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Outcomes after peri-operative SARS-CoV-2 infection in patients with proximal femoral fractures: an international cohort study

COVIDSurg Collaborative*

***Author contributions:** Full list of authors and roles within this research project are available in Supplementary files, titled Authorship (available to editors)

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ABSTRACT

Objectives: Studies have demonstrated high rates of mortality in people with proximal femoral fracture and SARS-CoV-2, but there is limited published data on the factors that influence mortality for clinicians to make informed treatment decisions. This study aims to report the 30-day mortality associated with peri-operative infection of patients undergoing surgery for proximal femoral fractures and to examine the factors that influence mortality in a multi-variate analysis.

Setting: Prospective, international, multicentre, observational cohort study.

Participants: Patients undergoing any operation for a proximal femoral fracture from 1st February to 30th April 2020 and with perioperative SARS-CoV-2 infection (either 7-days prior, or 30-days post-operative).

Primary outcome: 30-day mortality. Multivariate modelling was performed to identify factors associated with 30-day mortality.

Results: This study reports included 1063 patients from 174 hospitals in 19 countries. Overall 30-day mortality was 29.4% (313/1063). In an adjusted model, 30-day mortality was associated with male gender (OR 2.29, 95% CI 1.68-3.13, p=0.000), age >80 years (OR 1.60, 95% CI 1.1-2.31, p=0.013), pre-operative diagnosis of dementia (OR 1.57, 95% CI 1.15-2.16, p=0.005), kidney disease (OR 1.73, 95% CI 1.18-2.55, p=0.005) and congestive heart failure (OR 1.62, 95% CI 1.06-2.48, p=0.025). 30-day mortality was lower in patients with a pre-operative diagnosis of SARS-CoV-2 (OR 0.6, 95% CI 0.6 (0.42-0.85), p=0.004). There was no difference in mortality in patients with an increase to delay in surgery (p=0.220), or type of anaesthetic given (p=0.787).

Conclusions: Patients undergoing surgery for a proximal femoral fracture with a peri-operative infection of SARS-CoV-2 have a high rate of mortality. This study would support the need for providing these patients with individualised medical and anaesthetic care, including medical optimisation before theatre. Careful pre-operative counselling is needed for those with a proximal femoral fracture and SARS-CoV-2, especially those in the highest risk groups.

ARTICLE SUMMARY

Strengths and limitations of this study

- This is a large, international, multicentre cohort study from which the results are generalisable across populations in other countries.
- This study described specific risk factors for mortality, which patients and those who care for them should use to make informed decisions regarding care.
- To our current knowledge, this is the largest cohort of patients undergoing surgery for a proximal femoral fractures with SARS-CoV-2 infection diagnosed peri-operatively
- There is not control arm to assess contemporaneous patients with undergoing an operation for proximal femoral fractures without SARS-CoV-2 infection during the height of the pandemic. However with high-quality data present pre-pandemic strongly suggests a substantial increase in mortality.

MAIN TEXT

Background

The rapid worldwide spread of Coronavirus Disease-2019 (COVID-19), caused by the Severe Acute Respiratory Syndrome CoronaVirus-2 (SARS-CoV-2) has had a severe effect on the elderly and frail population. A fracture of the proximal femur (neck of femur fracture) is a critical event in the elderly, frail population, with a high rate of death despite medical and surgical intervention [1]. Since 2007, there has been a steady improvement in mortality after a proximal femoral fracture with 6.1% of patients dying within 30 days of injury in the UK in 2018 [2]. However, the emergence of COVID-19 presents a new and unquantified risk to this particularly vulnerable group.

Proximal femur fractures represent a large international burden with incidence between 43 and 920 per 100,000 population [3]. As most fractures of the proximal femur happen as a result of trips or falls in the home, people have continued to present with this injury despite social restrictions [4, 5]. These patients typically have multiple co-morbidities and frailty is common [1]. Resultantly, they are particularly vulnerable to pulmonary complications [1, 6]. It is widely accepted that elderly patients with existing co-morbidities are at higher risks of critical illness and mortality due to COVID-19, potentially due to a higher preponderance to release pro-inflammatory cytokines that result in severe disease [7-9].

Clinicians have been swift to respond to this pandemic with large re-organisation of service provision [10, 11]. In response to this, the COVIDSurg collaborative

(www.globalsurg.org/covidsurg) has collected an international, large volume dataset to inform the global community of the safety of surgery in patients with peri-operative SARS-CoV-2 infection. The first report has demonstrated a 30-day mortality of 23.8% across patients undergoing any type of surgery [12]. Data published so far has reported a high mortality rate in a small cohort of patients with proximal femoral fractures positive for SARS-CoV-2 infection, with a maximum cohort size of 114 patients (range 10-114 patients) [13-20]. However few reports have the sample size sufficient to explore the factors that influence outcome. Further, large-scale data are required to explore pre-operative and operative variables that influence outcomes in order to inform the clinical decision-making processes.

Aims

The primary aim of this study is to determine the mortality rate observed in patients undergoing surgery for proximal femoral fracture with peri-operative SARS-CoV-2 infection. Secondarily, we aim to explore the patient and treatment factors associated with these outcomes.

Methods

Setting

This is an international, multicentre cohort study including consecutive patients who underwent surgery for proximal femoral fracture from 1st February 2020 to 30th April 2020. This study is a pre-planned sub-analysis of a larger, ongoing study designed to assess outcomes following all surgery for patients with perioperative SARS-CoV-2 infection [12].

The COVIDSurg collaborative is an international, multicentre, multidisciplinary team with individual collaborators collecting data locally, which is collated centrally. The collaborative methodology, which is well described and validated was used for this project [21]. The study protocol was registered online (ClinicalTrials.gov identifier: NCT04323644).

Ethics Review Board

This observational study collected anonymised routine clinical data, using an established international trainee collaborative model [22]. Within the United Kingdom this was registered as a clinical audit or service evaluation at each participating trust following individual hospital policies and procedures, prior to initiating data collection at that site. In other countries, the principal investigator was responsible for obtaining local approval in line with local and/or national guidelines. In some participating countries, informed patient consent was taken, whilst in others the requirement was waived by local research committees. Country-specific

guidelines for site set-up were published on a dedicated study website (www.globalsurg.org/covidsurg).

Inclusion Criteria

Participating hospitals included consecutive patients undergoing surgery for proximal femoral fractures that had SARS-CoV-2 infection diagnosed either 7 days pre-operatively, or up to 30-days post-operatively. For those patients who underwent multiple procedures, the procedure closest to the time of confirmation of SARS-CoV-2 infection was defined as the index procedure.

Patients received laboratory confirmation of SARS-CoV-2 using quantitative Reverse Transcription Polymerase Chain Reaction (qRT-PCR). As qRT-PCR is not available in all participating hospitals, patients were included if their diagnosis was made by clinical or radiological findings. Clinical diagnosis was made in patients presenting with symptoms and a clinical pattern of COVID-19. These included cough, fever and/or myalgia [23]. Radiological diagnosis was made through computed tomography (CT) scanning of the thorax according to local protocols. All patients who were included solely on clinical or radiological suspicion but had a subsequent negative test were excluded from the database by individual collaborators.

Diagnosis

This study includes all patients identified as having an operation for a proximal femoral fracture. The diagnosis was established pragmatically by the local site teams according to their assessment of the fracture. The reported data was screened by a

central dedicated data cleaning team, with only confirmed proximal femoral fractures included in the cohort.

Patient Identification

Researchers at participating centres screened consecutive patients undergoing surgery to ensure all patients were identified. The study was initiated in some countries after their peak of infection, and therefore retrospective identification and data collection was permitted, as long as the data collection was consecutive at that site.

To reduce selection bias, a variety of written materials were distributed to site leads to highlight possible methods of identifying patients ensuring all eligible patients were included. Investigators were invited to social media groups and online teleconferences to trouble-shoot recruitment issues, share learning and ensure consistent recruitment into the wider cohort.

Outcome measures

The primary outcome measure was 30-day all-cause mortality, with the day of surgery defined as day zero. The secondary outcome measure was rate of pulmonary complications, which is a composite outcome defined previously from the Prevention of Respiratory Insufficiency after Surgical Management (PRISM) randomised controlled trial [24, 25].

Pulmonary complications were defined as pneumonia, acute respiratory distress syndrome (ARDS), and/or unexpected post-operative ventilation; these have been identified as the most frequent COVID-19-related pulmonary complications in

medical patients [23]. Unexpected post-operative ventilation was defined as either (i) any episode of non-invasive ventilation, invasive ventilation, or extracorporeal membrane oxygenation after initial extubation following surgery, or (ii) unexpected failure to extubate following surgery [12].

Data collection and quality assurance

Data was collected online using the Research Electronic Data Capture (REDCap) web application [26]. Demographic variables recorded consisted of age, sex, and American Society of Anesthesiologists physical status classification (ASA). Age was collected as a categorical variable by deciles of age. ASA at the time of surgery was dichotomized to (i) grades 1-2 and (ii) grades 3-5 for the purpose of analysis, time to surgery to (i) under 24 hours, (ii) 24-48 hours, and (iii) over 48 hours, and surgery to (i) hemiarthroplasty, (ii) total hip replacement, (iii) dynamic hip screw, (iv) cannulated screws and (v) intramedullary nail. The timing of SARS-CoV-2 diagnosis was recorded as either preoperative or post-operative.

Before data was entered into analysis, site principle investigators were required to confirm all consecutive eligible cases had been completed and uploaded. Where diagnosis was unclear, authors were contacted for clarification.

Statistical analysis

The study was reported according to STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines [27]. Proportions are expressed with 95% confidence intervals and the mean and 95% confidence intervals were used where data were assumed to be approximately normally distributed. Fishers exact test

was used for categorical data. Non-parametric data was summarised with the median and interquartile ranges. Statistical significance was assessed at the 5% level.

The risk of death at 30 days was chosen as the primary outcome for the study. Mixed-effects logistic regression analysis was used to assess the strength and significance of associations between a number of explanatory variables and death within 30-days. Random effects were included in the mixed-effects model to account for the hierarchical structure of the data (individual hospital effects are naturally nested within country effects) and fixed effects were included to adjust for a range of pre-operative variables that may influence mortality in this population, and relevant factors related to the injury or treatment (e.g. type of operation, time from admission to operation, type of anaesthetic). An additional analysis of the same factors was undertaken using the same model structure for the secondary outcome of pulmonary complications. All analyses were implemented in R (R Core Team (2020). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/.).

Patient and Public Involvement

Patients were not involved in the design, conduct or reporting of this study.

Results

Population

This study returned 30-day follow up for 1063 patients with proximal femoral fractures. Data was collected in 174 hospitals from 19 countries (Supplementary Table S1). Of these, 65.5% were female (696/1063). 7.8% (83/1063) patients were <70 years old, 17.8% (189/1063) were between 70-79 years, 47.7% (507/1063) were between 80-89 and 26.7% (284/1063) were 90+ years old.

Mortality

Overall 30-day mortality was 29.4% (313/1063). With each decile of age, mortality significantly increased, being highest in those patients >90 years old (38.7% [110/284], p=0.001).

In an adjusted model (Figure 1), 30-day mortality was associated with male gender (OR 2.29, 95% CI 1.68-3.13, p=0.000), age >80 years (OR 1.60, 95% CI 1.1-2.31, p=0.013), diagnosis of dementia (OR 1.57, 95% CI 1.15-2.16, p=0.005), chronic kidney disease (OR 1.73, 95% CI 1.18-2.55, p=0.005) and congestive heart failure (OR 1.62, 95% CI 1.06-2.48, p=0.025). 30-day mortality was lower in patients with a pre-operative diagnosis of SARS-CoV-2 (OR 0.60, 95% CI 0.42-0.85, p=0.004). Non-adjusted values are presented in Table S2.

Pulmonary complications

In an adjusted model (Figure 2), respiratory complications were associated with male gender (OR 1.7, 95% CI 1.27-2.28, p=0.000), diagnosis of dementia (OR 1.34, 95%

CI 1.01-1.79, p=0.044) and congestive heart failure (OR 1.76, 95% CI 1.17-2.63, p=0.006). Chronic Obstructive Pulmonary Disorder (COPD) showed a signal to be a risk factor, however was not significantly associated, (OR 1.42, 95% CI 0.96-2.09, p=0.076)

Diagnosis

The majority of diagnosis of SARS-CoV-2 was made via PCR swab testing 93.3% (992/1063) (Table S1 & S3) and there was no difference in mortality between those diagnosed clinically (p=0.668). The majority of patients received a diagnosis post-operatively 69% (733/1063).

Pre-operative variables

Pre-operative symptoms (Table S4), including breathlessness, cough and fever (>38 ° Celsius) were not significantly different in patients who were alive or dead at 30 days post-operatively. On examination of pre-operative observations, a high respiratory rate was predictive of mortality (OR 1.73 95% CI 1.18-2.55, p=0.025) (Figure 1). However, there was no significant difference in patient's heart rate, systolic or diastolic blood pressure (Table S5, Figure S1) between those who were alive or dead at 30 days.

Those patients with ASA grade 3-5 had a significantly higher mortality of 31.4% (281/899) versus ASA of 1-2 of 18.5% (28/151), p=0.001.

Procedures

The operations were carried out under a general anaesthetic in 49.6% (527/1063) of patients (Table S6). 67.2% (714/1063) of patients did not require any pre-operative oxygen therapy. 31.8% (338/1063) of patients had their operation within 24 hours of presentation to hospital, 21.1% (224/1063) had their operation between 24-47 hours and 19.2% (205/1063) of patients had their operation after 48 hours of presentation to hospital.

45.1% (479/1063) of patients underwent hemiarthroplasty with a further 4.2% undergoing total hip replacement (45/1063). For patients who underwent fixation, 26% (276/1063) underwent Dynamic Hip Screw (DHS) fixation, 22.9% (243/1063) patients underwent intramedullary fixation, 0.5% (5/1063) underwent cannulated screw fixation whilst a further 1.4% (15/1053) underwent internal fixation.

There was no difference in mortality between patients undergoing general and regional anaesthesia (29.9% [157/527 versus 29.0% [152/524], p=0.787). However, there was an increased mortality in those patients requiring pre-operative oxygen therapy (34.3% [115/336] versus 27.2% [194/714], p=0.031)

There was no significant difference in mortality for patients with delayed operation. The highest mortality was for patients operated between 24-47 hours of admission (34.4%, [77/224]) but was not significantly higher than less than those operated after 48 hours (p=0.220).

Mortality was highest in March (33.7%, 159/474) compared to April (27.0%, 150/558), and February (11.5%, 3/26), p=0.007 (Table S1).

316

317 **Data Sharing**

318 No additional data available. Requests for raw data can be requested via the

319 corresponding author.

Discussion

The 30-day mortality rate for patients with a peri-operative diagnosis of SARS-CoV-2 infection undergoing surgery for proximal femoral fracture is substantial. An overall rate of 29.4% compares to the reported 30-day mortality for fracture neck of femur in the UK National Hip Fracture Database of 6.1% in 2018 [2]. Further, elderly patients, and those with medical comorbidities such as dementia, chronic kidney disease and congestive heart failure were associated with higher risk of 30-day mortality. Notably, patients with a pre-operative diagnosis of SARS-CoV-2 infection had lower rates of 30-day mortality, likely reflecting early recognition and closer management of these patients. Findings from this study will be useful in guiding clinicians to identify high-risk patients that may warrant closer medical and surgical input during the COVID-19 pandemic.

Considering this high mortality, it is critical that patients with proximal femoral fractures are protected from contracting SARS-CoV-2 in the peri-operative period. A study by Kayani et al. has suggested that half of infections in patients with proximal femoral fractures occur in hospital, as denoted by having negative pre-operative samples [17]. Similarly, a study by Hall et al. has suggested nearly half of cases were due to nosocomial transmission [28]. Within this study, 733 (69%) of infections were diagnosed post-operatively. This may infer that infections have been transferred in hospital, although due to incubation period of the virus, it is hard to know the proportion that contracted the virus prior to presentation or in hospital. [7, 29] Higher mortality was observed in people who had a post-operative diagnosis, which emphasises the critical importance of avoiding in-hospital transmission. Hospitals

should consider implementation of careful infection control processes to minimise and prevent transmission of SARS-CoV-2 infection. Within the elective setting, the creation of COVID-19-free surgical pathways for elective patients has been shown to reduce infection and subsequent mortality [30-32] and whilst only some of the principles are transferrable to the emergency setting, it demonstrates the value of meticulous infection control processes throughout the hospital stay.

With the added risk associated with SARS-CoV-2 infection, and the need to continue managing this injury despite the ongoing pandemic, it is important for data to be used as part of the informed consent process. In patients with multiple high-risk factors such as those who are more elderly, have respiratory and cardiac co-morbidities, non-operative management may be considered following an appropriate discussion with the patient and/or their family. Every year in the UK, 2.5% of hip fractures are treated non-operatively [33]. A study performed before the pandemic reported that the mortality within thirty days for conservatively treated patients was 31.3% [34]. We do not know the mortality from non-operative management during the pandemic for patients with SARS-Cov-2, but the particularly high mortality associated with surgery in high-risk groups may change the balance of benefit and harm towards conservative treatment and this should be considered.

The 30-day mortality of 29.4% identified within this study is comparable to published literature, in the UK (range from 16.3%-35.6%) [15-17, 19, 28, 35], Italy (18.75%) [14], Spain (30.4%) [13] and the USA (range from 35.3%-56%) [18, 20]. From a study within the UK, the authors also found a correlation between male sex and increased mortality (OR 2.69), which is similar to that demonstrated in this study (OR

2.29) [16]. Additionally, another UK study reported having more than three co-morbidities as a risk factor for mortality [17]. This study has specifically delineated a diagnosis of dementia, chronic kidney disease and congestive heart failure as being independent risk factors for mortality. In a study from USA, the authors found those patients who died were older with multiple co-morbidities and this was reflected in statistically significant higher ASA scores in comparison to their negative counterparts [20].

This study found that there was no significant increase in mortality with delay to surgery. Current guidelines suggest early surgery should be undertaken [36] and this is associated with lower mortality [37]. This would suggest that those patients at the highest risk of mortality can have medical optimisation if appropriate and will not result in a higher mortality from SARS-CoV-2 infection. Similarly, previous studies have found a higher rate of mortality in patients undergoing general versus regional anaesthesia for proximal femoral fractures [38, 39]. This study reports no difference between general and regional anaesthetic (29.9% versus 29.0%, p=0.787). As a result, anaesthetic decisions in this population should not be influenced by a positive test for SARS-CoV-2. Out of all clinical features, respiratory rate at presentation was associated with higher mortality. Clinicians should focus on this as an important finding when counselling patients of their peri-operative mortality.

To our knowledge, this is the largest cohort of patients undergoing surgery for a proximal femoral fractures with SARS-Cov-2 infection diagnosed peri-operatively. This study was conducted in multiple centres, internationally, allowing it to be generalisable across populations in other countries.

Limitations

This study was conducted in hospitals in the early to mid-phase of the pandemic where routine testing was not available in all participating centres. As such, to be pragmatic, patients were included if a clinical diagnosis was made by the treating physician. Protocols were not standardised for clinical diagnosis and were left the senior treating physician. Laboratory diagnosis was made by qRT-PCR, from which false-negative results may have excluded patients from analysis. Indeed, the sensitivity of qRT-PCR testing for has shown to be as low as 32% for throat swabs [40]. However, in patients with negative results and high clinical suspicion of SARS-CoV-2 infection, multiple samples are often taken, including broncho-alveolar lavage. Thus, the number of patients excluded is expected to be low. Whilst this study reports a higher mortality from post-operative diagnosis of SARS-CoV-2 infection, it is unclear whether the infection was contracted pre-operatively or not, as has been discussed above.

This study does not have a control arm, assessing contemporaneous patients with undergoing an operation for proximal femoral fractures without SARS-CoV-2 infection during the height of the pandemic. However, comparison with high-quality pre-pandemic data strongly suggests a substantial increase in mortality. Patients and those who care for them should consider this carefully when making decisions in this common and challenging clinical scenario.

Conclusion

Patients undergoing surgery for a proximal femoral fracture with a peri-operative infection of SARS-CoV-2 have a high rate of mortality. The study would support the approach of providing these patients with individualised medical and anaesthetic care, including medical optimisation before theatre. It is imperative to prevent transmission of coronavirus in the hospital setting. Careful pre-operative counselling is needed for those with a proximal femoral fracture and SARS-CoV-2, especially those in the highest risk groups.

Tables & Figures

Fig. 1 Mixed-effects logistic regression model for 30 day mortality

Fig. 2. Mixed-effects logistic regression model for pulmonary complications

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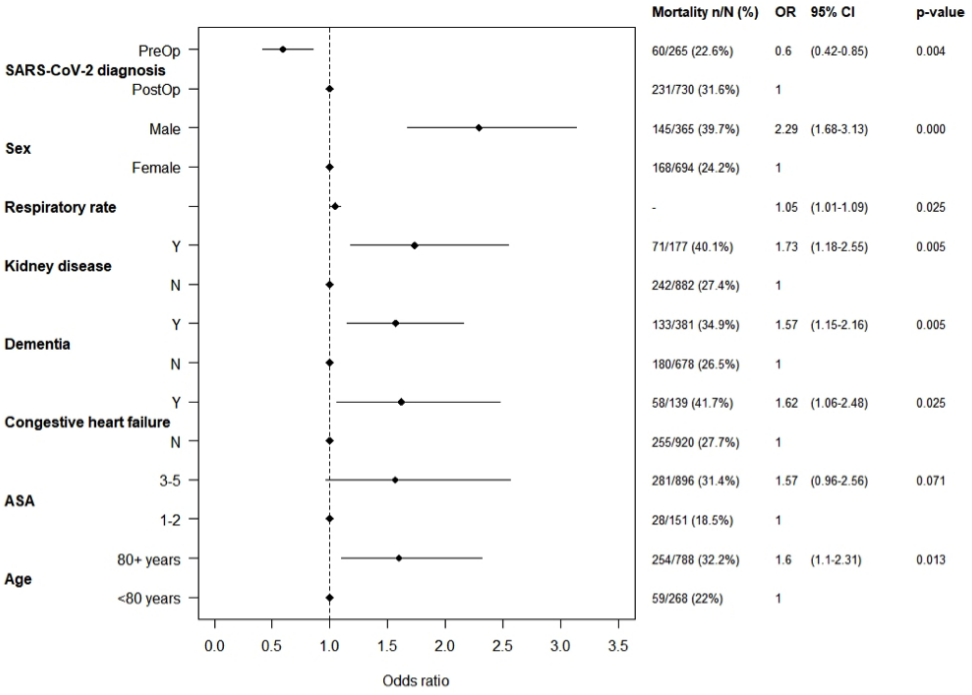


Fig. 1 Mixed-effects logistic regression model for 30 day mortality

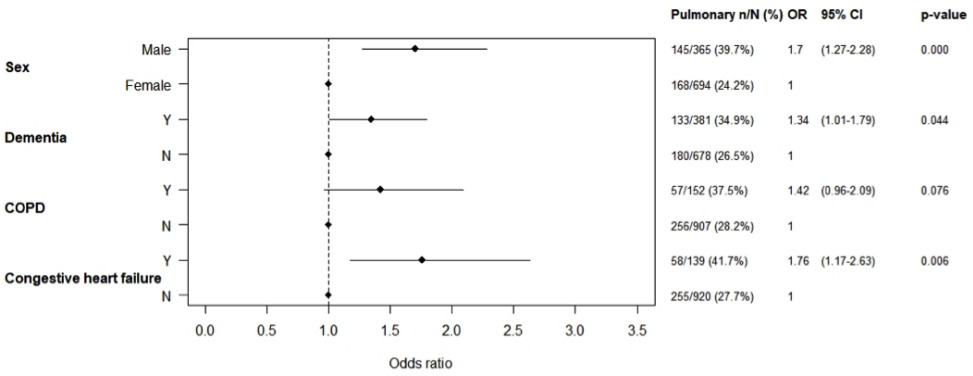


Fig. 2. Mixed-effects logistic regression model for pulmonary complications

Supplementary Material

Table S1. Baseline characteristics (sex, age, ASA grade, cardiac risk, time of diagnosis, method of diagnosis and month study participant recruited) of the full study population (n = 1063), and dead (n = 313) and alive (n =746) groups; p-values are for Fisher's exact tests comparing groups for each characteristic.

Characteristic	Full (n = 1063)	Alive (n = 746)	Dead (n = 313)	Dead (%)
*Sex (p-value = <0.001 ***)*				
Female	696 (65.5%)	526	168	24.2
Male	367 (34.5%)	220	145	39.7
Missing	0 (0.0%)	0	0	0.0
*Age (p-value = 0.001 **)*				
20-29 years	3 (0.3%)	3	0	0.0
30-39 years	2 (0.2%)	1	1	50.0
40-49 years	4 (0.4%)	3	1	25.0
50-59 years	24 (2.3%)	21	3	12.5
60-69 years	50 (4.7%)	39	11	22.0
70-79 years	189 (17.8%)	145	43	22.9
80-89 years	507 (47.7%)	360	144	28.6
90+ years	284 (26.7%)	174	110	38.7
Missing	0(0.0%)	0	0	0.0
*ASA (p-value = 0.001 **)*				
1-2	151 (14.2%)	123	28	18.5
3-5	899 (84.6%)	615	281	31.4
Missing	13(1.2%)	8	4	30.8

*Cardiac risk (p-value = <0.001 ***)*				
0	487 (45.8%)	372	114	23.5
1	349 (32.8%)	238	110	31.6
2	169 (15.9%)	106	61	36.5
3	44 (4.1%)	23	21	47.7
4	8 (0.8%)	5	3	37.5
5	1 (0.1%)	0	1	100.0
Missing	5 (0.47%)	2	3	60.0
*Time of diagnosis (p-value = 0.006 **)*				
Post-op	733 (69%)	499	231	31.6
Pre-op	266 (25%)	205	60	22.6
Missing	64 (6.0%)	42	22	34.4
Diagnosis (p-value = 0.668)				
Clinical	62 (5.8%)	42	20	32.3
Swab	992 (93.3%)	696	292	29.6
Missing				
*Month (p-value = 0.007 **)*				
February	26 (2.4%)	23	3	11.5
March	474 (44.6%)	313	159	33.7
April	558 (52.5%)	406	150	27.0
Missing	1(0.09%)	0	1	100.0

Table S2. Comorbidity data summaries by dead (n = 313) and alive (n =746) groups. Data tabulated are counts, with estimated odds ratios (OR), with 95% confidence intervals, and p-values from Fisher's exact tests for each comorbidity.

Comorbidity	Alive	Dead	OR	p-value

	(n = 746)	(n = 313)	(95% CI)		
	Y:N (%Y)	Y:N (%Y)			
Current smoker	34:712 (4.6%)	9:304 (2.9%)	0.62 (0.26, 1.34)	0.235	-
Asthma	53:693 (7.1%)	21:292 (6.7%)	0.94 (0.53, 1.62)	0.895	-
Current cancer diagnosis	57:689 (7.6%)	24:289 (7.7%)	1.00 (0.58, 1.68)	0.999	-
Chronic kidney disease (moderate/severe)	106:640 (14.2%)	71:242 (22.7%)	1.77 (1.25, 2.51)	0.001	**
Chronic obstructive pulmonary disease (COPD)	95:651 (12.7%)	57:256 (18.2%)	1.53 (1.05, 2.21)	0.027	*
Congenital abnormality - cardiac	4:742 (0.5%)	1:312 (0.3%)	0.60 (0.01, 6.04)	0.999	-
Congenital abnormality - non-cardiac	0:746 (0.0%)	4:309 (1.3%)	-	-	-
Congestive heart failure	81:665 (10.9%)	58:255 (18.5%)	1.87 (1.27, 2.73)	<0.001	***
Dementia	248:498 (33.2%)	133:180 (42.5%)	1.48 (1.12, 1.96)	0.005	**
Diabetes mellitus	142:604 (19.0%)	63:250 (20.1%)	1.07 (0.76, 1.51)	0.671	-
Hypertension	387:359 (51.9%)	186:127 (59.4%)	1.36 (1.03, 1.79)	0.026	*
Myocardial infarction or ischemic heart disease	103:643 (13.8%)	63:250 (20.1%)	1.57 (1.09, 2.25)	0.012	*
Peripheral vascular disease	34:712 (4.6%)	21:292 (6.7%)	1.51 (0.82, 2.72)	0.172	-
Stroke/ TIA	107:639 (14.3%)	57:256 (18.2%)	1.33 (0.92, 1.92)	0.114	-
Other (including other lung disease)	377:369 (50.5%)	158:155 (50.5%)	1.00 (0.76, 1.31)	0.999	-

Table S3. Diagnosis data summaries by dead (n = 313) and alive (n =746) groups. Data tabulated are counts, with estimated odds ratios (OR), with 95% confidence intervals, and p-values from Fisher's exact tests for each diagnosis method.

Diagnosis	Alive (n = 746)	Dead (n = 313)	OR (95% CI)	p-value	
	Y:N (%Y)	Y:N (%Y)			
Pre-op 4-7days					
CT thorax scan (negative for SARS-CoV-2)	10:736 (1.3%)	2:311 (0.6%)	0.47 (0.05, 2.24)	0.526	-

CT thorax scan (positive for SARS-CoV-2)	12:734 (1.6%)	0:313 (0%)	0.00 (0.00, 0.85)	0.023	*
Swab (negative for SARS-CoV-2)	17:729 (2.3%)	3:310 (1%)	0.42 (0.08, 1.45)	0.215	-
Swab (positive for SARS-CoV-2)	31:715 (4.2%)	8:305 (2.6%)	0.61 (0.24, 1.37)	0.283	-
Pre-op 1-3days					
CT thorax scan (negative for SARS-CoV-2)	8:738 (1.1%)	3:310 (1%)	0.89 (0.15, 3.75)	0.999	-
CT thorax scan (positive for SARS-CoV-2)	10:736 (1.3%)	3:310 (1%)	0.71 (0.13, 2.79)	0.765	-
Swab (negative for SARS-CoV-2)	41:705 (5.5%)	9:304 (2.9%)	0.51 (0.22, 1.08)	0.080	-
Swab (positive for SARS-CoV-2)	86:660 (11.5%)	15:298 (4.8%)	0.39 (0.20, 0.69)	<0.001	*
Pre-op surgery					
CT thorax scan (negative for SARS-CoV-2)	0:746 (0%)	0:313 (0%)	-	0.999	-
CT thorax scan (positive for SARS-CoV-2)	4:742 (0.5%)	0:313 (0%)	0.00 (0.00, 3.61)	0.326	-
Swab (negative for SARS-CoV-2)	13:733 (1.7%)	2:311 (0.6%)	0.36 (0.04, 1.62)	0.254	-
Swab (positive for SARS-CoV-2)	18:728 (2.4%)	7:306 (2.2%)	0.93 (0.32, 2.35)	1	-
Post-op Admission					
CT thorax scan (negative for SARS-CoV-2)	4:742 (0.5%)	1:312 (0.3%)	0.60 (0.01, 6.04)	0.999	-
CT thorax scan (positive for SARS-CoV-2)	8:738 (1.1%)	4:309 (1.3%)	1.19 (0.26, 4.50)	0.756	-
Swab (negative for SARS-CoV-2)	51:695 (6.8%)	12:301 (3.8%)	0.54 (0.26, 1.05)	0.064	-
Swab (positive for SARS-CoV-2)	317:429 (42.5%)	143:170 (45.7%)	1.14 (0.87, 1.50)	0.342	-
Discharge 30days					
CT thorax scan (negative for SARS-CoV-2)	4:742 (0.5%)	0:313 (0%)	0.00 (0.00, 3.61)	0.326	-
CT thorax scan (positive for SARS-CoV-2)	0:746 (0%)	1:312 (0.3%)	-	-	-
Swab (negative for SARS-CoV-2)	8:738 (1.1%)	0:313 (0%)	0.00 (0.00, 1.39)	0.114	-
Swab (positive for SARS-CoV-2)	75:671 (10.1%)	27:286 (8.6%)	0.85 (0.51, 1.36)	0.496	-
Diagnosis					
Positive SARS-CoV-2 swab - before surgery	122:624 (16.4%)	31:282 (9.9%)	0.56 (0.36, 0.86)	0.007	*
Positive SARS-CoV-2 swab - after surgery	409:337 (54.8%)	177:136 (56.5%)	1.07 (0.82, 1.41)	0.636	-

CT scan of the chest confirming SARS-CoV-2 - before surgery	20:726 (2.7%)	2:311 (0.6%)	0.23 (0.03, 0.97)	0.033	*
CT scan of the chest confirming SARS-CoV-2 - after surgery	9:737 (1.2%)	5:308 (1.6%)	1.33 (0.35, 4.46)	0.569	-
Clinical diagnosis or chest x-ray - suspected before time of surgery	39:707 (5.2%)	12:301 (3.8%)	0.72 (0.34, 1.43)	0.432	-
Clinical diagnosis or chest x-ray - suspected after time of surgery	67:679 (9%)	31:282 (9.9%)	1.11 (0.69, 1.77)	0.643	-

Table S4. SARS-CoV-2 symptoms data summaries by dead (n = 313) and alive (n =746) groups. Data tabulated are counts, with estimated odds ratios (OR), with 95% confidence intervals, and p-values from Fisher's exact tests for each symptom.

Symptom	Alive (n = 746)	Dead (n = 313)	OR (95% CI)	p-value	
	Y:N (%Y)	Y:N (%Y)			
Abdominal pain	11:735 (1.5%)	1:312 (0.3%)	0.21 (0.01, 1.49)	0.124	-
Breathlessness (dyspnoea)	54:692 (7.2%)	31:282 (9.9%)	1.41 (0.86, 2.28)	0.172	-
Cough	73:673 (9.8%)	35:278 (11.2%)	1.16 (0.73, 1.81)	0.505	-
Diarrhoea	8:738 (1.1%)	1:312 (0.3%)	0.30 (0.01, 2.22)	0.295	-
Fatigue	21:725 (2.8%)	10:303 (3.2%)	1.14 (0.47, 2.56)	0.695	-
Fever (>38 celsius)	61:685 (8.2%)	25:288 (8%)	0.98 (0.57, 1.61)	0.999	-
Haemoptysis	0:746 (0.0%)	0:313 (0.0%)	-	-	-
Myalgia	10:736 (1.3%)	3:310 (1%)	0.71 (0.13, 2.79)	0.765	-
Nausea/vomiting	13:733 (1.7%)	7:306 (2.2%)	1.29 (0.43, 3.52)	0.623	-
Sputum	8:738 (1.1%)	4:309 (1.3%)	1.19 (0.26, 4.50)	0.756	-
Other	311:435 (41.7%)	136:177 (43.5%)	1.08 (0.82, 1.42)	0.633	-

Table S5. Pre-surgery measures data (n, mean and sd) for the full study population (n = 1063), and dead (n = 313) and alive (n =746) groups, and the difference in means between groups, with 95% confidence interval, and p-values from unpaired t-tests.

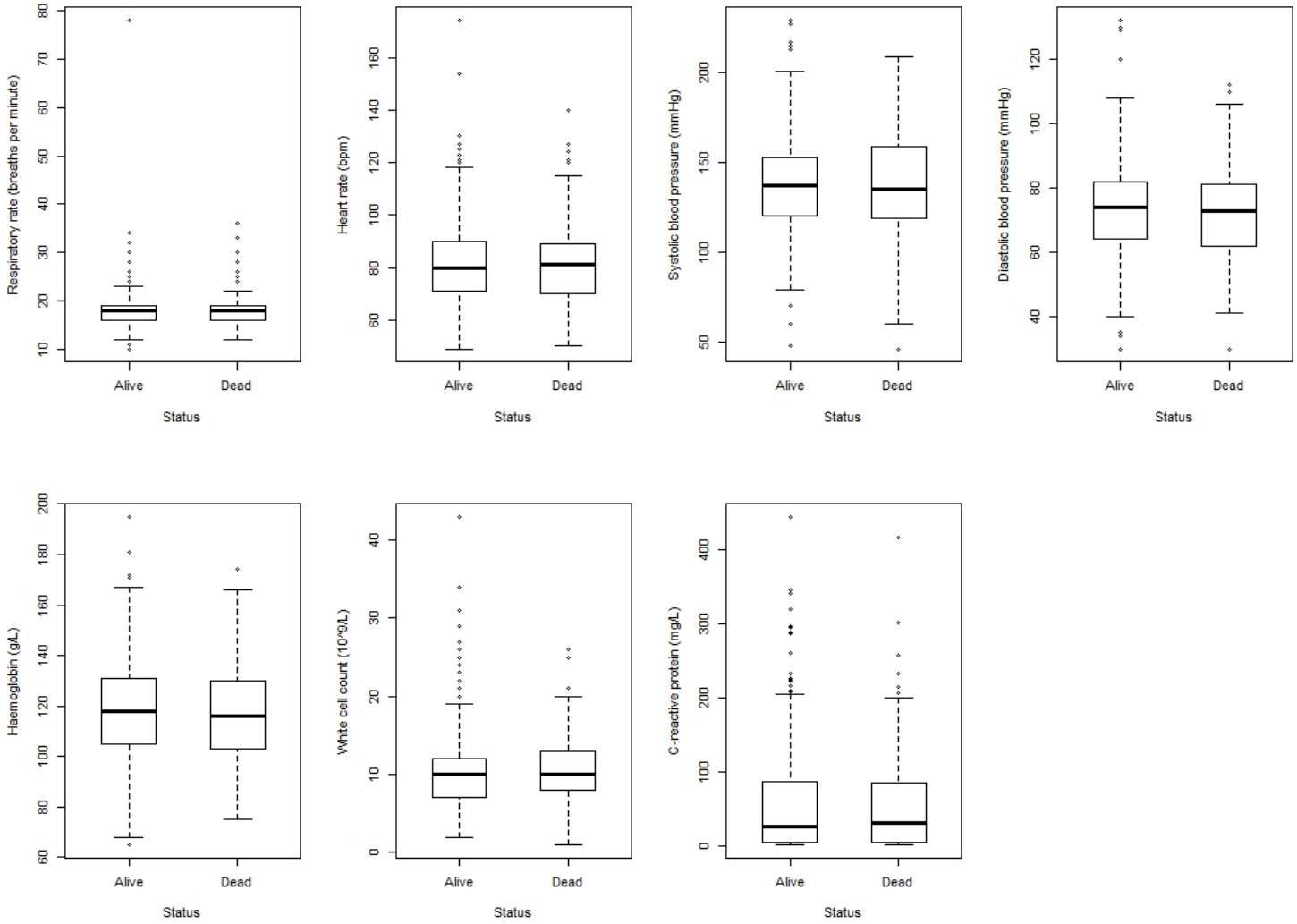
Measure	Full (n = 1063)		Alive (n = 746)		Dead (n = 313)		Difference (95%CI)	p-value
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)		
Respiratory rate (breaths/minute)	996	17.75 (3.52)	706	17.65 (3.68)	289	18.02 (3.09)	-0.37 (-0.85, 0.11)	0.132
Heart rate (bpm)	1022	81.10 (14.63)	723	81.16 (14.59)	298	80.95 (14.77)	0.22 (-1.76, 2.20)	0.830
Systolic blood pressure (mmHg)	1023	138.15 (26.04)	724	138.33 (25.85)	298	137.61 (26.53)	0.72 (-2.80, 4.24)	0.687
Diastolic blood pressure (mmHg)	1021	72.97 (13.89)	723	73.07 (13.86)	297	72.70 (14.00)	0.37 (-1.52, 2.25)	0.703
Haemoglobin (g/L)	1062	117.94 (19.22)	745	118.35 (19.21)	313	116.93 (19.26)	1.41 (-1.13, 3.95)	0.276
White cell count (10^9/L)	1060	10.33 (4.26)	744	10.33 (4.36)	313	10.34 (4.04)	-0.01 (-0.57, 0.56)	0.976
C-reactive protein (mg/L)	738	54.70 (66.26)	514	54.84 (67.68)	221	54.63 (63.34)	0.21 (-10.28, 10.70)	0.969

Table S6. Operation details for the full study population (n = 1063), and dead (n = 313) and alive (n =746) groups; p-values are for Fisher's exact tests comparing groups for each characteristic.

Characteristic	Full (n = 1063)	Alive (n = 746)	Dead (n = 313)	Dead (%)
Anaesthesia (p-value = 0.787)				
General	527 (49.6%)	368	157	29.9
Regional	524 (49.3%)	372	152	29.0
Missing	12 (27.8%)	6	4	33.3
*Pre-op respiration (p-value = 0.031 *)*				
None	714 (67.2%)	520	194	27.2
Oxygen	336 (31.6%)	220	115	34.3
Ventilated	2 (0.2%)	2	0	0.0
Missing	11(1.03%)	4	4	36.4
Pre-op delay (p-value = 0.220)				

< 6 hours	16 (1.5%)	11	5	31.2
6-23 hours	322 (30.3%)	232	88	27.5
24-47 hours	224 (21.1%)	147	77	34.4
48-71 hours	82 (7.7%)	61	21	25.6
72+ hours	123 (11.6%)	94	29	23.6
Missing	296 (27.8%)	201	93	31.4
*Procedure (p-value = 0.015 *)*				
LIMB - lower limb - total hip replacement	45 (4.2%)	41	4	8.9
LIMB - lower limb fracture - Cannulated Screws	5 (0.5%)	5	0	0.0
LIMB - lower limb fracture - Reduction and Internal Fixation	15 (1.4%)	10	5	33.3
LIMB - lower limb fracture - Dynamic Hip Screw	276 (26%)	195	81	29.3
LIMB - lower limb fracture - Reduction and Intramedullary Fixation	243 (22.9%)	169	73	30.2
LIMB - lower limb fracture - Partial Hip Replacement (Hemiarthroplasty)	479 (45.1%)	326	150	31.5
Missing	0 (0.0%)	0	0	0.0

Figure S1. Boxplots showing distributions of pre-surgery measures by outcome status (dead or alive). Boxes show interquartile range (IQR), bars medians and whiskers are 1.5 times IQR.


Respiratory rate (breaths per minute)
Heart rate (bpm)
Systolic blood pressure (mmHg)
Diastolic blood pressure (mmHg)
Haemoglobin (g/L)
White cell count (10^9/L)
C-reactive protein (mg/L)
Alive
Dead
Status

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1 & 2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6
Bias	9	Describe any efforts to address potential sources of bias	8
Study size	10	Explain how the study size was arrived at	N/A
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	8
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	9
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	9
Outcome data	15*	Report numbers of outcome events or summary measures over time	9

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	9-12
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9-12
Discussion			
Key results	18	Summarise key results with reference to study objectives	13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	16
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13-15
Generalisability	21	Discuss the generalisability (external validity) of the study results	13-15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	1

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Outcomes after peri-operative SARS-CoV-2 infection in patients with proximal femoral fractures: an international cohort study

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Outcomes after peri-operative SARS-CoV-2 infection in patients with proximal femoral fractures: an international cohort study

COVIDSurg Collaborative*

***Author contributions:** Full list of authors and roles within this research project are available in Supplementary files, titled Authorship (available to editors)

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ABSTRACT

Objectives: Studies have demonstrated high rates of mortality in people with proximal femoral fracture and SARS-CoV-2, but there is limited published data on the factors that influence mortality for clinicians to make informed treatment decisions. This study aims to report the 30-day mortality associated with peri-operative infection of patients undergoing surgery for proximal femoral fractures and to examine the factors that influence mortality in a multi-variate analysis.

Setting: Prospective, international, multicentre, observational cohort study.

Participants: Patients undergoing any operation for a proximal femoral fracture from 1st February to 30th April 2020 and with perioperative SARS-CoV-2 infection (either 7-days prior, or 30-days post-operative).

Primary outcome: 30-day mortality. Multivariate modelling was performed to identify factors associated with 30-day mortality.

Results: This study reports included 1063 patients from 174 hospitals in 19 countries. Overall 30-day mortality was 29.4% (313/1063). In an adjusted model, 30-day mortality was associated with male gender (OR 2.29, 95% CI 1.68-3.13, p<0.001), age >80 years (OR 1.60, 95% CI 1.1-2.31, p=0.013), pre-operative diagnosis of dementia (OR 1.57, 95% CI 1.15-2.16, p=0.005), kidney disease (OR 1.73, 95% CI 1.18-2.55, p=0.005) and congestive heart failure (OR 1.62, 95% CI 1.06-2.48, p=0.025). Mortality at 30-days was lower in patients with a pre-operative diagnosis of SARS-CoV-2 (OR 0.6, 95% CI 0.6 (0.42-0.85), p=0.004). There was no difference in mortality in patients with an increase to delay in surgery (p=0.220), or type of anaesthetic given (p=0.787).

Conclusions: Patients undergoing surgery for a proximal femoral fracture with a peri-operative infection of SARS-CoV-2 have a high rate of mortality. This study would support the need for providing these patients with individualised medical and anaesthetic care, including medical optimisation before theatre. Careful pre-operative counselling is needed for those with a proximal femoral fracture and SARS-CoV-2, especially those in the highest risk groups.

ARTICLE SUMMARY

Strengths and limitations of this study

- This is a large, international, multicentre cohort study from which the results are generalisable across populations in other countries.
- This study described specific risk factors for mortality, which patients and those who care for them should use to make informed decisions regarding care.
- There is not control arm to assess contemporaneous patients with undergoing an operation for proximal femoral fractures without SARS-CoV-2 infection during the height of the pandemic. However with high-quality data present pre-pandemic strongly suggests a substantial increase in mortality.

MAIN TEXT

Background

The rapid worldwide spread of Coronavirus Disease-2019 (COVID-19), caused by the Severe Acute Respiratory Syndrome CoronaVirus-2 (SARS-CoV-2) has had a severe effect on the elderly and frail population. A fracture of the proximal femur (neck of femur fracture) is a critical event in the elderly, frail population, with a high rate of death despite medical and surgical intervention [1]. Since 2007, there has been a steady improvement in mortality after a proximal femoral fracture with 6.1% of patients dying within 30 days of injury in the UK in 2018 [2]. However, the emergence of COVID-19 presents a new and unquantified risk to this particularly vulnerable group.

Proximal femur fractures represent a large international burden with incidence between 43 and 920 per 100,000 population [3]. As most fractures of the proximal femur happen as a result of trips or falls in the home, people have continued to present with this injury despite social restrictions [4, 5]. These patients typically have multiple co-morbidities and frailty is common [1]. Resultantly, they are particularly vulnerable to pulmonary complications [1, 6]. It is widely accepted that elderly patients with existing co-morbidities are at higher risks of critical illness and mortality due to COVID-19, potentially due to a higher preponderance to release pro-inflammatory cytokines that result in severe disease [7-9].

Clinicians have been swift to respond to this pandemic with large re-organisation of service provision [10, 11]. In response to this, the COVIDSurg collaborative

(www.globalsurg.org/covidsurg) has collected an international, large volume dataset to inform the global community of the safety of surgery in patients with peri-operative SARS-CoV-2 infection. The first report has demonstrated a 30-day mortality of 23.8% across patients undergoing any type of surgery [12]. Data published so far has reported a high mortality rate in a small cohort of patients with proximal femoral fractures positive for SARS-CoV-2 infection, with a maximum cohort size of 114 patients (range 10-114 patients) [13-20]. However few reports have the sample size sufficient to explore the factors that influence outcome. Further, large-scale data are required to explore pre-operative and operative variables that influence outcomes in order to inform the clinical decision-making processes.

Aims

The primary aim of this study is to determine the mortality rate observed in patients undergoing surgery for proximal femoral fracture with peri-operative SARS-CoV-2 infection. Secondarily, we aim to explore the patient and treatment factors associated with these outcomes.

Methods

Setting

This is an international, multicentre cohort study including consecutive patients who underwent surgery for proximal femoral fracture from 1st February 2020 to 30th April 2020. This study is a pre-planned sub-analysis of a larger, ongoing study designed to assess outcomes following all surgery for patients with perioperative SARS-CoV-2 infection [12].

The COVIDSurg collaborative is an international, multicentre, multidisciplinary team with individual collaborators collecting data locally, which is collated centrally. The collaborative methodology, which is well described and validated was used for this project [21]. The study protocol was registered online (ClinicalTrials.gov identifier: NCT04323644).

Inclusion Criteria

Participating hospitals included consecutive patients undergoing surgery for proximal femoral fractures that had SARS-CoV-2 infection diagnosed (laboratory, clinical or radiologically) either 7 days pre-operatively, or up to 30-days post-operatively. For those diagnosed pre-operative, this represents the timeframe where the majority of patients still active disease [22]. For those patients who underwent multiple procedures, the procedure closest to the time of confirmation of SARS-CoV-2 infection was defined as the index procedure.

Patients received laboratory confirmation of SARS-CoV-2 using quantitative Reverse Transcription Polymerase Chain Reaction (qRT-PCR). As qRT-PCR is not available in all participating hospitals, patients were included if their diagnosis was made by clinical or radiological findings. Clinical diagnosis was made in patients presenting with symptoms and a clinical pattern of COVID-19. These included cough, fever and/or myalgia [23]. Radiological diagnosis was made through computed tomography (CT) scanning of the thorax according to local protocols. All patients who were included solely on clinical or radiological suspicion but had a subsequent negative test were excluded from the database by individual collaborators.

Diagnosis

This study includes all patients identified as having an operation for a proximal femoral fracture. The diagnosis was established pragmatically by the local site teams according to their assessment of the fracture. The reported data was screened by a central dedicated data cleaning team, with only confirmed proximal femoral fractures included in the cohort.

Patient Identification

Researchers at participating centres screened consecutive patients undergoing surgery to ensure all patients were identified. The study was initiated in some countries after their peak of infection, and therefore retrospective identification and data collection was permitted, as long as the data collection was consecutive at that site.

To reduce selection bias, a variety of written materials were distributed to site leads to highlight possible methods of identifying patients ensuring all eligible patients were

included. Investigators were invited to social media groups and online teleconferences to trouble-shoot recruitment issues, share learning and ensure consistent recruitment into the wider cohort.

Outcome measures

The primary outcome measure was 30-day all-cause mortality, with the day of surgery defined as day zero. The secondary outcome measure was rate of pulmonary complications, which is a composite outcome defined previously from the Prevention of Respiratory Insufficiency after Surgical Management (PRISM) randomised controlled trial [24, 25].

Pulmonary complications were defined as pneumonia, acute respiratory distress syndrome (ARDS), and/or unexpected post-operative ventilation; these have been identified as the most frequent COVID-19-related pulmonary complications in medical patients [23]. Unexpected post-operative ventilation was defined as either (i) any episode of non-invasive ventilation, invasive ventilation, or extracorporeal membrane oxygenation after initial extubation following surgery, or (ii) unexpected failure to extubate following surgery [12].

Data collection and quality assurance

Data was collected online using the Research Electronic Data Capture (REDCap) web application [26]. Demographic variables recorded consisted of age, sex, and American Society of Anesthesiologists physical status classification (ASA). Age was collected as a categorical variable by deciles of age. ASA at the time of surgery was dichotomized to (i) grades 1-2 and (ii) grades 3-5 for the purpose of analysis, time to

surgery to (i) under 24 hours, (ii) 24-48 hours, and (iii) over 48 hours, and surgery to (i) hemiarthroplasty, (ii) total hip replacement, (iii) dynamic hip screw, (iv) cannulated screws and (v) intramedullary nail. The timing of SARS-CoV-2 diagnosis was recorded as either preoperative or post-operative.

Before data was entered into analysis, site principle investigators were required to confirm all consecutive eligible cases had been completed and uploaded. Where diagnosis was unclear, authors were contacted for clarification.

Statistical analysis

The study was reported according to STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines [27]. Proportions are expressed with 95% confidence intervals and the mean and 95% confidence intervals were used where data were assumed to be approximately normally distributed. Fishers exact test was used for categorical data. Non-parametric data was summarised with the median and interquartile ranges. Statistical significance was assessed at the 5% level.

The risk of death at 30 days was chosen as the primary outcome for the study. Mixed-effects logistic regression analysis was used to assess the strength and significance of associations between a number of explanatory variables and death within 30-days. Random effects were included in the mixed-effects model to account for the hierarchical structure of the data (individual hospital effects are naturally nested within country effects) and fixed effects were included to adjust for a range of pre-operative variables that may influence mortality in this population, and relevant factors related to the injury or treatment (e.g. type of operation, time from admission

to operation, type of anaesthetic). An additional analysis of the same factors was undertaken using the same model structure for the secondary outcome of pulmonary complications. This was an exploratory analysis with the significance level set at 5%, with no specific adjustments made for model testing. All analyses were implemented in R (R Core Team (2020). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/.).

Patient and Public Involvement

Patients were not involved in the design, conduct or reporting of this study.

Results

Population

This study returned 30-day follow up for 1063 patients with proximal femoral fractures. Data was collected in 174 hospitals from 19 countries (Supplementary Table S1). Of these, 65.5% were female (696/1063). 7.8% (83/1063) patients were <70 years old, 17.8% (189/1063) were between 70-79 years, 47.7% (507/1063) were between 80-89 and 26.7% (284/1063) were 90+ years old.

Mortality

Overall 30-day mortality was 29.4% (313/1063). With each decile of age, mortality significantly increased, being highest in those patients >90 years old (38.7% [110/284], p=0.001).

In an adjusted model (Figure 1), 30-day mortality was associated with male gender (OR 2.29, 95% CI 1.68-3.13, p<0.001), age >80 years (OR 1.60, 95% CI 1.1-2.31, p=0.013), diagnosis of dementia (OR 1.57, 95% CI 1.15-2.16, p=0.005), chronic kidney disease (OR 1.73, 95% CI 1.18-2.55, p=0.005) and congestive heart failure (OR 1.62, 95% CI 1.06-2.48, p=0.025). 30-day mortality was lower in patients with a pre-operative diagnosis of SARS-CoV-2 (OR 0.60, 95% CI 0.42-0.85, p=0.004). Non-adjusted values are presented in Table S2.

Pulmonary complications

In an adjusted model (Figure 2), respiratory complications were associated with male gender (OR 1.7, 95% CI 1.27-2.28, p<0.001), diagnosis of dementia (OR 1.34, 95%

CI 1.01-1.79, p=0.044) and congestive heart failure (OR 1.76, 95% CI 1.17-2.63, p=0.006). The presence of Chronic Obstructive Pulmonary Disorder (COPD) showed no significant association (OR 1.42, 95% CI 0.96-2.09, p=0.076).

Diagnosis

The majority of diagnosis of SARS-CoV-2 was made via PCR swab testing 93.3% (992/1063) (Table S1 & S3) and there was no difference in mortality between those diagnosed clinically (p=0.668). The majority of patients received a diagnosis post-operatively 69% (733/1063).

Pre-operative variables

Pre-operative symptoms (Table S4), including breathlessness, cough and fever (>38 ° Celsius) were not significantly different in patients who were alive or dead at 30 days post-operatively. On examination of pre-operative observations, a high respiratory rate was predictive of mortality (OR 1.73 95% CI 1.18-2.55, p=0.025) (Figure 1). However, there was no significant difference in patient's heart rate, systolic or diastolic blood pressure (Table S5, Figure S1) between those who were alive or dead at 30 days.

Those patients with ASA grade 3-5 had a significantly higher mortality of 31.4% (281/899) versus ASA of 1-2 of 18.5% (28/151), p=0.001.

Procedures

The operations were carried out under a general anaesthetic in 49.6% (527/1063) of patients (Table S6). 67.2% (714/1063) of patients did not require any pre-operative

oxygen therapy. In this cohort, 31.8% (338/1063) of patients had their operation within 24 hours of presentation to hospital, 21.1% (224/1063) had their operation between 24-47 hours and 19.2% (205/1063) of patients had their operation after 48 hours of presentation to hospital.

In this cohort, 45.1% (479/1063) of patients underwent hemiarthroplasty with a further 4.2% undergoing total hip replacement (45/1063). For patients who underwent fixation, 26% (276/1063) underwent Dynamic Hip Screw (DHS) fixation, 22.9% (243/1063) patients underwent intramedullary fixation, 0.5% (5/1063) underwent cannulated screw fixation whilst a further 1.4% (15/1053) underwent internal fixation.

There was no difference in mortality between patients undergoing general and regional anaesthesia (29.9% [157/527 versus 29.0% [152/524], p=0.787). However, there was an increased mortality in those patients requiring pre-operative oxygen therapy (34.3% [115/336] versus 27.2% [194/714], p=0.031).

There was no significant difference in mortality for patients with delayed operation. The highest mortality was for patients operated between 24-47 hours of admission (34.4%, [77/224]) but was not significantly higher than less than those operated after 48 hours (p=0.220).

Mortality was highest in March (33.7%, 159/474) compared to April (27.0%, 150/558), and February (11.5%, 3/26), p=0.007 (Table S1).

Discussion

The 30-day mortality rate for patients with a peri-operative diagnosis of SARS-CoV-2 infection undergoing surgery for proximal femoral fracture is substantial. An overall rate of 29.4% compares to the reported 30-day mortality in the literature for proximal femoral fractures ranging between 3.5-6.8% [2, 28-32]. This rate is higher than found at the one year time point [33]. Further, elderly patients, and those with medical comorbidities such as dementia, chronic kidney disease and congestive heart failure were associated with higher risk of 30-day mortality. Notably, patients with a pre-operative diagnosis of SARS-CoV-2 infection had lower rates of 30-day mortality, likely reflecting early recognition and closer management of these patients. Findings from this study will be useful in guiding clinicians to identify high-risk patients that may warrant closer medical and surgical input during the COVID-19 pandemic.

Considering this high mortality, it is critical that patients who present without a diagnosis SARS-CoV-2 with proximal femoral fractures are protected from contracting SARS-CoV-2 in the peri-operative period. A study by Kayani et al. has suggested that half of infections in patients with proximal femoral fractures occur in hospital, as denoted by having negative pre-operative samples [17]. Similarly, a study by Hall et al. has suggested nearly half of cases were due to nosocomial transmission [34]. Within this study, 733 (69%) of infections were diagnosed post-operatively. This may infer that infections have been transferred in hospital, although due to incubation period of the virus, it is hard to know the proportion that contracted the virus prior to presentation or in hospital. [7, 35] Higher mortality was observed in people who had a post-operative diagnosis, which emphasises the critical importance

of avoiding in-hospital transmission. Hospitals should consider implementation of careful infection control processes to minimise and prevent transmission of SARS-CoV-2 infection. Within the elective setting, the creation of COVID-19-free surgical pathways for elective patients has been shown to reduce infection and subsequent mortality [36-38] and whilst only some of the principles are transferrable to the emergency setting, it demonstrates the value of meticulous infection control processes throughout the hospital stay. Furthermore, patients should be reinforced of methods to reduce risk of transmission in the community after discharge, including (but not limited to) social distancing, isolation and hygiene.

For those patients presenting with SARS-CoV-2 (either existing diagnosis or clinical findings suggestive of) and a proximal femoral fracture, it is important for data to be used as part of the informed consent process. In patients with multiple high-risk factors such as those who are more elderly, have respiratory and cardiac co-morbidities, non-operative management may be considered following an appropriate discussion with the patient and/or their family. Every year in the UK, 2.5% of hip fractures are treated non-operatively [39]. A study performed before the pandemic reported that the mortality within thirty days for conservatively treated patients was 31.3% [40]. We do not know the mortality from non-operative management during the pandemic for patients with SARS-Cov-2, but the particularly high mortality associated with surgery in high-risk groups may change the balance of benefit and harm towards conservative treatment and this should be considered.

The 30-day mortality of 29.4% identified within this study is comparable to published literature, in the UK (range from 16.3%-35.6%) [15-17, 19, 34, 41], Italy (18.75%)

[14], Spain (30.4%) [13] and the USA (range from 35.3%-56%) [18, 20]. From a study within the UK, the authors also found a correlation between male sex and increased mortality (OR 2.69), which is similar to that demonstrated in this study (OR 2.29) [16]. Additionally, another UK study reported having more than three co-morbidities as a risk factor for mortality [17]. This study has specifically delineated a diagnosis of dementia, chronic kidney disease and congestive heart failure as being independent risk factors for mortality. In a study from USA, the authors found those patients who died were older with multiple co-morbidities and this was reflected in statistically significant higher ASA scores in comparison to their negative counterparts [20].

This study found that there was no significant increase in mortality with delay to surgery. Current guidelines suggest early surgery should be undertaken [42] and this is associated with lower mortality [43]. This would suggest that those patients at the highest risk of mortality can have medical optimisation, if appropriate, and will not result in a higher mortality from SARS-CoV-2 infection. This includes correction of concurrent medical issues often found in this population, examples of which include correction of acute renal failure, electrolyte disturbances and/or anticoagulation related issues. With regards to recovery from SARS-CoV-2 infection, it is important to consider that an increased risk of mortality for those undergoing surgery persists until seven weeks after diagnosis [44]. This risk reduces gradually after two weeks after diagnosis and should be considered.

Similarly, previous studies have found a higher rate of mortality in patients undergoing general versus regional anaesthesia for proximal femoral fractures [45,

46]. This study reports no difference between general and regional anaesthetic (29.9% versus 29.0%, p=0.787). Whilst this was not the primary outcome of this study, this suggests that a positive test for SARS-CoV-2 should not have a large influence on anaesthetic decisions. This should be interpreted with caution in the light of this being an exploratory study. Out of all clinical features, respiratory rate at presentation was associated with higher mortality. Clinicians should focus on this as an important finding when counselling patients of their peri-operative mortality.

This study has also found an increased mortality during the month of March 2020. This corresponds to the peak of caseload of infections internationally [47, 48]. Increased circulation of SARS-CoV-2 within countries has shown to increase mortality through higher viral loads [47, 49]. This study validates that surgical patients are particularly susceptible during surge of cases.

This is a large, varied cohort of patients undergoing surgery for a proximal femoral fractures with SARS-Cov-2 infection diagnosed peri-operatively. This study was conducted in multiple centres, internationally, allowing it to be generalisable across populations in other countries.

Limitations

This study was conducted in hospitals in the early to mid-phase of the pandemic where routine testing was not available in all participating centres. As such, to be pragmatic, patients were included if a clinical diagnosis was made by the treating physician. Protocols were not standardised for clinical diagnosis and were left the senior treating physician. Laboratory diagnosis was made by qRT-PCR, from which

false-negative results may have excluded patients from analysis. Indeed, the sensitivity of qRT-PCR testing for has shown to be as low as 32% for throat swabs [50]. However, in patients with negative results and high clinical suspicion of SARS-CoV-2 infection, multiple samples are often taken, including broncho-alveolar lavage. Thus, the number of patients excluded is expected to be low. Whilst this study reports a higher mortality from post-operative diagnosis of SARS-CoV-2 infection, it is unclear whether the infection was contracted pre-operatively or not, as has been discussed above.

This study does not have a control arm, assessing contemporaneous patients with undergoing an operation for proximal femoral fractures without SARS-CoV-2 infection during the height of the pandemic. However, comparison with high-quality pre-pandemic data strongly suggests a substantial increase in mortality. Patients and those who care for them should consider this carefully when making decisions in this common and challenging clinical scenario.

Conclusion

Patients undergoing surgery for a proximal femoral fracture with a peri-operative infection of SARS-CoV-2 have a high rate of mortality. The study would support the approach of providing these patients with individualised medical and anaesthetic care, including medical optimisation before theatre. It is imperative to prevent transmission of coronavirus in the hospital setting. Careful pre-operative counselling is needed for those with a proximal femoral fracture and SARS-CoV-2, especially those in the highest risk groups.

Tables & Figures

Fig. 1 Mixed-effects logistic regression model for 30 day mortality

Fig. 2. Mixed-effects logistic regression model for pulmonary complications

Competing interests

The collaborative group report no conflicts of interest

Contributor statement

CK is the lead author for this manuscript and was responsible for inception, analysis and writing of this manuscript alongside the COVIDSurg Collaborative.

Full list of authors and roles within this research project are available in Supplementary files, titled Authorship (available to editors)

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Data Sharing

No additional data available. Requests for raw data can be requested via the corresponding author.

Ethics Statement

This observational study collected anonymised routine clinical data, using an established international trainee collaborative model [51]. Within the United Kingdom this was registered as a clinical audit or service evaluation at each participating trust following individual hospital policies and procedures, prior to initiating data collection at that site. In other countries, the principal investigator was responsible for obtaining local approval in line with local and/or national guidelines. In some participating countries, informed patient consent was taken, whilst in others the requirement was waived by local research committees. The lead centre for this manuscript was University Hospitals Coventry & Warwickshire (approval number SE0233). Country-specific guidelines for site set-up were published on a dedicated study website (www.globalsurg.org/covidsurg).

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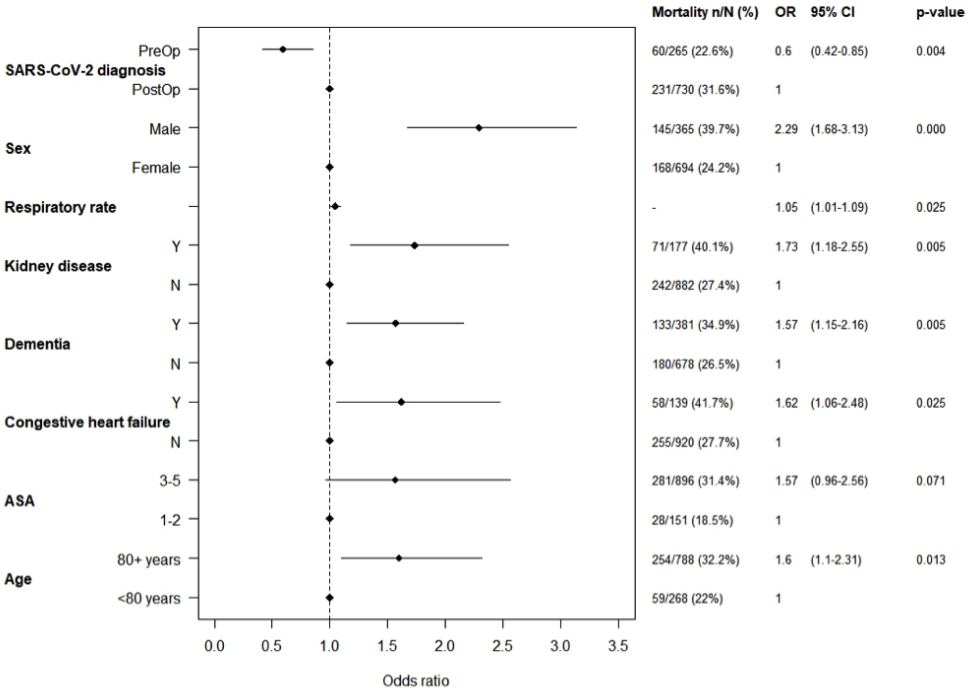


Fig. 1 Mixed-effects logistic regression model for 30 day mortality

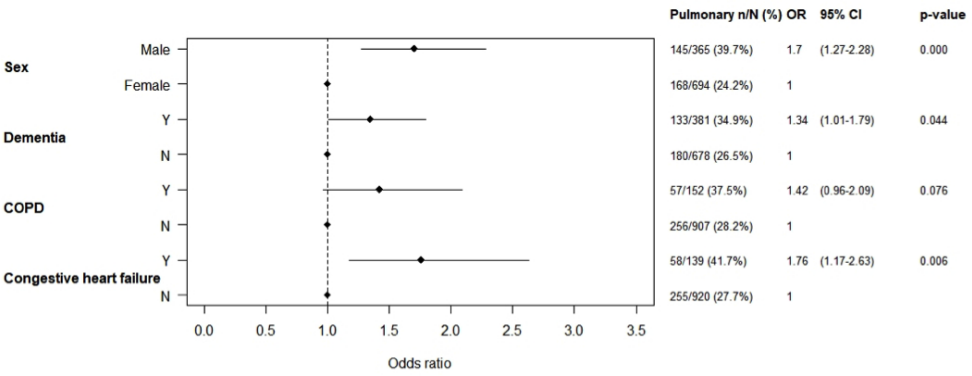


Fig. 2. Mixed-effects logistic regression model for pulmonary complications

Supplementary Material

Table S1. Baseline characteristics (sex, age, ASA grade, cardiac risk, time of diagnosis, method of diagnosis and month study participant recruited) of the full study population (n = 1063), and died (n = 313) and alive (n =746) groups; p-values are for Fisher's exact tests comparing groups for each characteristic.

Characteristic	Full (n = 1063)	Alive (n = 746)	Died (n = 313)	Died (%)
*Sex (p-value = <0.001 ***)*				
Female	696 (65.5%)	526	168	24.2
Male	367 (34.5%)	220	145	39.7
Missing	0 (0.0%)	0	0	0.0
*Age (p-value = 0.001 **)*				
20-29 years	3 (0.3%)	3	0	0.0
30-39 years	2 (0.2%)	1	1	50.0
40-49 years	4 (0.4%)	3	1	25.0
50-59 years	24 (2.3%)	21	3	12.5
60-69 years	50 (4.7%)	39	11	22.0
70-79 years	189 (17.8%)	145	43	22.9
80-89 years	507 (47.7%)	360	144	28.6
90+ years	284 (26.7%)	174	110	38.7
Missing	0(0.0%)	0	0	0.0
*ASA (p-value = 0.001 **)*				
1-2	151 (14.2%)	123	28	18.5
3-5	899 (84.6%)	615	281	31.4
Missing	13(1.2%)	8	4	30.8

*Cardiac risk (p-value = <0.001 ***)*				
0	487 (45.8%)	372	114	23.5
1	349 (32.8%)	238	110	31.6
2	169 (15.9%)	106	61	36.5
3	44 (4.1%)	23	21	47.7
4	8 (0.8%)	5	3	37.5
5	1 (0.1%)	0	1	100.0
Missing	5 (0.47%)	2	3	60.0
*Time of diagnosis (p-value = 0.006 **)*				
Post-op	733 (69%)	499	231	31.6
Pre-op	266 (25%)	205	60	22.6
Missing	64 (6.0%)	42	22	34.4
Diagnosis (p-value = 0.668)				
Clinical	62 (5.8%)	42	20	32.3
Swab	992 (93.3%)	696	292	29.6
Missing				
*Month (p-value = 0.007 **)*				
February	26 (2.4%)	23	3	11.5
March	474 (44.6%)	313	159	33.7
April	558 (52.5%)	406	150	27.0
Missing	1(0.09%)	0	1	100.0

Table S2. Comorbidity data summaries by died (n = 313) and alive (n =746) groups. Data tabulated are counts, with estimated odds ratios (OR), with 95% confidence intervals, and p-values from Fisher's exact tests for each comorbidity.

Comorbidity	Alive	Died	OR	p-value

	(n = 746)	(n = 313)	(95% CI)		
	Y:N (%Y)	Y:N (%Y)			
Current smoker	34:712 (4.6%)	9:304 (2.9%)	0.62 (0.26, 1.34)	0.235	-
Asthma	53:693 (7.1%)	21:292 (6.7%)	0.94 (0.53, 1.62)	0.895	-
Current cancer diagnosis	57:689 (7.6%)	24:289 (7.7%)	1.00 (0.58, 1.68)	0.999	-
Chronic kidney disease (moderate/severe)	106:640 (14.2%)	71:242 (22.7%)	1.77 (1.25, 2.51)	0.001	**
Chronic obstructive pulmonary disease (COPD)	95:651 (12.7%)	57:256 (18.2%)	1.53 (1.05, 2.21)	0.027	*
Congenital abnormality - cardiac	4:742 (0.5%)	1:312 (0.3%)	0.60 (0.01, 6.04)	0.999	-
Congenital abnormality - non-cardiac	0:746 (0.0%)	4:309 (1.3%)	-	-	-
Congestive heart failure	81:665 (10.9%)	58:255 (18.5%)	1.87 (1.27, 2.73)	<0.001	***
Dementia	248:498 (33.2%)	133:180 (42.5%)	1.48 (1.12, 1.96)	0.005	**
Diabetes mellitus	142:604 (19.0%)	63:250 (20.1%)	1.07 (0.76, 1.51)	0.671	-
Hypertension	387:359 (51.9%)	186:127 (59.4%)	1.36 (1.03, 1.79)	0.026	*
Myocardial infarction or ischemic heart disease	103:643 (13.8%)	63:250 (20.1%)	1.57 (1.09, 2.25)	0.012	*
Peripheral vascular disease	34:712 (4.6%)	21:292 (6.7%)	1.51 (0.82, 2.72)	0.172	-
Stroke/ TIA	107:639 (14.3%)	57:256 (18.2%)	1.33 (0.92, 1.92)	0.114	-
Other (including other lung disease)	377:369 (50.5%)	158:155 (50.5%)	1.00 (0.76, 1.31)	0.999	-

Table S3. Diagnosis data summaries by died (n = 313) and alive (n =746) groups. Data tabulated are counts, with estimated odds ratios (OR), with 95% confidence intervals, and p-values from Fisher's exact tests for each diagnosis method.

Diagnosis	Alive (n = 746)	Died (n = 313)	OR (95% CI)	p-value	
	Y:N (%Y)	Y:N (%Y)			
Pre-op 4-7days					
CT thorax scan (negative for SARS-CoV-2)	10:736 (1.3%)	2:311 (0.6%)	0.47 (0.05, 2.24)	0.526	-

CT thorax scan (positive for SARS-CoV-2)	12:734 (1.6%)	0:313 (0%)	0.00 (0.00, 0.85)	0.023	*
Swab (negative for SARS-CoV-2)	17:729 (2.3%)	3:310 (1%)	0.42 (0.08, 1.45)	0.215	-
Swab (positive for SARS-CoV-2)	31:715 (4.2%)	8:305 (2.6%)	0.61 (0.24, 1.37)	0.283	-
Pre-op 1-3days					
CT thorax scan (negative for SARS-CoV-2)	8:738 (1.1%)	3:310 (1%)	0.89 (0.15, 3.75)	0.999	-
CT thorax scan (positive for SARS-CoV-2)	10:736 (1.3%)	3:310 (1%)	0.71 (0.13, 2.79)	0.765	-
Swab (negative for SARS-CoV-2)	41:705 (5.5%)	9:304 (2.9%)	0.51 (0.22, 1.08)	0.080	-
Swab (positive for SARS-CoV-2)	86:660 (11.5%)	15:298 (4.8%)	0.39 (0.20, 0.69)	<0.001	*
Pre-op surgery					
CT thorax scan (negative for SARS-CoV-2)	0:746 (0%)	0:313 (0%)	-	0.999	-
CT thorax scan (positive for SARS-CoV-2)	4:742 (0.5%)	0:313 (0%)	0.00 (0.00, 3.61)	0.326	-
Swab (negative for SARS-CoV-2)	13:733 (1.7%)	2:311 (0.6%)	0.36 (0.04, 1.62)	0.254	-
Swab (positive for SARS-CoV-2)	18:728 (2.4%)	7:306 (2.2%)	0.93 (0.32, 2.35)	1	-
Post-op Admission					
CT thorax scan (negative for SARS-CoV-2)	4:742 (0.5%)	1:312 (0.3%)	0.60 (0.01, 6.04)	0.999	-
CT thorax scan (positive for SARS-CoV-2)	8:738 (1.1%)	4:309 (1.3%)	1.19 (0.26, 4.50)	0.756	-
Swab (negative for SARS-CoV-2)	51:695 (6.8%)	12:301 (3.8%)	0.54 (0.26, 1.05)	0.064	-
Swab (positive for SARS-CoV-2)	317:429 (42.5%)	143:170 (45.7%)	1.14 (0.87, 1.50)	0.342	-
Discharge 30days					
CT thorax scan (negative for SARS-CoV-2)	4:742 (0.5%)	0:313 (0%)	0.00 (0.00, 3.61)	0.326	-
CT thorax scan (positive for SARS-CoV-2)	0:746 (0%)	1:312 (0.3%)	-	-	-
Swab (negative for SARS-CoV-2)	8:738 (1.1%)	0:313 (0%)	0.00 (0.00, 1.39)	0.114	-
Swab (positive for SARS-CoV-2)	75:671 (10.1%)	27:286 (8.6%)	0.85 (0.51, 1.36)	0.496	-
Diagnosis					
Positive SARS-CoV-2 swab - before surgery	122:624 (16.4%)	31:282 (9.9%)	0.56 (0.36, 0.86)	0.007	*
Positive SARS-CoV-2 swab - after surgery	409:337 (54.8%)	177:136 (56.5%)	1.07 (0.82, 1.41)	0.636	-

CT scan of the chest confirming SARS-CoV-2 - before surgery	20:726 (2.7%)	2:311 (0.6%)	0.23 (0.03, 0.97)	0.033	*
CT scan of the chest confirming SARS-CoV-2 - after surgery	9:737 (1.2%)	5:308 (1.6%)	1.33 (0.35, 4.46)	0.569	-
Clinical diagnosis or chest x-ray - suspected before time of surgery	39:707 (5.2%)	12:301 (3.8%)	0.72 (0.34, 1.43)	0.432	-
Clinical diagnosis or chest x-ray - suspected after time of surgery	67:679 (9%)	31:282 (9.9%)	1.11 (0.69, 1.77)	0.643	-

Table S4. SARS-CoV-2 symptoms data summaries by died (n = 313) and alive (n =746) groups. Data tabulated are counts, with estimated odds ratios (OR), with 95% confidence intervals, and p-values from Fisher's exact tests for each symptom.

Symptom	Alive (n = 746)	Died (n = 313)	OR (95% CI)	p-value	
	Y:N (%Y)	Y:N (%Y)			
Abdominal pain	11:735 (1.5%)	1:312 (0.3%)	0.21 (0.01, 1.49)	0.124	-
Breathlessness (dyspnoea)	54:692 (7.2%)	31:282 (9.9%)	1.41 (0.86, 2.28)	0.172	-
Cough	73:673 (9.8%)	35:278 (11.2%)	1.16 (0.73, 1.81)	0.505	-
Diarrhoea	8:738 (1.1%)	1:312 (0.3%)	0.30 (0.01, 2.22)	0.295	-
Fatigue	21:725 (2.8%)	10:303 (3.2%)	1.14 (0.47, 2.56)	0.695	-
Fever (>38 celsius)	61:685 (8.2%)	25:288 (8%)	0.98 (0.57, 1.61)	0.999	-
Haemoptysis	0:746 (0.0%)	0:313 (0.0%)	-	-	-
Myalgia	10:736 (1.3%)	3:310 (1%)	0.71 (0.13, 2.79)	0.765	-
Nausea/vomiting	13:733 (1.7%)	7:306 (2.2%)	1.29 (0.43, 3.52)	0.623	-
Sputum	8:738 (1.1%)	4:309 (1.3%)	1.19 (0.26, 4.50)	0.756	-
Other	311:435 (41.7%)	136:177 (43.5%)	1.08 (0.82, 1.42)	0.633	-

Table S5. Pre-surgery measures data (n, mean and sd) for the full study population (n = 1063), and died (n = 313) and alive (n =746) groups, and the difference in means between groups, with 95% confidence interval, and p-values from unpaired t-tests.

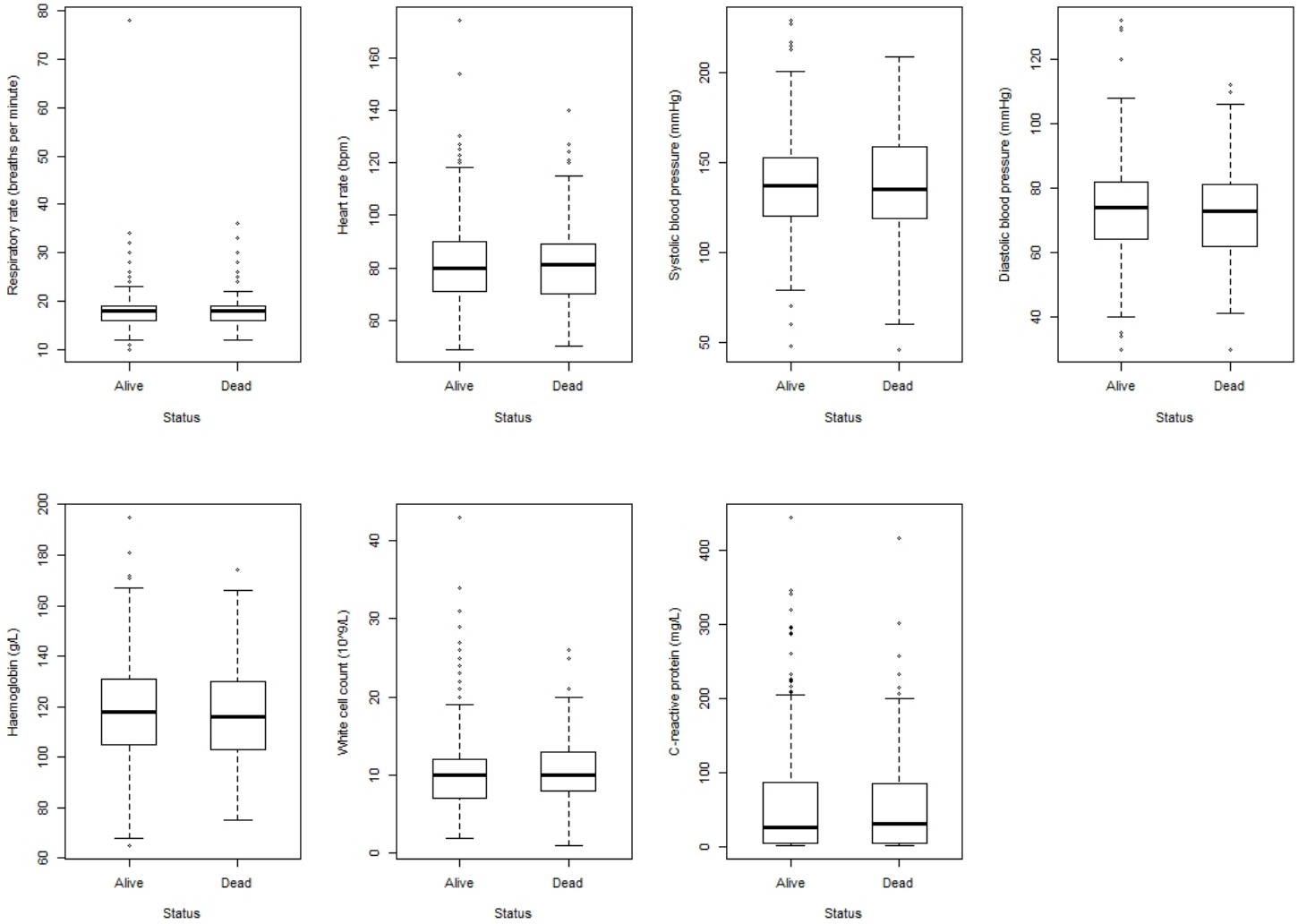
Measure	Full (n = 1063)		Alive (n = 746)		Died (n = 313)		Difference (95%CI)	p-value
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)		
Respiratory rate (breaths/minute)	996	17.75 (3.52)	706	17.65 (3.68)	289	18.02 (3.09)	-0.37 (-0.85, 0.11)	0.132
Heart rate (bpm)	1022	81.10 (14.63)	723	81.16 (14.59)	298	80.95 (14.77)	0.22 (-1.76, 2.20)	0.830
Systolic blood pressure (mmHg)	1023	138.15 (26.04)	724	138.33 (25.85)	298	137.61 (26.53)	0.72 (-2.80, 4.24)	0.687
Diastolic blood pressure (mmHg)	1021	72.97 (13.89)	723	73.07 (13.86)	297	72.70 (14.00)	0.37 (-1.52, 2.25)	0.703
Haemoglobin (g/L)	1062	117.94 (19.22)	745	118.35 (19.21)	313	116.93 (19.26)	1.41 (-1.13, 3.95)	0.276
White cell count (10^9/L)	1060	10.33 (4.26)	744	10.33 (4.36)	313	10.34 (4.04)	-0.01 (-0.57, 0.56)	0.976
C-reactive protein (mg/L)	738	54.70 (66.26)	514	54.84 (67.68)	221	54.63 (63.34)	0.21 (-10.28, 10.70)	0.969

Table S6. Operation details for the full study population (n = 1063), and died (n = 313) and alive (n =746) groups; p-values are for Fisher's exact tests comparing groups for each characteristic.

Characteristic	Full (n = 1063)	Alive (n = 746)	Died (n = 313)	Died (%)
Anaesthesia (p-value = 0.787)				
General	527 (49.6%)	368	157	29.9
Regional	524 (49.3%)	372	152	29.0
Missing	12 (27.8%)	6	4	33.3
*Pre-op respiration (p-value = 0.031 *)*				
None	714 (67.2%)	520	194	27.2
Oxygen	336 (31.6%)	220	115	34.3
Ventilated	2 (0.2%)	2	0	0.0
Missing	11(1.03%)	4	4	36.4
Pre-op delay (p-value = 0.220)				

< 6 hours	16 (1.5%)	11	5	31.2
6-23 hours	322 (30.3%)	232	88	27.5
24-47 hours	224 (21.1%)	147	77	34.4
48-71 hours	82 (7.7%)	61	21	25.6
72+ hours	123 (11.6%)	94	29	23.6
Missing	296 (27.8%)	201	93	31.4
*Procedure (p-value = 0.015 *)*				
LIMB - lower limb - total hip replacement	45 (4.2%)	41	4	8.9
LIMB - lower limb fracture - Cannulated Screws	5 (0.5%)	5	0	0.0
LIMB - lower limb fracture - Reduction and Internal Fixation	15 (1.4%)	10	5	33.3
LIMB - lower limb fracture - Dynamic Hip Screw	276 (26%)	195	81	29.3
LIMB - lower limb fracture - Reduction and Intramedullary Fixation	243 (22.9%)	169	73	30.2
LIMB - lower limb fracture - Partial Hip Replacement (Hemiarthroplasty)	479 (45.1%)	326	150	31.5
Missing	0 (0.0%)	0	0	0.0

Figure S1. Boxplots showing distributions of pre-surgery measures by outcome status (died or alive). Boxes show interquartile range (IQR), bars medians and whiskers are 1.5 times IQR.


Respiratory rate (breaths per minute)
Heart rate (bpm)
Systolic blood pressure (mmHg)
Diastolic blood pressure (mmHg)
Haemoglobin (g/L)
White cell count (10^9/L)
C-reactive protein (mg/L)
Alive
Dead
Status

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1 & 2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6
Bias	9	Describe any efforts to address potential sources of bias	8
Study size	10	Explain how the study size was arrived at	N/A
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	8
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	9
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	9
Outcome data	15*	Report numbers of outcome events or summary measures over time	9

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	9-12
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9-12
Discussion			
Key results	18	Summarise key results with reference to study objectives	13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	16
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13-15
Generalisability	21	Discuss the generalisability (external validity) of the study results	13-15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	1

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.