in the short-term stratified by screening protocol

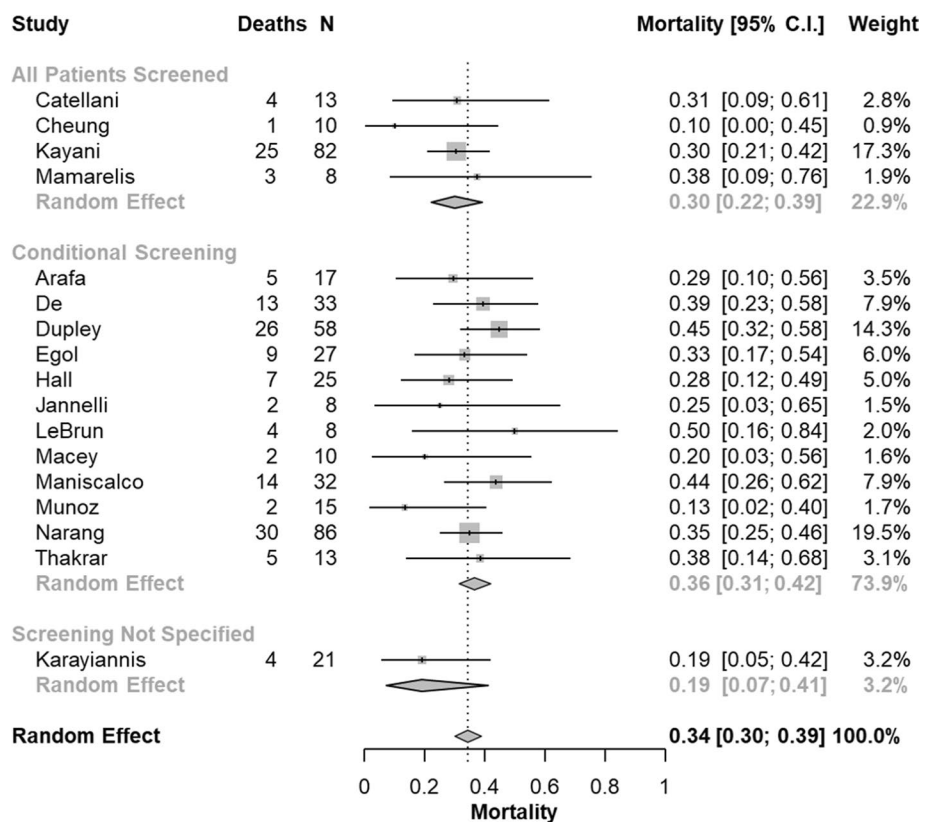
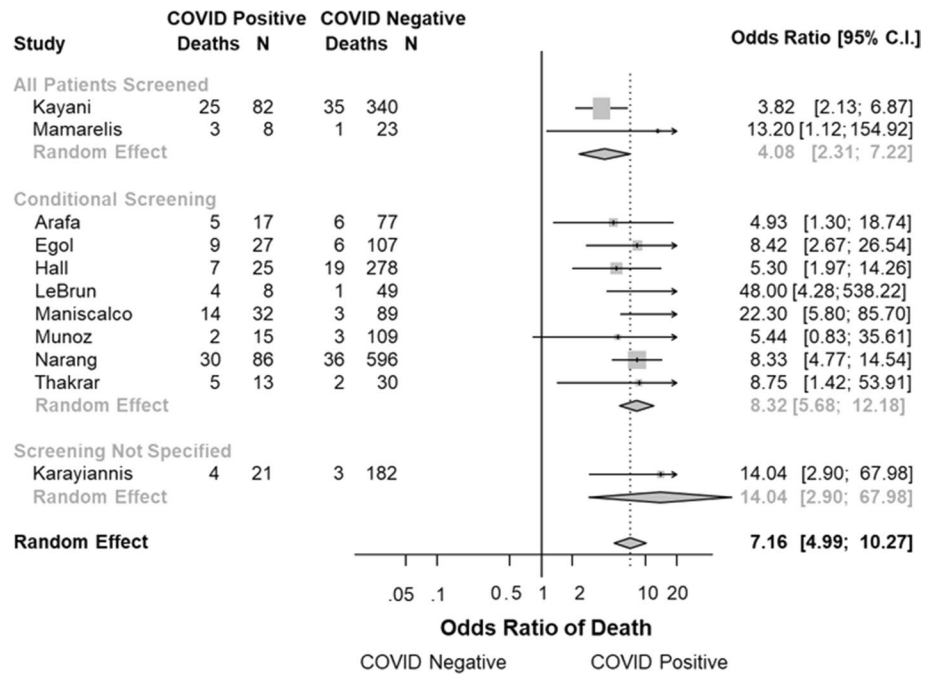


Fig. 3 Forest plot comparing postoperative CPHFP mortality to postoperative COVID-negative hip fracture patient mortality in the short-term stratified by screening protocol



association between COVID-19 positive status and short-term mortality in studies screening patients conditionally ($n=8$; 223 patients) produced an odds ratio of 8.32 (95% C.I., 5.68–12.18), which was higher than the odds ratio produced by studies that screened all patients ($n=2$; 90 patients) of 4.08 (95% C.I., 2.31–7.22). This difference was statistically significant ($P=0.04$).

There was no evidence of publication bias upon review of the funnel plots; though for short-term mortality, there were a few observations with higher mortality and larger standard error that were not completely balanced (Fig. 4). In

the two studies excluded from all meta-analyses, we could not extract discrete mortality rates for operatively managed CPHFPs [30, 32]. The two studies reported overall CPHFP mortality rates of 32.5 and 37.0% [30, 32].

Discussion

Our systematic review and meta-analysis of 17 studies ($n=466$ operative CPHFPs) revealed a sevenfold increase in 30-day postoperative mortality rate of CPHFPs compared

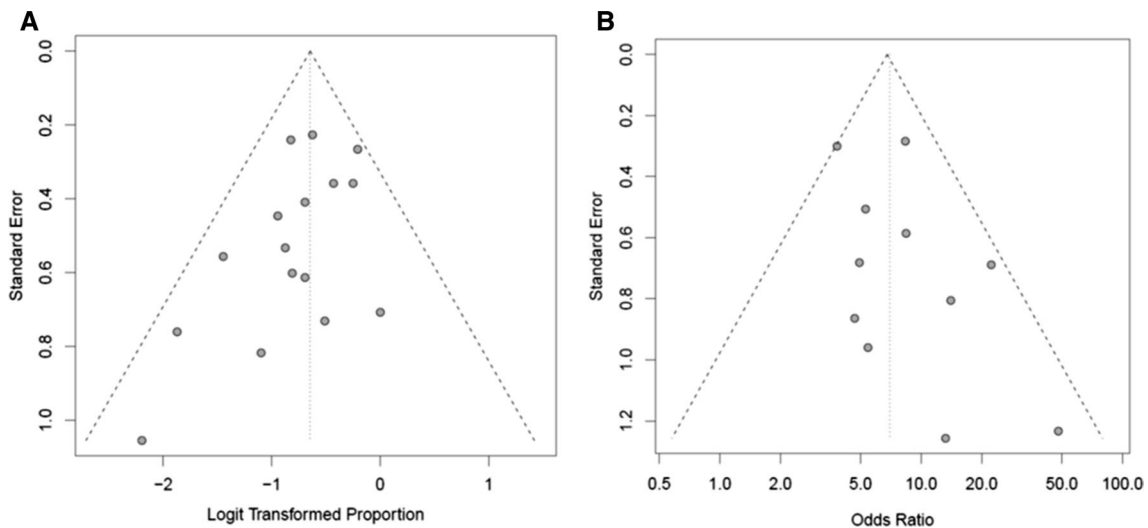


Fig. 4 Funnel plots **a** logit transformed proportion and **b** odds ratio

to operative COVID-negative hip fracture contemporary control. Overall, the short-term mortality rate of operative CPHFPs was approximately 34%. To our knowledge, the present review is the first to report CPHFP postoperative mortality by COVID-19 screening protocol. We are also the first to report on the association between COVID-19 positive status and short-term hip fracture mortality with contemporary control based on screening protocol. We attempted this to make our observations more germane to the prognosis, counseling, and management of CPHFPs. We also believe this sub-analysis to be the first attempt to objectively investigate the association between degree of CPHFP symptomatology and risk of mortality, albeit an indirect investigation with more research required. Finally, we attempted to mitigate the effect of outliers on our data set by excluding studies reporting < 10 CPHFPs, and the funnel plots generated represent no obvious concern for publication bias.

The present review has limitations. First, although we identified 19 clinical studies analyzing ≥ 10 CPHFPs, mortality rates among operatively managed CPHFPs ranged from 10.0 to 50.0% [7–11, 19–32]. Only three studies reported overall mortality rates less than 20.0% [21, 24, 28]. Cheung et al. [21] reported on a 10-patient cohort of CPHFPs, eight of whom were asymptomatic on presentation. They reported an inpatient mortality rate of only 10.0%, remarking that the mild nature of presentation could have contributed to their low mortality rate [21]. Concerning Munoz et al. [28], their follow-up period was shorter than most included studies at 14 days. Additionally, the mortality rates for the COVID-negative hip fracture controls in the Munoz et al. [28] and Karayiannis et al. [24] studies were two of the three lowest in this review, suggesting potentially broad confounding factors at play. Second, our data set exhibited a large range of sample sizes, though most were relatively small, particularly in some stratified analyses. Additionally, an inordinate number of patients was captured from studies in the United Kingdom (353/466 operative CPHFPs), limiting external validity. Third, designating some studies as having “conditional” screening protocols creates a heterogeneous group with wide-ranging protocols. Fourth, some operatively managed patients included in the CPHFP group were “presumed positive,” or those patients who were deemed COVID-positive on the basis on clinical judgment despite absent screening results. While a potential confounder, we reasoned that counseling a “presumed positive” hip fracture patient as a CPHFP would be more appropriate than counseling them as COVID-negative hip fracture patient if indeed symptomatology is a key outcome determinant. Fifth, as previously stated, most of the currently available literature is retrospective and characterized by broad heterogeneity in terms of patient treatment, data collection, and data reporting. One data category to be noted is follow-up period. Among the patients included in

this review, 78/466 operative CPHFPs were followed for less than 30 days. This may have contributed to underestimated mortality rate reporting. On the other hand, 58/466 operative CPHFPs patients included in this study were followed for 45 days. No trial or prospective data are available, and it is likely that the studies published thus far, and included in this review, will be the best available data to help guide future studies on this subject.

Nonetheless, our findings support a significantly higher early mortality with CPHFPs. Historical 30-day postoperative mortality rates for hip fractures in the elderly range from 5 to 7%, rising to 15.6% in nonagenarians and 20.7% in centenarians [33]. Even one-year mortality rates for hip fracture patients are estimated to be lower than our findings at 30% [21]. Moreover, the CPHFP mortality rates we observed are worse than those of COVID-19 patients with no reported comorbidities (0.9% mortality), COVID-19 patients overall (2.3% mortality), or COVID-19 patients aged ≥ 80 years (up to 30% mortality) [12]. Our findings corroborate those reported in a recent, smaller meta-analysis wherein the authors found an early postoperative CPHFP mortality rate of 32.6% in a sample of 365 patients [12]. The authors noted CPHFP mortality rates are more severe than those associated with hip fracture or COVID-19 alone, concluding that COVID-19 may exhibit an effect modification on the risk of mortality in hip fracture patients [12].

Our analysis of CPHFP mortality did not identify significant differences based upon screening protocols. It should be noted that, should a significant difference actually exist, our small sample size may have been underpowered for detection. Among the 11 studies that reported a control group of contemporary COVID-negative hip fracture patients, CPHFPs demonstrated an odds ratio of mortality of 7.16 (95% C.I., 4.99–10.27). This result is similar to previous meta-analyses, which have reported relative risk ratios for CPHFPs versus contemporary COVID-negative hip fracture patients of 7.45 and 5.66 [2, 12]. Interestingly, when stratified by screening protocol, the odds ratios of mortality among studies that screened all patients ($n=2$; combined sample size of 90) and those that screened patients conditionally ($n=8$; combined sample size of 223) were 4.08 (95% C.I., 2.31–7.22) and 8.32 (95% C.I., 5.68–12.18), respectively. This difference was statistically significant ($P=0.04$). This observation lends credence to the theory that CPHFPs who are asymptomatic or minimally symptomatic of COVID-19 on admission may demonstrate lower rates of mortality compared to more severely symptomatic patients. If this were true, then capturing and grouping asymptomatic or minimally symptomatic CPHFPs with more symptomatic CPHFPs (as in studies that screened all patients) would decrease the overall mortality rate of the CPHFP group, as we have potentially observed. Indeed, some individual findings among studies included suggest potentially lower rates

of mortality among asymptomatic CPHFPs. As previously stated, Cheung et al. [21] reported a 10.0% mortality rate among 10 CPHFPs, eight of whom were asymptomatic on presentation. Conversely, Maniscalco et al. [27] reported nine deaths among 19 CPHFPs who were symptomatic on admission versus two asymptomatic CPHFPs who both survived through follow-up.

One potential reason underlying the poor CPHFP outcomes we report may be the overlapping pathophysiological mechanisms between orthopedic injury and SARS-CoV-2 infection [13–15]. SARS-CoV-2 infection causes an uncontrolled immune response leading to cytokine release syndrome (CRS) and potentially acute respiratory distress syndrome [34–36]. These circumstances can be exacerbated by fracture itself and any additional surgical insult, the latter of which can be a detrimental “second hit” [13, 37]. If this is the case, we might expect COVID-positive patients with other orthopedic injuries to also tolerate surgery poorly, and there is some literature to support this theory. For example, the COVIDSurg Collaborative, an observational cohort study of 1128 COVID-19 patients undergoing surgery of any kind (26.8% were orthopedic), reported an overall 30-day mortality rate of 23.8% (28.8% for orthopedic surgeries) [38]. In a matched cohort study of 41 COVID-19 patients undergoing different types of surgeries (53.7% underwent orthopedic surgeries), Doglietto et al. [39] reported a 30-day mortality of 19.5 versus 2.44% in the control group (COVID-negative surgical patients). In sum, CPHFPs present at the intersection of multiple jeopardizing factors: they face three potentiators of CRS (COVID-19, fracture, and orthopedic surgery) [13, 37]. Additionally, they are an elderly population with a high comorbidity burden [5–11, 13, 31, 37].

While it is reasonable to regard CPHFPs as a susceptible group, questions still remain. For example, while there is some evidence in the present review that the severity of COVID-19 symptoms on admission may have an association with mortality, this information was rarely reported. Thus, we are unable to draw strong conclusions. Questions also remain about outcomes aside from mortality, such as rates of venous thromboembolism and optimal prophylactic regimens. Given the continued prevalence of hip fractures amid the pandemic, we believe that undertaking more prospective research concerning CPHFP surgical outcomes could furnish relevant data and insight.

Conclusions

Our findings suggest that COVID-positive hip fracture patients have a sevenfold increased risk (34%) of 30-day postoperative mortality. Screening all patients led to decreased mortality risk. This suggests mortality prognostication should consider how COVID-19 infection was

identified as asymptomatic patients may fare slightly better. Undertaking larger scale prospective studies could provide valuable data for evidence-based management of this population.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s00590-022-03228-9>.

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Declarations

Conflict of interest The authors have no competing interests to declare that are relevant to the content of this article. Postoperative Mortality in the COVID-Positive Hip Fracture Patient, a Systematic Review and Meta-Analysis.

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