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One Hundred Twenty-Day Mortality Rates for Hip Fracture Patients with COVID-19 Infection

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Background: Increased 30-day mortality rates have been reported for patients with hip fractures and a concurrent diagnosis of coronavirus disease 19 (COVID-19) infection. Due to nosocomial spread of infection and the variable incubation period with the virus, follow-up past 30 days after injury is required to evaluate the true mortality amongst these patients. We aim to assess 120-day mortality rates in hip fracture patients with COVID-19 infection and compare this to hip fracture patients without COVID-19 infection presenting during the same time period.

Methods: This is a retrospective multicenter review of all patients aged \ge 60 years admitted with a fractured neck of femur between March 5 and April 5, 2020, at nine U.K. trauma units. COVID-19 status, demographic data, comorbidities, and date of death (if applicable) were collected.

Results: Data were collected for 265 hip fracture patients. Forty-six patients (17.4%) tested positive for COVID-19 infection. There were no significant differences in age or Charlson comorbidity score between those with or without COVID-19. Those with CO-VID-19 infection were more likely to be male (p = 0.01). Patients with COVID-19 had a 30-day mortality of 35% versus 10% in patients without (p < 0.01). One hundred twenty-day mortality was also greater in those with COVID-19 infection at 63% compared to those without at 17% (p < 0.01). Previous history of myocardial infarction was the only independent factor that showed to increase mortality rate (p = 0.03). Subgroup analysis also revealed significantly increased mortality rates at 120 days in men (27% vs. 67%), women (14% vs. 59%), and those undergoing surgery (56% vs. 30%).

Conclusions: We report a significantly increased mortality rate at 30 and 120 days after injury in an already high-risk cohort of surgical patients. With nearly half of patients being diagnosed with COVID-19 at 14 days or greater following admission, this study highlights the importance of taking appropriate measures to decrease the incidence of nosocomial infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in hip fracture patients.

Keywords: Hip fracture, COVID-19, SARS-CoV-2, Femoral neck fractures, Mortality

As of February 2021, the novel coronavirus (coronavirus disease 19 [COVID-19]), which was initially reported in

Received November 25, 2020; Revised January 27, 2021; Accepted March 1, 2021 Correspondence to: Leanne Dupley, MRCSEd Department of Trauma and Orthopaedics, Health Education North West, Manchester, M1 3BN, UK Tel: +44-7966054793 E-mail: Leannedupley@doctor.org.uk Wuhan, China, had infected over 100 million people globally and caused nearly 2.5 million deaths.¹⁾ Risk factors for severe infection and mortality have been identified, with increasing age being a strong predictor of mortality.²⁾ Other factors include male sex and major comorbidities, including cardiac or pulmonary diseases, chronic kidney disease, chronic neurological disorders, dementia, and obesity.²⁾ Hip fracture patients are typically frail, elderly, and comorbid and are therefore high risk for poor outcomes if infected with COVID-19.

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Thirty-day mortality rates for hip fracture patients with concurrent COVID-19 infection have been reported in the literature. A multi-center study from London, England, including 82 patients reported a 30-day mortality rate of 30.5%.³⁾ A Scottish study including 27 COVID-19 positive hip fracture patients reported a mortality rate of 35.5% at 30 days.⁴⁾ These studies have reported significantly higher mortality rates than expected for the time of year, prior to the COVID-19 pandemic. Information from the National Hip Fracture Database (NHFD), which records data on hip fracture patients in the United Kingdom, states that 30-day mortality during March and April of 2019 were 6.75% and 6.8% respectively.⁵⁾ In a previously published paper, we have reported a mortality rate of 32.8% in 64 COVID-19 positive hip fracture patients at 30 days in North West England.

One hundred twenty-day mortality for hip fracture patients with COVID-19 infection has not been reported previously, but the published studies of 30-day mortality, including ours, have indicated that there is a continuing increase in mortality rates in this group of patients beyond 30 days.^{4,6)} Mortality at 120 days for hip fracture patients, prior to the pandemic, has been reported between 12.5% and 20.1%.⁷⁻¹⁰⁾ We aim to assess 120-day mortality for hip fracture patients, comparing mortality rates of those with a concurrent diagnosis of COVID-19 based on antigen testing to those without a diagnosis of COVID-19. We hypothesize that the 120-day mortality will be significantly greater in those with COVID-19.

METHODS

Study Design

This study was performed as a multicenter retrospective study, which was carried out across nine trauma units in the UK. Ethical approval was not required due to retrospective analysis of data already collected on a secure database at participating trusts. No patient-identifiable data was collected during the data collection, and local information governance procedures were followed.

Participants

All patients aged \geq 60 years admitted during a 1-month period between March 5, 2020, and April 5, 2020, to nine trauma units across the UK with a hip fracture were included in the study. Fracture types included were those defined by the NHFD as "hip fractures": displaced intracapsular, undisplaced intracapsular, grade A1/A2 trochanteric, grade A3 trochanteric (including reverse oblique), and subtrochanteric fractures.¹¹⁾ Midshaft femoral fractures, distal femoral fractures, periprosthetic fractures, and polytrauma patients were excluded from the study. Diagnosis of COVID-19 infection was confirmed by detection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) on quantitative reverse transcription polymerase chain reaction (RT-PCR) on respiratory tract samples within 7 days preoperatively, or within 30 days postoperatively. During the period of data collection, testing for SARS-CoV-2 at all centers was limited only to patients with known symptoms of COVID-19 infection; namely, a new cough, pyrexia, and breathing difficulties.

Data Collection

Data were collected retrospectively by review of patient notes and radiographic imaging. Patient demographics, including date of birth and sex. Date and time of radiological fracture diagnosis, fracture classification in line with NHFD classification, date of positive SARS-CoV-2 antigen test, date, time and type of surgery (if applicable), and date of death (if applicable) were recorded. Comorbidities incorporated in the Charlson comorbidity index were also recorded.¹²

Statistical Analysis

Continuous variables were presented as means with standard deviation (SD). Comparison was made using unpaired *t*-tests between patients with a confirmed diagnosis of COVID-19 infection and those without. Categorical variables were presented as frequencies with percentages, and comparison was made using Pearson's chi-square test between patients with a confirmed diagnosis of COV-ID-19 infection and those without. Kaplan-Meier survival analysis was performed with survival measured as the time from diagnosis of hip fracture to death in days. Patients who remained alive at 120-day follow-up were censored at 120 days. No patients were lost to follow-up. Survival analysis for patients with COVID-19 was performed using Cox regression analysis in two stages. Univariate analysis was performed to assess the association between patient characteristics and survival times for patients with confirmed COVID-19 diagnosis. Multivariate analysis was performed using a backwards selection procedure to sequentially remove nonsignificant variables. Data were presented as hazard ratios (HRs) with 95% confidence intervals (CIs). A two-sided *p*-value ≤ 0.05 was considered statistically significant. Statistical analysis was performed using IBM SPSS ver. 25.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Demographics and Characteristics

Eligibility criteria were met by 265 patients; data were collected for all 265 patients. Eighty (30%) were men and 185 (70%) were women. The mean age in the cohort was 82 years (SD, 9; range, 60-101 years), Mean Charleston comorbidity index was 7 (SD, 3). The characteristics of patients included in the study are shown in Table 1. Most frequently occurring comorbidities were dementia (84 patients), chronic lung disease (61 patients), moderate or severe kidney disease (66 patients), diabetes (56 patients), cerebrovascular disease (49 patients), congestive cardiac failure (48 patients), and previous myocardial infarction (46 patients). Intracapsular displaced fractures accounted for nearly half of all fractures (n = 123), followed by AO type A1 and A2 intertrochanteric fractures (n = 70). Thirty-five patients sustained undisplaced intracapsular fractures, followed by subtrochanteric fractures (n = 23) and

finally AO A3 type intertrochanteric fractures (n = 14).

Fifteen patients were treated conservatively whilst 250 underwent surgery. Of those patients undergoing surgery; 75 had a hemiarthroplasty with a cemented unipolar prosthesis; 61 had fixation with a dynamic hip screw; 39 had hemiarthroplasty with a cemented bipolar prosthesis; 25 had fixation with a long intramedullary nail; 20 had fixation with a short intramedullary nail; 15 underwent cemented total hip arthroplasty; 10 had fixation with cannulated screws; and 5 patients had another procedure.

Patients with a Confirmed COVID-19 Diagnosis Versus Those without

Forty-six patients had a confirmed diagnosis of COVID-19 compared to 219 without. Patients with COVID-19 were more likely to be male (p < 0.01) with men accounting for 52% of COVID-19 cases but only 26% of non-COVID-19 cases. In all 46 patients with a positive test confirming a diagnosis of COVID-19, the diagnosis was made on or

Table 1. Characteristics of All Patients with a Neck of Femur Fracture with and without a Positive SARS-CoV-2 Test Result					
Variable	All patients (n = 265)	Patients with SARS-CoV-2 positive result (n = 46)	Patients without SARS-CoV-2 positive result (n = 46)	<i>p</i> -value	
Age (yr)	82 ± 9	84 ± 7	82 ± 9	0.07	
Sex					
Male	80 (30)	24 (52)	56 (26)	< 0.01*	
Female	185 (70)	22 (48)	163 (74)	< 0.01*	
Comorbidity [†]					
Charlson score	7 ± 3	7 ± 2	6 ± 3	0.51	
Myocardial infarction	46 (17)	10 (22)	36 (16)	0.39	
Congestive cardiac failure	48 (18)	13 (28)	35 (16)	0.05	
Dementia	84 (32)	18 (39)	66 (30)	0.24	
Cerebrovascular disease	49 (18)	7 (15)	42 (19)	0.53	
Chronic lung disease	61 (23)	11 (24)	50 (23)	0.87	
Diabetes	56 (21)	14 (29)	43 (20)	0.19	
Moderate or severe kidney disease	66 (25)	13 (28)	53 (24)	0.42	
Tumor	35 (13)	6 (13)	29 (13)	0.97	
Management					
Surgical	250 (94)	49 (85)	211 (96)	< 0.01	
Conservative	15 (6)	7 (15)	8 (4)	< 0.01	

Values are presented as mean ± standard deviation or number (%).

SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.

*A *p*-value denotes difference between those who tested positive for SARS-CoV-2 and those who did not. [†]Comorbidities with a prevalence < 30 have been excluded from the table.

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after the day of diagnosis of hip fracture. The median time of diagnosis of COVID-19 was 13.5 days after the diagnosis of hip fracture. Twenty-three patients (50%) were diagnosed with COVID-19 at 14 day or greater following fracture diagnosis. Fig. 1 demonstrates time of SARS-CoV-2 diagnosis after fracture diagnosis.

Mean age of patients with COVID-19 infection was 84 years (SD, 7 years), compared to 82 years (SD, 9 years) for patients without confirmed COVID-19; however, this difference was not statistically significant (p = 0.07). Charlson comorbidity index was higher in patients who tested positive for SARS-CoV-2 when compared to those who did not at 7 (SD, 2) and 6 (SD, 3), respectively; however, this difference was not statically significant (p = 0.51).



Fig. 1. Bar chart demonstration time of positive swab result after diagnosis of fracture for patients testing positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).



Mortality

Kaplan-Meier Survival analysis was performed for all patients with and without COVID-19 (Fig. 2), as well as for men and women individually (Fig. 3) and for all patients who underwent surgery (Fig. 4). Overall mortality at 30 days was 14%. This was significantly greater in patients



Fig. 2. Kaplan-Meier survival plots with 95% confidence intervals for all hip fracture patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) positive test results and those without. Solid lines show those without COVID-19 infection, dotted lines are those with COVID-19 infection.



Fig. 3. Kaplan-Meier survival plots with 95% confidence intervals for male (A) and female (B) hip fracture patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) positive test results and those without. Solid lines show those without COVID-19 infection, dotted lines are those with COVID-19 infection.

with COVID-19 at 35% (95% CI, 29%–49%) compared to 10% (95% CI, 6%–14%) in patients without COVID-19 (p < 0.01). Overall mortality increased to 25% at 120 days. This was also significantly greater in patients with COV-ID-19 at 63% (95% CI, 49%–77%) compared to 17% (95% CI, 12%–22%) in patients without COVID-19 (p < 0.01).

Patients with COVID-19 were more likely to be male or undergo conservative treatment. Male sex has been shown to be a risk factor for increased mortality following COVID-19, whilst conservative treatment is a known risk factor for increased mortality following hip fracture. To control for these factors, subgroup analysis was performed to review mortality rates for men, women, and patients undergoing surgery, independently. Mortality at 120 days was significantly increased in all three groups. In men, this was 67% (95% CI, 48%–86%) vs. 27% (95% CI, 15%–38%) for non-COVID-19 positive patients and



Fig. 4. Kaplan-Meier survival plots with 95% confidence intervals for hip fracture patients undergoing surgery with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) positive test results and those without. Solid lines show those without COVID-19 infection, dotted lines are those with COVID-19 infection.

COVID-19 positive patients, respectively. In women, this was 59% (95% CI, 38%–80%) vs. 14% (95% CI, 19%–9%) and for patients undergoing surgery, this was 56% (95% CI, 41%–80%) vs. 16% (95% CI, 11%–20%). Table 2 shows 120-day mortality rates.

Survival analysis for patients with COVID-19 was performed using Cox regression analysis in two stages. Univariate analysis was performed, to determine the association between baseline demographics and treatment with survival time; looking at age > 80 years, sex, Charlson comorbidity index, surgical treatment and individual comorbidities with a prevalence of > 30 in the study group. Previous myocardial infarction was associated with a statistically significantly decreased survival time (HR, 4.68; 95% CI, 1.50–14.61; p < 0.01) whilst surgical treatment was associated with an increased survival time (HR, 0.15; 95% CI, 0.04–0.58; p < 0.01). HRs are shown in Table 3.

Multivariate analysis was performed using a backwards selection procedure to sequentially remove non-significant variables. This also demonstrated a significantly decreased survival time in patients with a history of previous myocardial infarction (HR, 2.8; 95% CI, 1.19–6.95) and increased survival time in patients undergoing surgical treatment (HR, 0.11; 95%, CI, 0.37–0.33), as seen in Table 4.

DISCUSSION

We report a mortality rate of 63% at 120 days for patients with a fractured neck of femur and confirmed COVID 19 infection, compared to 17% in fractured neck of femur patients without. We also report a significantly increased mortality in men and women, and in patients undergoing surgery, controlling for an increased proportion of men and reduced surgical treatment amongst COVID-19 positive patients. At the time of writing, this is the first study to review mortality rates in this group of patients at 120

 Table 2. Mortality Rate at 120 Days for Patients with and without a Positive SARS-CoV-2 Test Result for All Patients, Men, Women, and Those Undergoing Surgery

Variable —	Patients with SARS-CoV-2 positive result		Patients without SARS-CoV-2 positive result		n voluo
	Mortality (%)	95% CI	Mortality (%)	95% CI	<i>p</i> -value
All patients	63.04	49.21-77.33	17.35	12.36-22.55	< 0.01
Male	66.67	47.87-85.69	26.78	15.08-38.45	< 0.01
Female	59.09	38.41-79.85	14.11	8.74–19.48	< 0.01
Surgery	56.41	40.91-79.92	15.64	10.68-20.25	< 0.01

SARS-CoV-2: severe acute respiratory syndrome coronavirus 2, CI: confidence interval.

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Table 3. Univariate Analyses Examining the Association between Patient Characteristics upon Survival Times in Patients with a Positive SARS-CoV-2 Test Result Variable HR 95% Cl p-value

Variable	HR	95% CI	<i>p</i> -value
Age > 80 yr	0.89	0.25–3.13	0.89
Male sex	1.35	0.51–3.59	0.55
Surgical treatment*	0.15	0.04–0.58	< 0.01
Charlson comorbidity index	1.01	0.88–1.27	0.54
Myocardial infarction	4.68	1.50-14.61	< 0.01
Congestive cardiac failure	0.91	0.33–2.52	0.85
Dementia	0.53	0.17-1.70	0.29
Chronic lung disease	1.33	0.44–3.99	0.61
Diabetes mellitus	1.68	0.63-4.46	0.30
Moderate or severe kidney disease	1.01	0.38–2.70	0.98

SARS-CoV-2: severe acute respiratory syndrome coronavirus 2, HR: hazard ratio, CI: confidence interval. *Patients who underwent surgery for management of hip fracture.

Table 4. Multivariate Analyses Examining the Association between Patient Characteristics upon Survival Times in Patients with a Positive SARS-CoV-2 Test Result				
Variable	HR	95% CI	<i>p</i> -value	
Surgical treatment*	0.11	0.37–0.33	< 0.01*	
Myocardial infarction	2.87	1.19–6.95	0.03*	

SARS-CoV-2: severe acute respiratory syndrome coronavirus 2, HR: hazard ratio, CI: confidence interval.

*Patients who underwent surgery for management of hip fracture.

days. Mortality rates at 120-days following hip fractures have been reported to be between 10% and 20% in the literature, prior to the COVID-19 pandemic.^{7-10,13)} Our finding of 17% mortality for those without a concurrent COVID-19 infection is similar to that in the literature of previous pre-COVID-19 studies. Thirty-day mortality rate, however, which is audited nationally in the United Kingdom through the NHFD, was 6.1% overall in 2019 in the UK and ranged from 4.2% to 8.6% across the nine hospitals in this study.⁵⁾ There are seasonal variations, however: for March 2016–2019 the mean 30-day mortality rate nationally was 6.75%.⁵⁾ Our finding of 14% mortality in 30 days after injury in those without COVID-19 is higher than expected for time of year.

There have been a number of studies reporting on 30-day mortality for fractured neck of femur patients, which have shown much higher rates than expected for those who test positive for COVID-19. A Scottish study of 317 fractured neck of femur patients (27 COVID-19 positive patients) reported a 30-day mortality of 35.5% in those test-

ing positive vs. 8.5% for those who did not.⁴⁾ Interestingly, the authors found that after extrapolation of the survival curve for patients who contract COVID-19 during admission or who become unwell with COVID-19 for a period longer than the 30-day follow-up may demonstrate patterns of early mortality consistent with that of patients who had active infection with a positive diagnosis on admission. Another U.K. study of mortality rates in COVID-19 positive hip fracture patients over a 6-week period⁶⁰ reported a mortality rate of 32.8% at 30 days, which increased to 50% at 45 days after injury, concluding that a longer follow-up period is required to reveal the true mortality.

All studies, including this one, have shown higher than expected 30-day mortality rates in patients without COVID-19 in the United Kingdom during the pandemic. Reasons for this could be a decline in the usual standards of care due to staff sickness, theatre delays, and lack of personal protective equipment, which were some of the problems faced during the first peak of the pandemic.¹⁴⁾ Delays to theatre are known to increase 30-day and 1-year

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mortality in hip fracture patients.¹⁵⁾ The recommended timing of surgical hip fracture management is within 36 hours of injury, delays past this time have been shown to negatively affect mortality.¹⁶⁾ The multi-center studies discussed previously have stated delays to theatre from the recommended 36 hours after injury; however, none were significantly different between the COVID-19 positive and negative groups.^{3,4)}

The COVID-19 positive patients in this study all tested positive for COVID-19 on or after the diagnosis of the hip fracture (Fig. 1), of these, 50% (n = 23) tested positive at 14 days or later. The incubation period for COVID-19 is between 5 and 14 days and during this time patients may be asymptomatic, but contagious.¹⁷⁾ Those that tested positive within the first 14 days could have contracted COVID-19 prior to admission; however, those testing positive after 14 days are likely to be nosocomial infections.^{17,18)} This mirrors findings in other studies, suggesting nosocomial infections have been a problem across the United Kingdom amongst hip fracture patients.^{4,6)} Nosocomial spread of COVID-19 has been widely documented, highlighting the need for strategies to minimize spread within hospitals and other institutions, which have been implemented since the initial peak of COVID-19.^{19,20)}

Despite a higher than expected 30-day mortality rate for patients without a concurrent diagnosis of COVID-19, the 120-day mortality rate of 17% is similar to that in the literature. We found no statistically significant differences in age, Charlson comorbidity index, or individual comorbidities between those testing positive for COVID-19 versus those who did not. Patients with COVID-19 were more likely to be male (p < 0.01) with men accounting for 50% of COVID-19 cases but only 25% of non-COVID-19 cases. Risk factors for mortality following COVID-19 infection alone include male sex, increasing age, and previous comorbidities, including diabetes, cardiovascular disease, respiratory disease, hypertension, and obesity.^{2,21)} Despite a higher proportion of COVID-19 positive patients being male in this study, we do not demonstrate an increase in mortality for males nor those aged over 80 or with an increased Charlson comorbidity index score. Previous myocardial infarction was the only independent factor associated with a statistically significant increase in mortality in our cohort of patients.

We recognize the limitations of this study. Diagnosis of COVID-19 infection was confirmed with SARS-CoV-2 quantitative RT-PCR antigen testing. Estimates on the sensitivity of this test vary widely in the literature. Low-level evidence studies have reported this to be as low as 46%, although 70% is a more widely quoted value for the lower estimate.^{22,23)} Sensitivity of testing in the United Kingdom, however, has been reported to be as high as 95%.²⁴⁾ Sensitivity is also known to vary depending on time since exposure and the site that the test sample is taken from.^{25,26)}

We therefore accept that a number of patients in the non-confirmed COVID-19 cohort may have in fact have had COVID-19 infection. We hypothesize that inclusion of these patients in the non-confirmed COVID-19 cohort may have led to an artificially increased mortality rate of 12% at 30 days compared to 6.7% during the same month the previous year.

Delays to theatre are known to increase 30-day mortality rates in hip fracture patients.¹⁵⁾ This study did not compare time to theatre amongst patients with and without confirmed COVID-19 infection, which may have been increased in patients with COVID-19 although other similar studies have not demonstrated this.^{3,4)} Similarly, mortality rate may also be influenced by method of anesthesia, which was not reported in this study. Although routine screening on admission for all patients in U.K. hospitals is now widespread and has now been adopted across all the hospitals in this study, at the time of the study, screening was limited to only symptomatic patients across all nine centers included. With the literature suggesting that up to 80% of cases are asymptomatic, we are unable to conclude whether an increased mortality rate is also generalizable to patients with neck of femur fractures who do not have symptoms of COVID-19, but test positive for SARS-CoV-2 on routine admission screening.²⁷⁾ Furthermore, studies have also shown that elderly patients can have atypical presentations of COVID-19, such as delirium, which could contribute to mortality, without typical respiratory complications that were expected at the time of data collection.^{18,28)}

At the time of writing, this is the first study to report 120-day mortality rates for patients with hip fractures and concurrent COVID-19 infection. We report a significant increase in mortality for patients with COVID 19 infection of 60% compared to 17% for those without. Previous history of myocardial infarction was shown to be a predictor of increased mortality. Knowledge of this significant increase in mortality rates is useful for clinicians when planning treatment, and consenting and counselling patients and their relatives on admission to hospital with a fractured neck of femur. This study highlights the importance of taking appropriate measures to decrease the incidence of nosocomial infection with SARS-CoV-2 in patients with neck of femur fractures. 142

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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