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Mortality escalates in patients of proximal femoral fractures with COVID-19: A systematic review and meta-analysis of 35 studies on 4255 patients

Mohit Kumar Patralekh [a], Vijay Kumar Jain [b, *], Karthikeyan P. Iyengar [c], Gaurav Kumar Upadhyaya [d], Raju Vaishya [e]

[a] Department of Orthopaedics, Vardhman Mahavir Medical College and Safdarjung Hospital, New Delhi, 110 029, India
[b] Department of Orthopaedics, Atal Bihari Vajpayee Institute of Medical Sciences, Dr Ram Manohar Lohia Hospital, New Delhi, 110001, India
[c] Trauma and Orthopaedic Surgeon, Southport and Ormskirk NHS Trust, Southport, PR8 6PN, UK
[d] Department of Orthopaedics, All India Institute of Medical Sciences, Rae Bareli, UP, India
[e] Department of Orthopaedics, Indraprastha Apollo Hospital, Sarita Vihar, Mathura Road, 110076, New Delhi, India

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ABSTRACT

Background: Concerns have been raised about the escalated mortality in patients of proximal femoral fractures (PPFs) with COVID-19. A meta-analysis to evaluate the mortality in patients with PPFs managed during the current COVID-19 pandemic was conducted.

Methods: A systematic review and meta-analysis of all published studies were conducted with a search on PubMed, Scopus, Web of Science, and Cochrane Library databases using appropriate keywords from January 01, 2020 to January 29, 2021.

Results: 35 relevant studies reporting 4255 patients with hip fracture in the current ongoing pandemic, out of which 692 patients were COVID-19 positive. Twenty studies reported mortality and other relevant statistics on hip fracture patients with and without COVID-19 (4123 hip fracture patients in the year 2020 −21, out of which 560 had or were suspected of having COVID -19). A meta-analysis of mortality statistics in patients with and without COVID revealed increased odds of mortality among COVID patients [odds ratio (OR) 6.31, 95% confidence interval (CI) [5.09, 7.83] and meta-analysis on the subgroup of surgically treated patients also showed markedly increased mortality risk among those with COVID-19 (OR) 5.99, 95% CI [3.88,9.24].

Conclusion: The mortality risk is markedly increased in hip fracture with concomitant COVID-19 as compared to those without it. This increased risk persisted in those managed surgically. It could be due to the inflammation induced by the fracture or surgery for fracture fixation, further exacerbating inflammation, leading to cytokine storm. It is imperative that such patients are informed regarding increased mortality risk during the consent and shared decision-making process.

1. Introduction

The novel Coronavirus SARS-CoV-2 outbreak started in Wuhan, China, in December 2019, spread globally and has been declared a pandemic by the World Health Organisation on 11th March 2,020.[1] Since the novel Coronavirus SARS-CoV-2 outbreak is highly contagious; managing acute trauma and orthopedics had to be rationalized and re-organized to avoid viral transmission and provide a continuity of care.[2] Management of patients with acute orthopedic trauma during the COVID-19 pandemic has been guided by national governments' recommendations and specialist orthopedic associations.[3–5]

Fragility hip fractures in the elderly are obligatory injuries that require prompt surgical management to allow immediate post-operative full weight-bearing mobilization supported by a multi-

* Corresponding author. Department of Orthopaedics, Atal Bihari Vajpayee Institute of Medical Sciences Dr. Ram Manohar Lohia Hospital New Delhi, 110001, India.
E-mail addresses: mohit_patralekh@yahoo.in (M.K. Patralekh), drvijayortho@gmail.com (V.K. Jain), kartikp31@hotmail.com (K.P. Iyengar), drgkupadhyaya@yahoo.in (G.K. Upadhyaya), raju.vaishya@gmail.com (R. Vaishya).

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disciplinary team to expedite rehabilitation and early supported discharge.[1] The management of proximal femoral fractures (PFF) is still a surgical priority now, with an additional risk factor of COVID-19.[2–4]

Traditionally the 30-day mortality rate in patients with PFF has been reported to be 5%–8%.[1] However, early limited evidence published so far suggests poor outcomes with high postoperative mortality in patients with a hip fracture and concomitant COVID-19 infection (available studies indicate a mortality rate greater than 30%).[5–73] We have undertaken a systematic review and metanalysis to evaluate the impact of COVID-19 on patients with PFF and assessed associated mortality.

2. Material and methods

The protocol for this systematic review has been preregistered on PROSPERO and bears the number CRD42020194409.

Eligibility criteria: We identified studies that met the following criteria.

2.1 Population: patients who sustained a proximal femoral fracture (PFF) in the context of COVID-19 or articles focussed on this topic.

2.2 Intervention: Replacement arthroplasty for intracapsular fractures. Compression hip screw or intramedullary fixation of the trochanteric or subtrochanteric fractures or nonoperative treatment.

2.3 Exclusion criteria: Fracture shaft and distal femur, fracture acetabulum, hip dislocation, revision hip arthroplasty, articles not published in peer-reviewed journals, articles published in other languages were also excluded.

2.1Information sources, literature search, study identification, and search

A systematic search of the PubMed, Scopus, Web of Science, and Cochrane Library databases was performed from January 01, 2020 to January 29, 2021. The keywords used were ('COVID-19' OR 'Coronavirus') AND ('trauma*' OR 'fracture') AND ('hip' OR 'proximal femur' OR 'neck femur' OR 'neck of femur' OR 'femoral neck' OR 'intertrochanteric' OR 'subtrochanteric'). We aimed to identify relevant articles reporting PFF during the COVID-19 pandemic. Reference lists of articles were also screened. A general internet search was undertaken for more relevant papers. We also have hand-searched popular premier Asian orthopedic journals publishing COVID-related papers (e.g., IJO, JCOT, ABJS) and general medical journals (JAMA, Lancet) to avoid missing any article. Any editorials, opinions, and reviews were considered for qualitative summarization. We excluded articles reporting on non-orthopedic injuries.

Data extraction: Two authors (MKP and VKJ) individually performed the searches, screen the titles and or abstracts, and assessed them. The full text of the potentially eligible studies was independently assessed. Any disagreement was resolved by consultation with the third author (KPI).

Statistical Analysis: We prepared tables to present a narrative synthesis of the findings from the included studies. The descriptive data regarding patient characteristics available from all studies were summarized in tabulated form. Studies reporting data only on COVID -19 patients were analyzed separately. Median (range) was used to summarize the data for continuous variables and frequency/percentage for categorical variables, and appropriate graphics were used for data depiction. Microsoft Excel version 2016 (Windows) was used for analysis.

Meta-analysis on mortality statistics was performed explicitly on studies reporting data on both COVID-19 confirmed/suspect and Non-COVID-19 patients with hip fractures. Study quality of individual studies was accessed using the Newcastle Ottawa scale, wherever applicable. A separate sensitivity analysis was undertaken considering the COVID-19 test positive versus COVID-19 test-negative patients, as reported in the parent studies. Subgroup analysis was also performed for surgically treated patients. We pooled the results using a random-effects meta-analysis (e.g., DerSimonian and Laird method) or fixed-effect meta-analysis as appropriate (A fixed-effects model was employed when $I^2<40\%$ and a random-effects model when $I^2 \geq 40\%$) and reported odds ratio for mortality in hip fracture patients with and without COVID 19. Heterogeneity between the studies in effect measures was assessed using the Chi^2 and I^2 statistics. Suitable Forest plots and Funnel plots (to depict possible publication bias if we had at least ten studies) were generated. A two-sided P value < 0.05 was taken as statistically significant. RevMan software version 5.3. was used for all meta-analysis.

3. Results

3.1. Literature search

The systematic search yielded 132 articles on PubMed, 67 on Scopus (All Fields), and 73 on Web of Science. No extra papers were found in the Cochrane library (All Text). Five more papers were discovered on hand search. After screening duplicates and excluding unrelated articles based on the title, 65 papers[8–72] with 35 having hip fracture data were finally considered for review after full-text assessment. (Fig. 1, PRISMA flowchart).

Out of these fifteen relevant papers reporting hip fracture, patients with COVID-19 were considered qualitative summarization (Table 1). Twenty papers reported data on both COVID-19 and non-COVID -19 patients with hip fractures and were considered for meta-analysis of 30-day mortality statistics. Rest articles were opinion pieces (4), general epidemiological studies (16), Specialist society guideline (1)[23] infographic analysis (1), errata (2), and reviews (7).These 35 studies in total[8–18,22,24,25,27,28,30–33,41,42,44,51,52] reported a total of 4255 patients with hip fracture in the current ongoing pandemic, out of which 692 patients were positive for COVID -19 (Tables 1 and 2A and 2B).

Fifteen studies, reporting data separately for 158 patients (132 hip fracture patients) with COVID- 19 were summarized separately.[8–14,22,24,25,32,33,41,42,52](Table 1). Apart from these, 20 studies reported mortality and other relevant statistics on hip fracture patients with and without COVID -19 {reporting 4123 hip fracture patients in the year 2020–21, out of which 560 had or were suspected to be having COVID- 19}, but individual patient data was not reported.[15–18,27,28,30,31,44,51] (Tables 2A and 2B). Study quality of these was accessed using the Newcastle Ottawa scale (Table 3).

Vives et al. reported 136 (123 survived and 13 died) patients, among whom PCR for COVID-19 was done only 23 (16.91%) patients; they did not perform PCR test in the rest of the patients due to low suspicion.[15] They reported detailed data of the seven patients experiencing mortality.

Data from different countries: The majority of papers concerned with hip fractures and COVID-19 came from UK (14) and USA (6). It was followed by articles from Iran (3), Italy (3), China (3), Korea (2), France (2), and Spain (2).

Patient demographics: Among the 132 patients (covered in 15 studies reporting data on only COVID -19 fracture patients), the age range was 28 years–93+ years. There were 56 males and 76 females.

Diagnosis of COVID -19: In the 15 studies, diagnosis of COVID- 19

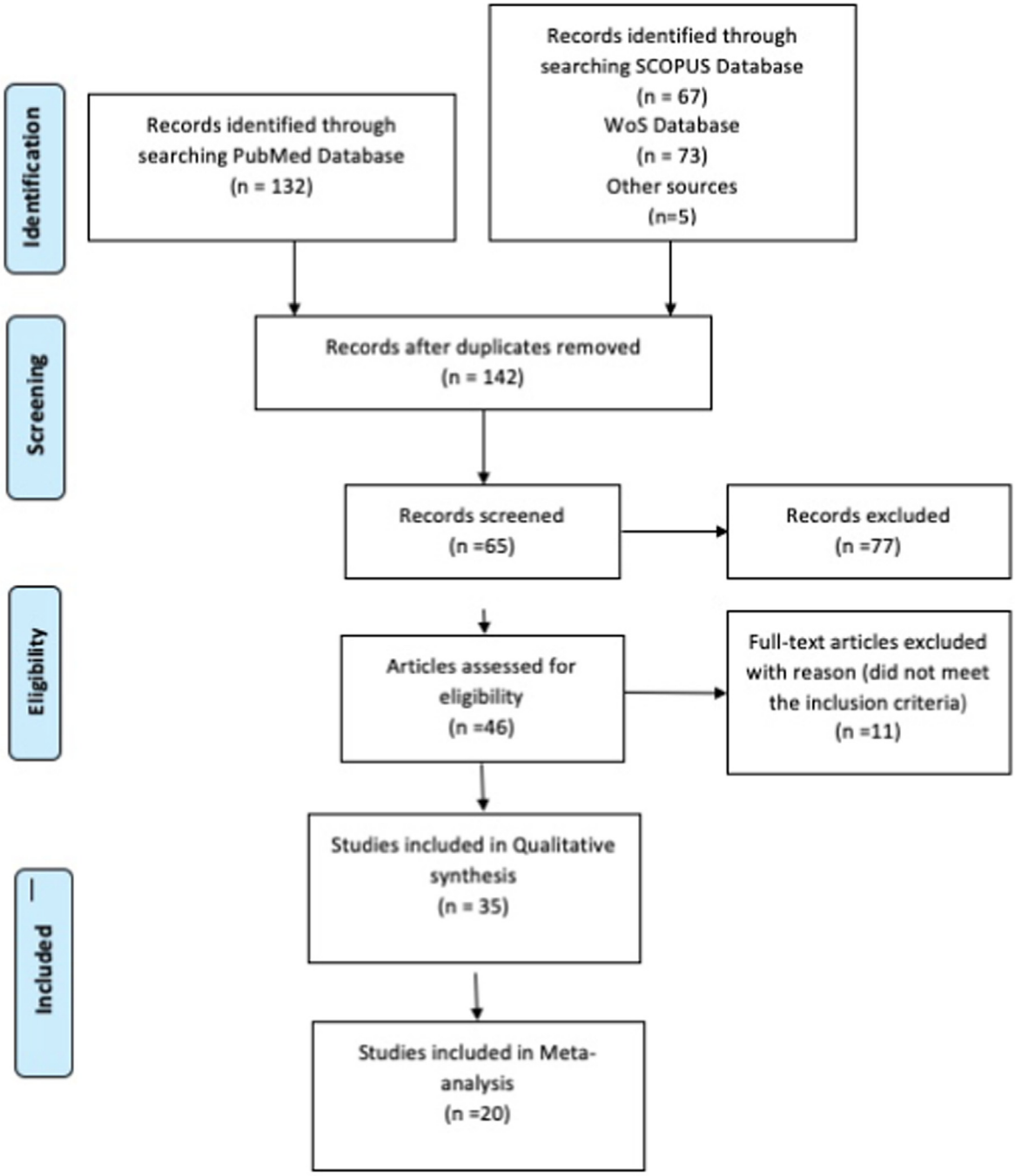

Fig. 1. PRISMA flowchart of the study selection process.

was established based on positive Computed Tomography scan (CT) or a chest radiograph findings in 32 patients, while 38 patients had a positive Reverse Transcription-Polymerase Chain Reaction (RT-PCR) test report. The RT-PCR availability was limited at several centers in the initial part of the pandemic; therefore, classical chest CT findings were used for COVID-19 diagnosis in most of these patients. However, these tests were positive in all the patients.

Comorbidities: Twenty-one patients were hypertensive, and 51 suffered cardiac disease. Forty had type 2 diabetes mellitus. These comorbidities have been reported as risk factors for mortality in COVID -19 patients in previous studies.[19] Obesity and Chronic Obstructive Pulmonary Disease (COPD) were also considered risk factors for mortality. Some studies also reported patients with prior stroke, Alzheimer's disease, kidney disease, hypothyroidism, asthma, and cancer (Table 1).

Surgery and nonoperative, conservative care: Out of 132 patients in the 15 studies which report only COVID-19 positive patients with associated PFF, the hip fractures were treated surgically in 116 patients (87.88%). The remaining 16 patients were managed non-operatively (due to comorbidities). All the authors have not explicitly mentioned the exact type of surgery, but in general, it was steered by the fracture morphology, patient comorbidity, and medical fitness. The surgery types varied from an internal fixation with cannulated screws and Dynamic Hip Screw (DHS), or

Table 1
Summary of studies reporting series on only COVID 19 positive fracture cases (with hip fracture patients).

S no	Author	Journal	No. of cases	Hip Fractures	Age (Range) OR Mean (SD)	Sex M/F	Mode of Injury	Country	Surgery/ Total patients	RT PCR+	CT Chest/ radiograph +	Mortality	Co morbidities	Antiviral Drug Treatment	Remarks
1	Mi B et al.[13]	JBJS Am	10	6	50–85	2/4	Low energy trauma 8, MVA-1, Fall-1	China	3/6	4	ALL	3 (50%)	HTN-3 DM-2 CAD-1 Alzheimer & Cirrhosis-1, Coinfections (candida, EBV, Coxsackievirus-1 each) Osteoporosis-2	Oseltamivir	All had fever and cough, 2 had sore throat and 2 had limited activity lymphopenia in 1, leukocytosis in 4
2	Catellani F et al.[14]	JBJS Am	16	16	74–90	10/6	Fall at home	Italy	13/16	16	14 +ve 2-ve	Before surgery 3 After surgery 4 (43.75%)	All had comorbidity HTN-10 DM-5 Cardiac disease 6 COPD CKD-2 BPH-2 Hepatitis C-1 Previous CVA-1 Mental issues 3 Obesity-1	HCQ 200 mg + Azithromycin 500 mg BD as per hospital protocol	Stabilization of respiratory parameters observed after surgery, due to improved patient comfort mobilization
3	Rabie H et al.[15]	ABJS	7	4	72–91	1/3	Simple fall	Iran	1/4	4	3	2 (50%)	Bladder cancer with metastasis 1 HTN, DM, cured breast cancer −1	No	Leukocytosis in 1, lymphopenia in 1
4	Shariraye MJ et al.[16]	ABJS	3	3	69–93	2/1	Fall from height	Iran	2/3	3	1	1 (33.3%)	NA	Oseltamivir and HCQ for all	PPE N95, 2 layers shield and gloves and waterproof clothes use for operated cases
5	Sadighi M et al.[17]	ABJS	13	3	28–81	3/0	High energy trauma (RTA)-2 Slipping-1	Iran	3/3	NA	3	0 (0%)	NA	NA	The interval period time between diagnosis of COVID-19 infection and surgery was 1–5 days. Before surgery, all patients have admitted to COVID-19 dedicated wards.
6	Song SK et al.[18]	Acta Orthopaedica	2	2	81–83	0/2	Fall-1 Fall from bed 1	Korea	2/2 (1-DHS + TSP 1-HA) DHS	2	1	0 (0%)	DM, CKD, COPD, atrial fibrillation, (Pacemaker was implanted in 2007 to treat sick sinus syndrome), mitral valve replacement surgery because of mitral valve stenosis 1, Prior femur nailing, HTN and dementia- 1	HCQ-1, Antivirals only (lopinavir + ritonavir)- 1	All surgical procedures were conducted in a negative-pressure operating room dedicated to patients with infectious diseases and located in a remote corner of the operating complex, with separate access. All equipment for surgery and anesthesia was prepared and covered with sterile drapes in advance of the patient entering the operating room. Biological isolation chambers with negative-pressure filtration systems were used to move the patients from the isolation ward to the operating room. Patients wore KF 94 face masks throughout the entire surgical procedure, except when they were intubated under general anesthesia.
7	Chung ZB et al.[19]	JOO	10	10	67–90	2/8	Low energy	USA	10/10	10 (3 nosocomial)	1 pre op	1 (10%)	All had multiple comorbidities HTN-7 DM-3 CAD-3 Malignancy (1 pancreatic + RCC,1 breast 0–2 Mental issues 3 Hypothyroid-3 Asthama-2	HCQ only-1, HCQ + azithromycin-3	5 cases had increases oxygen demand after surgery and 4 had prolonged stay. One had postoperative AKI that required treatment with intravenous fluids over several days.
8	Rizkallah M et al.[27]	Injury	12	4	82.52 −93.21	3/1	NA	France	3/4						

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Table 1 (*continued*)

S no	Author	Journal	No. of cases	Hip Fractures	Age (Range) OR Mean (SD)	Sex M/ F	Mode of Injury	Country	Surgery/ Total patients	RT PCR+	CT Chest/ radiograph +	Mortality	Co morbidities	Antiviral Drug Treatment	Remarks
										Infection was confirmed in all by RT-PCR/Chest CT. All had ASA grade 3; 3 cases were operated (one male patient was not operated due to high risk). All four of them expired later.(100%) (Letter to Editor)					
9										Dizdarevic, A.[29]	Journal of Clinical Anesthesia	3	2	76–89	0/2
	Fall (1)	USA	2/2	Hypertension, diabetes mellitus 2 (DM2) and atrial fibrillation on anticoagulation (1) diabetes mellitus 2 (DM2) (1), Both discharged (0%) Authors' recommendations: "Employ multidisciplinary planning with evidence-based approach Utilize preoperative testing with high level of clinical judgment Decide on appropriate timing of surgery given risk and severity of COVID-19 and underlying medical condition Use universal contact and droplet precautions, with aerosol whenever indicated Choose most optimal surgery and anesthesia technique, with regional anesthesia preferred over general Postoperative course may be further unpredictable with yet unknown morbidity and mortality"										
10	Dupley, L.[30]	EJOST	64	64	46–100	29/ 35	NA	UK	58	Comorbidity % (total) MI 11 (17) (Significant) CCF 14 (22) Dementia 27 (42) Cerebrovascular disease 10 (16) Chronic lung disease 12 (19) Diabetes 17 (27) Moderate or severe kidney disease 15 (23) Tumour 8 (13) •All diagnosed COVID 19 by antigen testing				
11	Liu, J.,[37]	Chinese Journal of Orthopedic Trauma	1	1	50	0/1	Fall	China	1	Diagnosed by CT imaging.Antiviral treatment: Alpha-interferon nebulized inhalation (5 million U/time, 2 mL water for injection nebulized inhalation, 2 times/d), ritonavir oral (50 mg per capsule, 2 capsules/time, 2 times/d Mortality 0%					
12	Luk MH[38]	JBJS CC	1	1	83	0/1	Fall	Hong Kong (*People's Republic of China*)	1	Diagnosed by RTPCR Comorbidities: dementia, diabetes, hyperlipidemia, and ischemic heart disease Mortlity 0%					
13	Morelli I[46]	JOSR	10	10	72–98	2/8	NA	Italy	10	8 nailing, 2 Hemiarthroplasty 4 patients developed systemic complications 2 died (20%)					
14	Muse IO[47]	Journal of Clinical Anesthesia	5	5	67–89	1/4	NA	USA	5	1 hemiarthoplasty (neck femur fracture) 4 nailings (pertrochanteric fractures) Multiple comorbidities Mortlity 0%					
15	Um SH[57]	CIOS	1	1	86	1/0	Fall	Korea	1	1 hemiarthroplasty Comorbidities: diabetes mellitus, chronic obstructive pulmonary disease, and Alzheimer's dementia Successful surgery and rehabilitation of patient. Staff safety ensured. Mortlity 0%					

Abbreviations: ABJS- Archives of bone and joint surgery; AKI- Acute Kidney Injury; ASA- American society of Anaesthesiologists classification; BPH- Benign prostate hyperplasia; CAD- Coronary artery disease; COPD- Chronic obstructive pulmonary disease; COVID-19 – Coronavirus disease 2019; CKD- Chronic kidney disease; CT- Computed Tomography scan; CVA- Cerebrovascular Accident; DHS- Dynamic hip screw surgery; DM- Diabetes Mellitus; EBV- Epstein Barr virus; F- Female; HCQ- Hydroxychloroquine; HTN- Hypertension; JBJS Am- Journal of Bone and joint surgery American; JOO- Journal of Orthopaedics; M-Male; MVA- Motor vehicle accident; NA- Not available; No.- Number; PPE N95- Personal protective equipment N95 mask; RCC- Renal cell carcinoma; RTA- Road Traffic Accident; RT PCR- Reverse Transcriptase Polymerase Chain Reaction; SD- Standard Deviation; TSP- Trochanteric stabilization plate; USA- United States of America.

Table 2A
Summary of studies reporting mortality and other relevant statistics on hip fracture patients with and without COVID 19.

Author	Journal	Noof cases	Hip Fractures	Age (Range) OR Mean (SD)	Sex M/F	Mode of Injury	Country	Surgery/Total patients	RT PCR+	CT Chest/radiograph +	Mortality
Vives JMM et al.[15]	JBJS Am	136	136	65–101	34/102	Low energy	Spain	124/136	23	NA	13 (9.6%) [7 RT PCR + ve (30.4%)], 12 non operative
Egol KE et al.[16]	JOT	138 recent {115 h historical (2019, same period)}	Same 138	83.0 ± 10.2	50/88	Low energy-136 High Velcity-2	USA	134/138	17	Not mentioned, 14 suspects who were negative on RT-PCR, but suspected clinic-radiologically	17 (12.3%) Inpatient: C + ve-6 (35.3%) C Susp-1 (7.1%) C -ve −1
LeBrun DG et al.[17]	JOT	59	59	C + ve-86.5 (7.9)) C-ve −84.7 (7.5	3/6 12/38	Fall from standing height 9 in C + ve and 49 in C -ve. Fall from Bicycle 1 in C -ve.	USA	57/59 Two C + ve cases had expired before surgery	9	22	9 (15.25%)
Maniscalco P et al.[18]	Acta Biomedica	121 Piacenza Hospital −61 Parma Hospital −60	121	41–99 55–97 41–99	32/121 16/45 16/44	NA	Italy	121/121	32 21 11	20 9 11	17 11 6 14/32 (43.75%) vs 3/89 (3.37%)
Kayani B et al.[28]	The Bone and Joint Journal	422 (340 C-ve and 82 C + ve)	422	NA	NA	NA	United Kingdom	NA	NA	NA	25/82 (30.49%), 35/340 (10.3%)
Fadulelmola, A. et al.[27]	Trauma	75 (55 C-ve and 20 C + ve)	75	NA	22/53 (15/40 c- 7/13group c+)	NA	United Kingdom	72/75	20	NA	4/55 (7.3%) vs 10/20 (50%)
Thakrar A et al.[31]	JOT	43 (study group), 51 group A, 48 group B,55, control group C	197	81.6 (study group), 81.6 (group A), 84 (group B), 81.5 (group C)	23/20 study group, 13/38 (group A), 12/36 (group B), 6/40 (group C)	NA	United Kingdom	Study group-43, Others NA	12	–	4/12 (33.33%) vs 3/31 (9.7%) [7 (4 were C + ve), 5 group A, 1 group B, 2.3 group C]
Narang, A et al.[44]	International Orthopaedics	682(C+86/C-596)	682	86/83	(32/53)/(169/424)	NA	UK	667/682 (All c + had surgery)	Antigen testing	Antigen testing	30/86 (34.9%) 36/596 (6%)
Stobi A et al.[51]	JCOT	94	94	83.526	NA	NA	UK	82	6 (TEST NOT MENTIONED)	6 (TEST NOT MENTIONED)	3/6 (50%) 6/88 (6.8%)
Konda SR et al.[30]	JOT	1278	136 current	81.6	NA	Low energy (defined as a fall from standing or from less than 2 stairs).	USA	1256/1278 (136 Treated during Covid 19 pandemic) October 2014 and April 2020	17	NA	11/31 (35.48%) vs 6/105 (5.7%)
Arafa M et al.[53]	BJO	157	157 (97 in the year 2020)	60-99 covid − 68-96 covid +	(21/57)/(9/10)	NA	UK	Six patients (two in COVID-positive, one in COVID-negative, and three in the 2019 group) were medically unfit for surgery and died preoperatively. Two patients in the 2020 group underwent conservative management, though they failed and needed surgery.	17	+2(False negative on PCR)	14/97 (14.43%) 7/19 (36.84%) vs 7/78 (8.97%)
Chui K et al.[54]	BJO	47	47	mean age COVID 86.8, range 79 −100 vs	‘COVID site’, five (42%) males and seven (58%) females COVID-free’ site, 23 (66%) males and 12 (34%) females	NA	UK		6	6	5/47 (10.6%) 3/12 (25%) vs 2/35 (5.7%)

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Table 2A (*continued*)

Author	Journal	Noof cases	Hip Fractures	Age (Range) OR Mean (SD)	Sex M/F	Mode of Injury	Country	Surgery/Total patients	RT PCR+	CT Chest/radiograph +	Mortality
				NON-COVID 78.5, range 37−96 years							
Clough TM et al.[55]	BJO	84	84	NA	covid + 4 males/3 females covid - 28 males/49 females	NA	UK	84	7	NA	5/84 (5.9%) 5/7 (71.4%) VS 0/77 (0%)
Macey ARM et al.[59]	BJO	76	76	83 (73–87)	58 M/18F	NA	UK	73/76	10	NA	11/76 (14.47%) 2/10 (20%) VS 9/66 (13.63%)
Segarra B et al.[60]	JOT	68	76	82	21 M/47F	NA	Spain	64/68	2	NA	8/68 (11.76%) ½ (50%) vs 7/66 (10.6%)
Hall AJ et al.[57]	BJJ	317	317	NA	NA	NA	Scotland	NA	NA (total 27)		33/317 (9/27 vs 24/290)
Clement ND et al.[56]	BJJ	1659 total	354	NA	NA	NA	UK	NA	NA (total 47)		67/354 (17/47 vs 50/307)
Hall AJ et al.[61]	BJJ	833	833	80 (50−103)	277 M/556F	NA	Scotland	NA	NA (total 78)		(27/78 vs 68/755)
Wignall A et al.[52]	JOSER	580 (276 in COVID period)	580 (276 in COVID period)	81.3 (11.2)	51.3:45.7	NA	UK	261/276	34/276		27/276 (13/34 vs 14/242)

Abbreviations: CAD- Coronary artery disease; CCS- Surgery with Cannulated cancellous screws; COPD- Chronic obstructive pulmonary disease; C + ve - Coronavirus disease 2019 positive; C susp- Coronavirus disease 2019 suspected; C-ve - Coronavirus disease 2019 negative; CKD- Chronic kidney disease; CT- Computed Tomography scan; CVA- Cerebrovascular accident; DHS- Dynamic hip screw surgery; DM- Diabetes Mellitus; F- Female; FN- Femoral neck fracture; GT- Greater trochanter fracture; HA- Hemiarthroplasty hip; HCQ- Hydroxychloroquine; HTN- Hypertension; ILN- Interlocking nail surgery; IT- Intertrochanteric fracture; JBJS Am- Journal of Bone and joint surgery American; JOT- Journal of Orthopedic Trauma; M-Male; NA- Not available; No.- Number; ORIF- Open reduction and internal fixation; PVD- Peripheral vascular disease; RTA- Road Traffic Accident; RT PCR- Reverse Transcriptase Polymerase Chain Reaction; SD- Standard Deviation; ST- Subtrochanteric fracture; THR- Total Hip Replacement; USA- United States of America.BJO-Bone and Joint Open, JOSER-Journal of Orthopedic Surgery and Research.

Total fractures: Neck femur/intracapsular- Pertrochanteric/extracapsular-.

prosthetic replacement using hemi or total hip arthroplasty.[9–14,41,42,52] Among the rest 19 studies, Egol et al. and LeBrun et al. have reported data on fracture and surgery types in different groups.[16,17] Vives et al. reported 52 FNF and 84 intertrochanteric fractures. Surgery was performed in 124 patients, and the rest 12 were managed conservatively. However, further details were not available.[15] Fracture types and surgery have also been mentioned by Maniscalco et al.[18] Fadulelmola et al.[27] Konda et al.[30] Thakrar A et al.[31] Chui K et al., and Sobti et al.[51] (Tables 1 and 2A and 2B).

Treatment of COVID-19: Oxygen therapy with a mask was used in most patients of COVID-19, and ventilators were also used whenever required. Nevertheless, not all authors have not provided complete data. Information regarding antiviral therapy was available in 7 manuscripts. The usage pattern has been depicted (Table 1).

Personal Protective Equipment (PPE) Usage: Most authors did not report data regarding PPE usage. Rabie et al. used PPE in 2 patients and mentioned details in one patient.[10] Shariraye et al. used an N 95 face mask (personal communication).[11]

3.2. *Mortality risk in hip fractures with and without COVID-19: Meta-analysis*

Mortality risk was markedly higher among proven COVID-19 patients/suspected patients with hip fractures than those without it, as depicted in the metanalysis of 20 studies. (Mantel Haenszel Odds Ratio (MH-OR) 6.31, 95% confidence interval (CI) [5.09, 7.83]; $Z = 16.75$, $p < 0.0001$, $I^2 = 26\%$ so Fixed effects model was used) (Fig. 2A and B).Overall, out of 560 covid positive or suspected hip fracture cases, 205 (36.61%) had expired, in contrast to only 306 (8.6%) deaths among non covid cases.

The separate sensitivity analysis considering test positive versus COVID-19 test-negative patients, as reported in the parent studies, also revealed significantly higher among those who test positive for COVID -19 patients with hip fractures than those without it. (MH-OR 5.99, 95% CI [3.88,9.24]; $Z = 11.89$, $p < 0.001$, $I^2 = 18\%$ so Fixed effects model was used). (Fig. 3A and B). 110 (36.1%) COVID positive hip fracture patients had expired, out of 305 positive hip fracture cases.

Subgroup analysis performed for surgically treated patients revealed significantly higher mortality in hip fracture patients with COVID-19 patients along similar lines (MH-OR 5.99, 95% CI 3.88 to 9.24, $Z = 8.08$, $p < 0.001$, $I^2 = 28\%$ so Fixed effects model was used) (Fig. 4). Among surgically treated hip fracture cases 55 (38.73%) experienced mortality out of 162 cases with covid, in contrast to only 55 (7.8%) out of 705 cases without covid.

4. Discussion

Several studies have evaluated the outcome of hip fracture surgery in COVID-19 patients [13–78]. It appears equivocal that COVID-19 had an overwhelming effect on managing hip fracture patients during the pandemic, with reportedly increased morbidity and mortality in these patients' cohorts. However, surgical practice in treating principles has remained the same.[16]

Our meta-analysis shows that PFF patients with COVID-19 have higher mortality rates than those without COVID-19. This effect of COVID -19 infection leading to elevated mortality rates persists in the PFF patients treated surgically. A biologically plausible explanation for this effect could be the fracture inflammation or surgery for fracture fixation, further exacerbating inflammation in COVID -19 positive patients, leading to cytokine storm.[23] This must be explained to all patients with PFF and their relatives while undertaking informed consent for surgery. It should form part of the shared decision process. LeBrun et al.[17] have suggested monitoring

Table 2B
Summary of studies reporting mortality and other relevant statistics on hip fracture patients with and without COVID 19.

Author	Co-morbidities	Orthopaedic- Diagnosis and surgery										
Vives JMM et al[15]	Three had dementia.	Separate individual patient data for the seven C +ve RT PCR positive fracture patients, who had expired, was provided by Vibes et al., 1 had femoral neck fracture and rest 6 had intertrochanteric fracture.										
Egol KE et al.[16]	C +ve		C Susp	C -ve	Fracture	C +ve	C susp	C -ve	Surgery	C +ve	C susp	C -ve
	HTN	11	11	67	IT	7	5	48	ILN	5	5	54
	DM	7	2	20	FN	10	9	52	DHS	0	0	7
	Dyslipidemia	7	8	38	ST	0	0	7	HA	5	7	30
	CAD	8	6	40					THR	0	0	6
	Dementia	6	1	27					CCS	3	2	10
LeBrun DG et al.[17]		C +ve	C -ve	Fracture		C +ve	C-ve	Surgery			C +ve	C -ve
	CAD	1	12	IT/GT		6	28	ILN			4	32
	PVD	1	5	FN		20	52	DHS			0	7
	COPD	1	7	ST		0	2	HA			2	11
	Dementia	6	17					THR			0	2
	CVA	1	5									
	Liver Disease	1	3					CCS			1	4
	DM	3	14									
	CKD	1	5									
								ORIF			0	1
	Malignancy	2	9									
Maniscalco P et al[18]	NA					Piacenza Hosp	Parma Hosp		Piacenza Hosp	Parma Hosp		
				FN		22	29	THR	4	7		
				IT/GT		32	27	HA	9	12		
				ST		6	4	CCS	7	7		
				Others		1	0	ILN	39	34		
								Others	2			
	Elevated number of deaths within 21 days after surgery. In the first two months of the Italian epidemic, in the cities of Piacenza and Parma over 80% of deaths have occurred in patients over 70 years old.											
Kayani B et al[28]	Multiple			NA								
Fadulelmola, A. et al[27]	Multiple					Intra-capsular 38/351 Extra-capsular46/232						
						Surgery		COVID +ve	COVID -ve			
						Cemented hemiarthroplasty		10 (50%)	36 (65.5)			
						Uncemented hemiarthroplasty1		(5%)	0 (0%)			
						Dynamic hip screw		6 (30%)	11 (20%)			
						Intra-medullary nail		2 (10%)	3 (5.5%)			
						THR		0 (0%)	3 (5.4%)			
						Conservative		1 (5%)	2 (3.6%)			
Thakrar A et al[31]				NA		DHS 7 CCS 3 HA 15 ILN- 13 THR- 1 Revision THR- 4 (in study group) For other groups - NA						
Narang, A et al[44]	Intra-capsular	11 (55%), 39 (71.9%)		NA		NA	NA		NA		NA	
	Extra-capsular	9 (45%), 16 (29.1%)										
Stobi A et al[51]	Neck of femur			NA		NA	47 patients had hemi-arthroplasty and the remaining 35 had fixation (Intra-medullary nail, Dynamic hip screw fixation).		Complications:Hemiarthroplasty dislocation (1) • Wound ooze (1) • Heel ulcers (2) • Wound infection (1)			
Konda SR et al[30]	Fractures			C+ve/Susp		C-ve	Surgeries		C+ve/Susp		C-ve	
	FN			19		511	Short IMN		8		508	
	IT			12		653	Long IMN		2		170	
	ST			00		83	DHS		0		89	
							HA		12		286	
							THR		0		79	
							CCS		5		97	
Chui K et al[54]	Multiple(including anaemia and cancer, all comorbidities more in covid cases-not significant)			**Operations** DHS 3 vs 6 Cannulated screws 0 vs 3 Hemiarthroplasty 9 vs 9 IM Nail 0 vs 12 THR 0 vs 3 Revision 0 vs 2								
Wignall A et al[52]	Multiple(Charlson comorbidity index 5.2 (2.2) in cases presenting in COVID period)			**Fracture type** Extracapsular 110 Intracapsular 148 Subtrochanteric 6 Perirosthetic 8 Others 4		**Operations** DHS 71 Cannulated screws 8 Hemiarthroplasty 110 IM Nail 55 THR 13 ORIF 4						

inflammatory markers and delaying surgery until they show a downward trend. However, it is well-known fracture stabilization surgery allows for earlier mobilization and faster rehabilitation.

Male gender and older age are shown to be risk factors for increased mortality in hip fracture patients with COVID-19. However, there is gathering evidence about PFF with COVID-19 infection in younger patients and the unique challenges associated with polytrauma and milder symptoms of COVID-19 in such patients.[12]

Elderly patients with hip fractures often present with comorbidities such as diabetes, hypertension, cardiac diseases, COPD, and obesity. Such patients have been noted to face worse with COVID-19 concomitant infection due to their low functional reserves and weaker immunity.[8,9] A combination of comorbidities and elderly age could make these patients who sustain PFFs more vulnerable to respiratory illness due to their limited pre-injury ambulatory status.[24]

PFF is an obligatory injury that requires prompt surgical management to allow early mobilization, reduce pain, and prevent problems associated with recumbency.[9,14] According to the prioritization list of surgical procedures, PFF belongs to the group IA requiring surgery to be undertaken 24 h or so from the presentation. Hence appropriate pre-operative medical optimization and an emphasis for surgical stabilization to be undertaken throughout the COVID-19 situation has been a clinical goal.[4] The usual recommendation has been that hip fracture patients should be operated on as soon as they are medically fit. More than 48 h after admission, any surgical delays may escalate the odds of 30-day all-cause mortality.[9]

Early and limited available evidence suggests poor outcomes with high postoperative mortality of more than 20%–30% in patients contracting COVID-19 in the perioperative phase.[5,6,74] A recent study focused on mortality in surgery (all type) patients with COVID-19; the overall mortality was 23.8% (268/1128). Further analysis revealed 86 deaths from 299 COVID-19 positive orthopedic patients, which comprise 28.8% of the cohort. This study included 115 PFF (DHS and Hemiarthroplasty) patients out of a total of 299 surgical interventions but did not show the deaths within these patients.[6]

A recent meta-analysis found that COVID-19 led to deterioration in outcomes in elderly patients with hip fractures and was associated with higher short term mortality. Authors recommended a multidisciplinary approach to manage such “pandemic within a pandemic".[73]

Doglietto et al. described mortality in 57 PFF patients, out of which 19 were COVID-19 positive. Twelve patients underwent femoral nail fixation, and hip hemiarthroplasty was performed in seven patients. It was not clear from the study how many patients had a proximal femur fracture and deaths or complications.[25] Intertrochanteric fractures were more commonly seen than the femoral neck and subtrochanteric fractures. The incidence of mortality was slightly higher in intertrochanteric fractures.

Though there has been an earlier pandemic phase, subsequent studies still recount significantly higher 30-day mortality rates than the traditionally quoted figures of 5%–8%.[5–19]

Egol et al.[16] stated that surgery for COVID-19 positive hip fracture patients was delayed by about one day (to allow for optimization) than non -COVID-19 patients. They have expressed concern whether this delay might have contributed to increased mortality.

Konda et al. found that the STTGMA tool can be utilized for the COVID-19 virus, thus providing a robust risk evaluation technique. COVID-19 positive/suspected status in hip fracture patients indicates a high risk for perioperative morbidity and mortality. These authors suggest that surgery should be deferred for hip fractures in these patients until symptoms improve or resolve. Patients should be reassessed for surgical treatment versus conservative care.[30]

Segarra et al. reported surgery in two hip fractures; none of them received intensive care unit support. One patient expired, and the other recovered after 48 h of supportive care and was discharged.[49]

Mi et al. studied 145 hip fractures (delayed surgery 108, nonoperative 37) and concluded that delayed surgery is more beneficial and has fewer complications than conservative treatment. Furthermore, delayed surgery led to decreased pain which increased mobilization and better function.[63]

Recently, data on a large multicentre study (IMPACT Scort 2)[61] found that the COVID-19 was independently associated with three times higher 30-day mortality risk in hip fracture patients. And, nearly half were acquired during hospital stay (i.e., nosocomial COVID 19). Diagnosis of COVID-19 within six days was associated with male sex and COVID-19 symptoms. In contrast, Diagnosis of COVID-19 between 7 and 30 days of hospital admission was associated independently with male sex, Nottingham Hip Score $\geq$7, lung disease, ASA grade $\geq$3, and length of stay $\geq$ nine days.[61]

The orthopedic community’s challenge is finding a balance of providing an effective treatment option for PFF and achieving the best eventual outcome for these patients to reduce mortality and be mindful of associated risk factors and comorbidities.

4.1. Limitations of the study

These studies were done in different geographical populations. Consequently, availability, quality of medical care, and surgical facilities may vary. These factors may reflect on clinical outcomes. Only a few studies focussed on the PFF exclusively, whereas others had included all types of fractures. All relevant variables were not reported uniformly in the studies. There is a lack of uniformity in the patient population, which may affect the risk of mortality and morbidity. Follow up period of patients was also variable, and relatively short-term outcomes have been reported. Extended outcomes have not been described. In-patient and 30- day mortality was explicitly mentioned in a few studies only.

Another limitation of the study has been the nature of studies that have been reported and available for analysis. Any study based on the recruitment of retrospective cohort studies is prone to various bias and confounding factors, particularly of publication and detection bias. However, we have utilized funnel plots to explore the potential of publication bias. To mitigate detection bias, evaluation of relevant recent literature and application of PRISMA reporting principles of a systematic review have been incorporated.

5. Conclusion

This systematic review and meta-analysis confirm that hip fracture patients with COVID-19 have significantly higher mortality rates than non-COVID patients. The 30-day mortality rates are also higher in these groups of patients. The enhanced effect of COVID-19 infection leading to elevated mortality rates persists in hip fracture patients treated surgically. The likely contributory factors for increased mortality are inflammation caused by the fracture and the surgery (leading to Cytokine-storm), advanced age, male sex, and perhaps early surgical intervention. Informed consent must include a disclosure of the increased risk of mortality after the surgery of PFF and must be explained clearly to the patient and their relatives. The treating surgical team should carefully do a due risk-benefit analysis. A comprehensive best practice guideline to mitigate the risk posed by COVID-19 will help healthcare professionals worldwide improve clinical outcomes.

Table 3
Study quality of non randomised studies included.

Study	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability	Assessment of outcome	Follow-up long enough for outcomes	Adequacy of follow up of cohorts	Total
Egol KA et al., 2020(Prospective Cohort study)	1	1	1	1	1/1	1	0	0	7
LeBraun DG et al. 2020 (Multicenter retrospective cohort study)	1	1	1	1	1/1	1	0	0	7
Maniscalo P et al. 2020 (Retrospective study)	1	1	1	1	0/0	1	0	0	5
Vibes JMM et al. 2020 (Retrospective study)	1	1	1	1	0/0	1	0	0	5
Kayani B et al., 2020 (multicentre cohort study)	1	1	1	1	1/1	1	0	0	7
Fadulelmola, A. et al., 2020 (Retrospective study)	1	1	1	1	0/0	1	0	0	5
Thakrar A et al., 2020 (Prospective study)	1	1	1	1	1/1	1	0	0	7
Narang, A et al., 2020 (multicentre prospective study	1	1	1	1	1/1	1	0	0	7
Stobi A et al., 2020 (Prospective study)	1	1	1	1	1/1	1	0	0	7
Konda SR et al., 2020 (Retrospective study)	1	1	1	1	0/0	1	0	0	5
Arafa M et al.[58]	1	1	1	1	1/1	1	0	0	7
Chui K et al.[59]	1	1	1	1	1/1	1	0	0	7
Clough TM et al.[60]	1	1	1	1	0/0	1	0	0	5
Macey ARM et al.[64]	1	1	1	1	0/0	1	0	0	5
Segarra B et al.[65]	1	1	1	1	0/0	1	0	0	5
Hall AJ et al.[62]	1	1	1	1	0/0	1	0	0	5
Clement ND et al.[61]	1	1	1	1	0/0	1	0	0	5
Wignall A et al.[52]	1	1	1	1	0/0	1	0	0	5

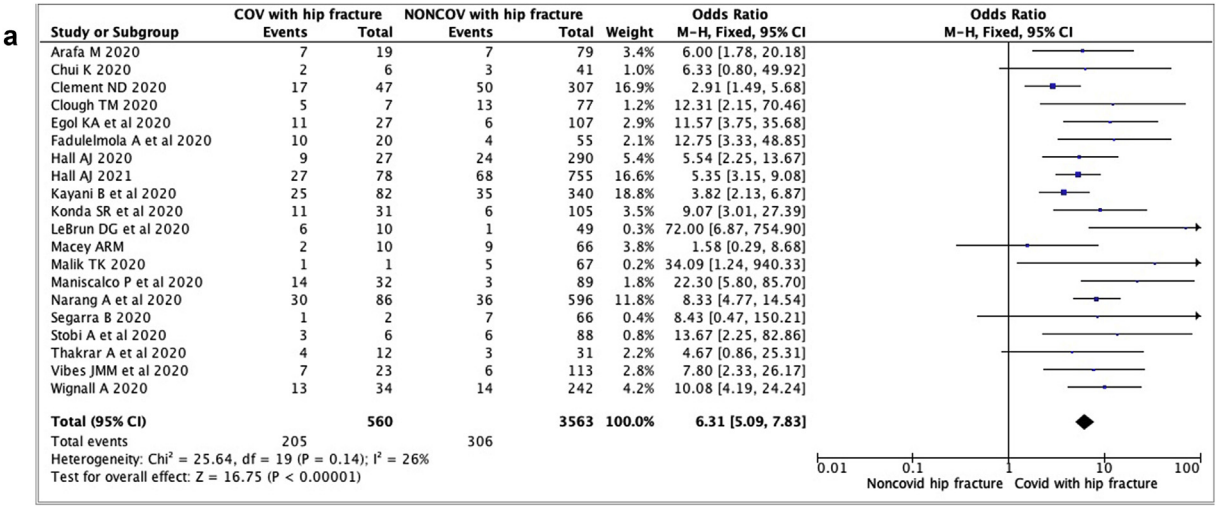

Fig. 2A. Forrest and Funnel plots of comparison of hip fractures mortality rates among COVID-19 patients suspects vs. non-COVID-19 patients.

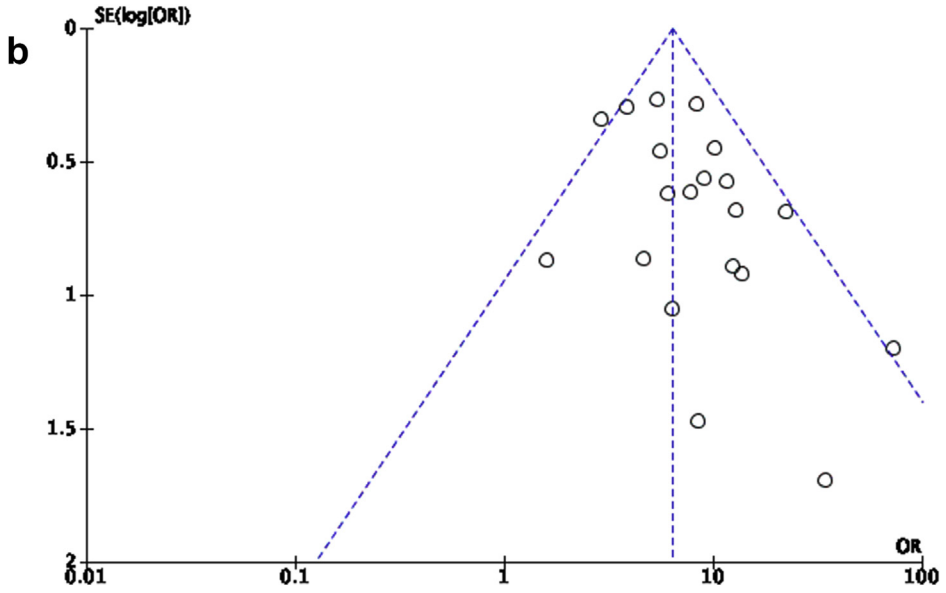

Fig. 2B. Forrest and Funnel plots of comparison of hip fractures mortality rates among COVID-19 patients suspects vs. non-COVID-19 patients.

a

Study or Subgroup	hip fracture with COVID + Events	Total	hip fracture without COV Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Vibes JMM et al 2020	7	23	6	113	6.1%	7.80 [2.33, 26.17]
Thakrar A et al 2020	4	12	1	6	3.9%	2.50 [0.21, 29.25]
Stobi A et al 2020	3	6	5	47	2.5%	8.40 [1.32, 53.40]
Narang A et al 2020	30	86	36	596	25.7%	8.33 [4.77, 14.54]
Maniscalco P et al 2020	11	32	3	89	4.5%	15.02 [3.84, 58.67]
LeBrun DG et al 2020	5	9	2	50	1.2%	30.00 [4.35, 206.93]
Konda SR et al 2020	4	12	1	5	4.1%	2.00 [0.16, 24.33]
Kayani B et al 2020	25	82	35	340	41.1%	3.82 [2.13, 6.87]
Fadulelmola A et al 2020	10	20	4	55	4.6%	12.75 [3.33, 48.85]
Egol KA et al 2020	9	17	8	121	4.0%	15.89 [4.82, 52.35]
Chui K 2020	2	6	2	24	2.3%	5.50 [0.59, 51.19]
Total (95% CI)		**305**		**1446**	**100.0%**	**6.97 [5.06, 9.59]**
Total events	110		103			

Heterogeneity: $Chi^2 = 12.20$, df = 10 (P = 0.27); $I^2 = 18\%$
Test for overall effect: Z = 11.89 (P < 0.00001)

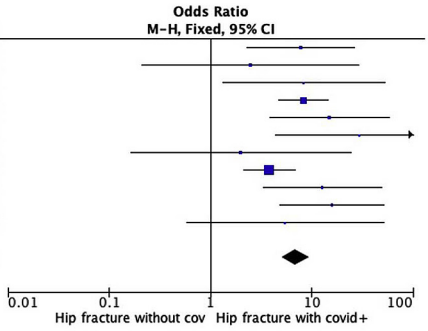

Fig. 3A. Forrest and Funnel plots of comparison of hip fractures mortality rates among COVID-19 positive vs. non- COVID-19 positive patients.

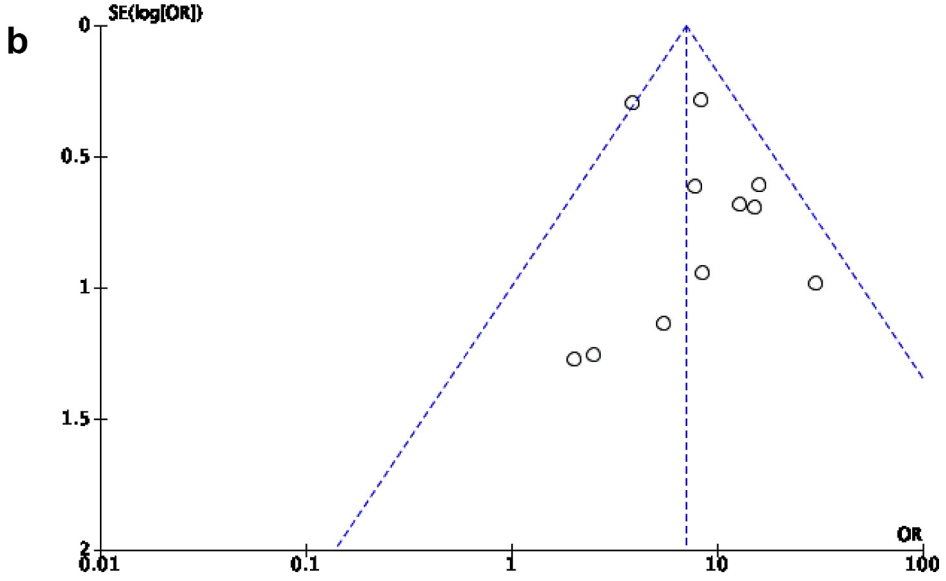

Fig. 3B. Forrest and Funnel plots of comparison of hip fractures mortality rates among COVID-19 positive vs. non- COVID-19 positive patients.

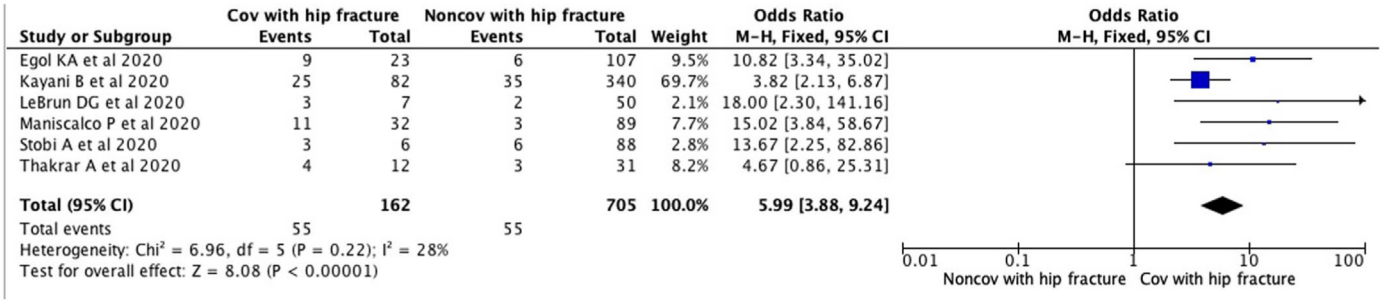

Fig. 4. Forest plot- Comparing hip fracture mortality rates among surgically treated patients (COVID-19 vs. non COVID-19).

Statement of ethics

All our clinical procedures were fully compliant with the ethical standards following the local consenting and ethics guidelines. The current submitted article is not a clinical study and does not involve any patients.

Author's contributions

VJ and GKU involved in Conceptualization, literature search, manuscript writing, and editing. MKP and KPI Literature search, manuscript writing, references, data analysis, and editing. RV supervised overall submission and approved the final draft. All authors read and agreed the final draft was submitted.

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Disclosure statement

Nothing to disclose. "The authors declare no conflict of interest."

Declaration of competing interest

Authors have no competing interests to declare.

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