Risk of Mortality for Proximal Femoral Fracture in Patients With and Without COVID-19. A Retrospective Cohort Study

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Abstract

Background: SARS-CoV-2 (COVID-19) has resulted in a widespread loss of lives, morbidity, and major disruptions to the healthcare system. Hip fractures are an emergent condition which require early intervention to reduce increased risk of mortality and morbidity. Infection of SARS-CoV-2 may contribute to increased mortality due to the role of infection and immune response. This study investigated the impact of COVID-19 infection (defined by clinical symptoms) on mortality following proximal femoral fracture (PFF) repair procedures. Methods: This study was a retrospective cohort study. Data from the Premier Healthcare Database® was extracted for patients presenting for PFF during 2019 for control, and February 2020-September 2020 to represent a COVID time-period. Results: A total of N = 73,953 subjects were enrolled for the 2019 period, and a total of N = 34,842 subjects were enrolled for the COVID period. For the 2019 period, subjects who had a PFF procedure and who had flu/COVID-like illness had 2.47 (CI: 2.11, 2.88) times the odds of mortality compared to those who did not have flu/COVID-like illness. Subjects who had a PFF procedure and who had flu/COVID-like illness during the COVID period had 2.85 (CI: 2.36, 3.42) the odds of mortality compared to those who did not have flu/COVID-like illness. For the COVID period, within subjects who did not have a PFF procedure, those with flu/COVID-like illness had increased odds of mortality compared to those who did not have flu/COVID-like illness (OR: 2.26, CI: 1.57, 3.21). Conclusions: Hip fractures present high risk for mortality and morbidity, where timely intervention is critical to improved outcomes. Presence of infection such as flu/COVID-like illness may influence mortality in patients undergoing hip fracture repair procedures. Consideration of infection status as a comorbidity is important to proper management and achieving optimal outcomes.

Keywords

COVID-19, hip fracture, proximal femoral fracture, SARS-cov-2, mortality, real world data

Introduction

SARS-CoV-2 emerged as novel coronavirus in December 2019 and quickly became a widespread pandemic with millions of cases and a large loss of lives. Symptoms of COVID-19 are commonly described as flu-like but vary broadly and may include loss of smell/taste, gastrointestinal symptoms, cough, fever, fatigue, shortness of breath, pain, and others. Long-term effects resulting in significant morbidity have been associated with COVID, ranging from mild to severe. This includes respiratory complications, cardiovascular disease, and other organ system failures. The impact of COVID-19 on the healthcare system has been profound, with a surge in hospitalizations and deaths.

Methods

This study was a retrospective cohort study. Data from the Premier Healthcare Database® was extracted for patients presenting for proximal femoral fracture (PFF) repair procedures during 2019 for control, and February 2020-September 2020 to represent a COVID time-period. The Premier Healthcare Database® is a comprehensive, de-identified database of healthcare encounters from over 1,000 hospitals in the United States. It includes detailed information on patient demographics, medical history, procedures performed, and outcomes.

Results

A total of N = 73,953 subjects were enrolled for the 2019 period, and a total of N = 34,842 subjects were enrolled for the COVID period. For the 2019 period, subjects who had a PFF procedure and who had flu/COVID-like illness had 2.47 (CI: 2.11, 2.88) times the odds of mortality compared to those who did not have flu/COVID-like illness. Subjects who had a PFF procedure and who had flu/COVID-like illness during the COVID period had 2.85 (CI: 2.36, 3.42) the odds of mortality compared to those who did not have flu/COVID-like illness. For the COVID period, within subjects who did not have a PFF procedure, those with flu/COVID-like illness had increased odds of mortality compared to those who did not have flu/COVID-like illness (OR: 2.26, CI: 1.57, 3.21).

Conclusions

Hip fractures present high risk for mortality and morbidity, where timely intervention is critical to improved outcomes. Presence of infection such as flu/COVID-like illness may influence mortality in patients undergoing hip fracture repair procedures. Consideration of infection status as a comorbidity is important to proper management and achieving optimal outcomes.
from chronic fatigue to multi-system organ damage.\textsuperscript{3,4} COVID-19 is most deadly to elder adults and those with underlying conditions such as hypertension and diabetes.\textsuperscript{5} Elderly patients presenting with hip fractures represent an emergency and in this vulnerable population careful consideration of risks and benefits is essential.\textsuperscript{6}

Hip fractures are a critical public health concern due to significant morbidity and mortality, especially among older adults.\textsuperscript{6} Cumulative mortality of proximal femoral fracture (PFF) 1-year post fracture is estimated to be 20-40%, with the highest risk of mortality immediately following fracture. PFF has also been associated with an increased risk of mortality from all other causes ranging from >2 to up to 8 times.\textsuperscript{7-9} A number of studies have demonstrated mortality following PFF may be increasing.\textsuperscript{8,10} Delays of >24 hours to surgery are associated with increased risk for minor complications, while delays of >48 hours are associated with major complications, with a handful of studies citing an increased risk of mortality in delays of 12-72 hours.\textsuperscript{11-13} As a result, immediate surgical intervention is recommended, though a subset of patients may not be eligible due to fragility or severe comorbidities.\textsuperscript{14} As such, pre-operative risk assessment is critical to optimizing outcomes.\textsuperscript{15}

Given the widespread nature of COVID it is not unexpected that some patients presenting for PFF may be positive. It is therefore important to broaden our understanding of COVID’s impact on PFF so that we may better inform treatment. There is a need to determine if infection by SARS-CoV-2, in a patient with PFF but otherwise “fit for surgery” is increasing the patient’s risk for post-operative mortality and if this mortality is beyond the expected risks related to either COVID or hip surgery, separately. To assess the occurrence of these outcomes, this study utilized 2 objectives: (1) estimate mortality risk following PFFs, in patients with and without flu/COVID-like symptoms and (2) estimate mortality risk following hip fractures in patients with flu/COVID-like symptoms during the COVID epidemic vs patients with flu-like symptoms pre-dating the COVID epidemic.

**Methods**

**Study Design and Data Sources**

This study is a retrospective cohort study designed to evaluate risk of mortality of patients presenting with PFF and flu/COVID-like symptoms (ie, cough, fever, anosmia, ageusia, body aches, etc.) as defined by ICD-10 codes. Due to testing limitations in the United States, especially during the period prior to COVID specific medical codes, flu-like illness and other COVID related symptoms were defined using codes for flu, pneumonia, COVID, and associated symptoms. Classification of COVID severity was defined using codes corresponding to the NIH classification of severity of COVID which is based on presence of symptoms.\textsuperscript{16}

This study used data from the Premier Healthcare Database\textsuperscript{®} (PHD).\textsuperscript{17} The PHD is a population-based hospital research database that contains healthcare records contributed by a convenience sample of several hundred US hospitals that are members of the Premier healthcare performance improvement alliance, representing approximately 25% of annual US inpatient discharges. The PHD has been widely used for epidemiologic and health outcomes research, forming the basis of over 600 peer-reviewed publications since 2006.

Symptoms consistent with flu/COVID-like illness were used as a proxy for COVID status and were assessed in 2 cohorts representing 2 distinct time periods:

1) 2019 to represent a period without high probability of true COVID cases (Figure 1A) and
2) February 2020-September 2020 to represent a period where COVID may have occurred (Figure 1B).

Within each time period the following groups of patients were created to assess the role of flu/COVID-like illness and the role of surgery on mortality:

1) Patients with PFF and repair with flu/COVID-like illness,
2) Patients with PFF and repair without flu/COVID-like illness,
3) Patients with PFF and \textit{no} repair with flu/COVID-like illness, and
4) Patients with PFF and \textit{no} repair without flu/COVID-like illness (Figure 1).

This analysis of the PHD was conducted under an exemption from Institutional Review Board oversight for US-based studies using de-identified healthcare records, as dictated by Title 45 Code of Federal Regulations (45 CFR 46.101(b) (4)).\textsuperscript{18} No attempts to re-identify patients were made. Only records with complete data were used for analysis.

**Outcome and Covariates**

The primary outcome of this study was mortality, defined as death during the hospital admission period or discharge to palliative care. Patient factors included were: age, gender, marital status and tobacco use 3 months prior to admission. Patient medical conditions were extracted from the medical record and defined using medical codes consistent with coding for the Elixhauser Comorbidity
Index (ECI) and the Charlson Comorbidity Index (CCI). Most conditions were defined according to the ECI, with the exception of cancer which was defined according to the CCI due to it being more comprehensive in terms of diagnoses. COVID severity was defined according to the NIH classification (see Supplemental Table 1). Due to small cell counts the mild and moderate COVID severity categories were combined for the main analyses.

**Statistical Analyses**

Means and standard deviations were conducted for continuous values. Variables relevant for adjustment were selected according to a priori review of the literature and consideration of conditions related to COVID risk as defined by the Centers for Disease Control and Prevention (CDC). Medical conditions included within the CDC list were then matched to corresponding variables including ECI or CCI values. Variables related to COVID and mortality were assessed based on a priori knowledge and existing literature. Variables related to increased mortality risk from COVID were considered within the context of the outcome mortality following PFF repair to determine variables relevant for adjustment, as presented in the adjusted models. Unadjusted and adjusted logistic regression models were used to quantify the odds of mortality associated with PFF repair surgery and flu/COVID-like status. Additional methods of model selection were employed including Backward Bayesian information criterion (BIC) selection (backward, stepwise selection) which is presented alongside the adjusted models. Results from the adjusted OR models were used for discussion.

**Results**

A total of $N = 73,953$ subjects were enrolled for the 2019 period, and a total of $N = 34,842$ subjects were enrolled for the COVID period. Demographics and percentages of descriptive information for the 2019 and COVID period (February 2020 – September 2020) cohorts are found in Tables 1 and 2 respectively. On average, the 2019 and COVID period cohorts were similarly aged (81.2 years). Both samples were largely women (70.4% and 69.7%), white (89.9% and 90.5%) and not...
Table 1. Descriptive Statistics of Demographics and Covariates for the 2019 Time-Period Cohort Overall and as Stratified by Proximal Femoral Fracture Repair and Flu/COVID-like Status Groups.

| Variable                        | Overall | Fracture repair-Flu/COVID like | Fracture repair-No Flu/COVID like | No fracture repair-Flu/COVID-like | No fracture repair-No Flu/COVID-like |
|---------------------------------|---------|---------------------------------|-----------------------------------|-----------------------------------|-------------------------------------|
|                                 | Total N | N %                            | N %                               | N %                               | N %                                 |
| All                             | 73 953  | 100.00%                         | 2323                              | 100.00%                           | 64 397                              | 100.00%                             | 258 100.00%                          | 6975 100.00%                          |
| Gender                          |         |                                 |                                    |                                   |                                     |                                     |                                     |                                     |
| Female                          | 52 032  | 70.36%                          | 1473                              | 63.41%                            | 45 440                              | 70.56%                             | 167 64.73%                          | 4952 71.00%                          |
| Race                            |         |                                 |                                    |                                   |                                     |                                     |                                     |                                     |
| White                           | 66 503  | 89.93%                          | 2134                              | 91.86%                            | 57 940                              | 89.97%                             | 224 86.82%                          | 6205 88.96%                          |
| Black                           | 2768    | 3.74%                           | 64                                | 2.76%                             | 2376                                | 3.69%                              | 13 5.04%                           | 315 4.52%                            |
| Other                           | 4682    | 6.33%                           | 125                               | 5.38%                             | 4081                                | 6.34%                              | 21 8.14%                           | 455 6.52%                            |
| Marital status                  |         |                                 |                                    |                                   |                                     |                                     |                                     |                                     |
| Married                         | 26 563  | 35.92%                          | 802                               | 34.52%                            | 23 440                              | 36.40%                             | 81 31.40%                          | 2240 32.11%                          |
| Not married                     | 47 390  | 64.08%                          | 1521                              | 65.48%                            | 40 957                              | 63.60%                             | 177 68.60%                          | 4735 67.89%                          |
| Tobacco use prior 3 Months      |         |                                 |                                    |                                   |                                     |                                     |                                     |                                     |
| Yes                             | 28 482  | 38.51%                          | 1145                              | 49.29%                            | 24 515                              | 38.07%                             | 134 51.94%                          | 2688 38.54%                          |
| Medication use prior 3 Months   |         |                                 |                                    |                                   |                                     |                                     |                                     |                                     |
| Mortality                       |         |                                 |                                    |                                   |                                     |                                     |                                     |                                     |
| Alive                           | 72 682  | 98.28%                          | 2221                              | 95.61%                            | 63 534                              | 98.66%                             | 227 87.98%                          | 6700 96.06%                          |
| Died                            | 1271    | 1.72%                           | 102                               | 4.39%                             | 863                                 | 1.34%                              | 31 12.02%                          | 275 3.94%                            |
| Mortality including hospice     |         |                                 |                                    |                                   |                                     |                                     |                                     |                                     |
| Alive                           | 70 816  | 95.76%                          | 2124                              | 91.43%                            | 62 452                              | 96.98%                             | 190 73.64%                          | 6050 86.74%                          |
| Died                            | 3137    | 4.24%                           | 199                               | 8.57%                             | 1945                                | 3.02%                              | 68 26.36%                          | 925 13.26%                           |
| NIH COVID severity rating*      |         |                                 |                                    |                                   |                                     |                                     |                                     |                                     |
| No COVID                        | 71 372  | 96.51%                          | 0.00%                             | 64 397 100.00%                    | 0.00%                               | 6975 100.00%                       | 0.00%                               | 6975 100.00%                        |
| Mild COVID                      | 5       | 0.01%                           | 5                                 | 0.22%                             | 63 534 96.66%                       | 0.00%                               | 109 42.25%                         | 0.00%                               | 0.00%                               |
| Moderate COVID                  | 1241    | 1.68%                           | 1132                              | 48.73%                            | 0.00%                               | 40 957 63.60%                      | 0.00%                               | 258 100.00%                         |
| Severe COVID                    | 483     | 0.65%                           | 424                               | 18.25%                            | 0.00%                               | 258 100.00%                       | 0.00%                               | 258 100.00%                         |
| Critical COVID                  | 352     | 0.48%                           | 309                               | 13.30%                            | 0.00%                               | 40 957 63.60%                      | 0.00%                               | 258 100.00%                         |
| Flu/COVID-like status           |         |                                 |                                    |                                   |                                     |                                     |                                     |                                     |
| Flu/COVID-like                  | 2581    | 3.49%                           | 2323                              | 100.00%                           | 0.00%                               | 258 100.00%                       | 0.00%                               | 258 100.00%                         |
| No Flu/covid-like               | 71 372  | 96.51%                          | 0.00%                             | 64 397 100.00%                    | 0.00%                               | 6975 100.00%                       | 0.00%                               | 6975 100.00%                        |
| Surgery status                  |         |                                 |                                    |                                   |                                     |                                     |                                     |                                     |
| Proximal femoral fracture repair procedure | 66 720  | 90.22%                          | 2323                              | 100.00%                           | 64 397 100.00%                    | 0.00%                               | 0.00%                               | 0.00%                               |
| No fracture repair procedure    | 7233    | 9.78%                           | 0.00%                             | 0.00%                             | 258 100.00%                       | 6975 100.00%                       | 0.00%                               | 0.00%                               |
| Continuous variables            | Mean    | Sd     | Mean    | Sd     | Mean    | Sd     | Mean    | Sd     | Mean    | Sd     |
| Age                             | 81.21   | 7.28   | 81.53   | 6.97   | 81.14   | 7.28   | 81.99   | 7.47   | 81.67   | 7.36   |
| Length of stay                  | 5.27    | 4.06   | 7.85    | 7.01   | 5.27    | 3.57   | 6.12    | 6.74   | 4.30    | 5.94   |
| CCI score                       | 1.99    | 1.88   | 2.47    | 2.00   | 1.95    | 1.86   | 2.77    | 2.06   | 2.15    | 1.98   |
| ECI score                       | 3.45    | 2.02   | 4.14    | 2.10   | 3.40    | 2.00   | 4.45    | 2.07   | 3.60    | 2.10   |

*Note: totals for NIH Severity do not add to total sample and represent a subset due to missing information on symptoms used to create severity.

married (64.1% and 65.3%). Information on medical conditions for both cohorts can be found in Supplemental Tables 2 and 3.

Across both the total 2019 and COVID period cohorts, subjects who received surgery had 0.22 times the odds (CI:0.20,0.23) and (CI:0.20,0.25), respectively) of mortality compared to not receiving surgery (Table 3). The odds of mortality were further stratified within each cohort by presence of flu/COVID-like illness. Within the 2019 cohort, for those with flu/COVID-like illness, the
odds of mortality associated with receiving a PFF repair procedure compared to not receiving a PFF repair procedure was 0.26 (CI: 0.19, 0.37). Within the 2019 cohort, those without flu/COVID-like illness had 0.21 (CI: 0.19, 0.23) times the odds of mortality associated with receiving a PFF repair procedure compared to not receiving a PFF repair procedure. For the 2020 COVID cohort, in those who had flu/COVID-like illness the odds of mortality for those who had a PFF repair procedure were 0.29 (CI: 0.20, 0.43) times the odds of those who had

Table 2. Descriptive Statistics of Demographics and Covariates for February 2020-September 2020 COVID Time-Period Cohort Overall and as Stratified by Proximal Femoral Fracture Repair and Flu/COVID-Like Status Groups.

| Variable                        | Overall | Fracture repair-Flu/COVID-like | Fracture repair-No Flu/COVID-like | No fracture repair-Flu/COVID-like | No fracture repair-No Flu/COVID-like |
|---------------------------------|---------|---------------------------------|-----------------------------------|-----------------------------------|--------------------------------------|
|                                 | Total N | %                               | N %                               | N %                               | N %                                 |
| All                             | 34 842  | 100.00%                         | 1457 100.00%                      | 30 063 100.00%                    | 179 100.00%                         | 3143 100.00% |
| Gender                          |         |                                 |                                   |                                   |                                      |                       |
| Female                          | 24 274  | 69.67%                          | 937 64.31%                        | 21 030 69.95%                     | 119 66.48%                          | 2188 69.62%          |
| Race                            |         |                                 |                                   |                                   |                                      |                       |
| White                           | 31 518  | 90.46%                          | 1295 88.88%                      | 27 226 90.56%                    | 161 89.94%                          | 2836 90.23%          |
| Black                           | 1347    | 3.87%                           | 66 4.53%                         | 1142 3.80%                       | 9 5.03%                             | 130 4.14%            |
| Other                           | 1977    | 5.67%                           | 96 6.59%                         | 1695 5.64%                       | 9 5.03%                             | 177 5.63%            |
| Marital status                  |         |                                 |                                   |                                   |                                      |                       |
| Married                         | 12 081  | 34.67%                          | 475 32.60%                       | 10 543 35.07%                    | 46 25.70%                           | 1017 32.36%          |
| Not married                     | 22 761  | 65.33%                          | 982 67.40%                       | 19 520 64.93%                    | 133 74.30%                          | 2126 67.64%          |
| Tobacco use prior 3 months      |         |                                 |                                   |                                   |                                      |                       |
| Yes                             | 13 812  | 39.64%                          | 668 45.85%                       | 11 802 39.26%                    | 91 50.84%                           | 1251 39.80%          |
| Mortality                       |         |                                 |                                   |                                   |                                      |                       |
| Alive                           | 34 191  | 98.13%                          | 1383 94.92%                      | 29 658 98.65%                    | 157 87.71%                          | 2993 95.23%          |
| Died                            | 651     | 1.87%                           | 74 5.08%                         | 405 1.35%                        | 22 12.29%                           | 150 4.77%            |
| Mortality including hospice     |         |                                 |                                   |                                   |                                      |                       |
| Alive                           | 33 206  | 95.30%                          | 1306 89.64%                      | 29 071 96.70%                    | 127 70.95%                          | 2702 85.97%          |
| Died                            | 1636    | 4.70%                           | 151 10.36%                       | 992 3.30%                        | 52 29.05%                           | 441 14.03%           |
| NIH COVID severity ratinga      |         |                                 |                                   |                                   |                                      |                       |
| No COVID                        | 33 206  | 96.56%                          | - 0.00%                          | 30 063 100.00%                   | - 0.00%                             | 3143 100.00%         |
| Mild COVID                      | 27      | 0.88%                           | 24 2.29%                         | - 0.00%                          | 3 2.17%                             | - 0.00%              |
| Moderate COVID                  | 652     | 1.90%                           | 579 55.30%                       | - 0.00%                          | 73 53.68%                           | - 0.00%              |
| Severe COVID                    | 284     | 0.83%                           | 247 23.59%                       | - 0.00%                          | 37 27.21%                           | - 0.00%              |
| Critical COVID                  | 220     | 0.64%                           | 197 18.82%                       | - 0.00%                          | 23 16.91%                           | - 0.00%              |
| Flu/COVID-like status           |         |                                 |                                   |                                   |                                      |                       |
| Flu/COVID-like                  | 1636    | 4.70%                           | 1457 100.00%                     | - 0.00%                          | 179 100.00%                         | - 0.00%              |
| No Flu/COVID-like               | 33 206  | 95.30%                          | - 0.00%                          | 30 063 100.00%                   | - 0.00%                             | 3143 100.00%         |
| Surgery status                  |         |                                 |                                   |                                   |                                      |                       |
| Proximal femoral fracture repair | 31 520  | 90.47%                          | 1457 100.00%                     | 30 063 100.00%                   | - 0.00%                             | 3143 100.00%         |
| No fracture repair procedure    | 3322    | 9.53%                           | - 0.00%                          | - 0.00%                          | 179 100.00%                         | 3143 100.00%         |
| Continuous variables            | Mean    | Sd                               | Mean Sd                           | Mean Sd                           | Mean Sd                             | Mean Sd              |
| Age                             | 81.16   | 7.26                            | 81.71 7.12                        | 81.11 7.26                        | 82.04 7.52                          | 81.41 7.37           |
| Length of stay                  | 5.19    | 3.41                            | 7.99 6.11                        | 5.96 3.14                        | 5.97 5.26                           | 4.13 3.31            |
| CCI score                       | 2.08    | 1.91                            | 2.53 1.97                        | 2.03 1.90                        | 2.85 2.03                           | 2.24 1.98            |
| ECI score                       | 3.55    | 2.04                            | 4.06 2.08                        | 3.50 2.03                        | 4.33 2.09                           | 3.75 2.09            |

aNote: totals for NIH Severity do not add to total sample and represent a subset due to missing information on symptoms used to create severity.
flu/COVID-like illness but did not have a PFF repair procedure. Within the 2020 COVID cohort, the odds of mortality associated with having a PFF repair procedure in those who did not have flu/COVID-like illness was 0.21 (CI:0.19,0.23) times the odds when compared to those who did not have flu/COVID-like illness and did not have a PFF repair procedure.

Table 4 displays odds ratios and 95% confidence intervals for mortality related to flu/COVID-like illness compared to no flu/COVID-like illness by time defined cohorts, as stratified by PFF repair and no PFF repair patient status. The odds of mortality in patients with flu/COVID-like illness for the 2020 COVID period were OR:2.67 (CI:2.27,3.13). The odds of mortality in patients with flu/COVID-like illness for the 2019 period were OR:2.29 (CI:1.90,2.61). The use of the 2019 period as a control period indicates that COVID status is playing a role in increased mortality for PFF patients independent of surgical status (Table 3). However, even within the 2019 cohort, patients exhibiting symptoms consistent with flu/COVID-like illness who received fracture repair surgery had increased odds of mortality (OR:2.47, CI:2.11,2.88) compared to patients who also received a fracture repair but did not have flu/COVID-like illness. Patients who did not receive a fracture repair and had flu/COVID-like illness had 2.04 (CI:1.50,2.75) times the odds of mortality compared to those who did not receive a fracture repair and did not have flu/COVID-like illness.

For comparison, within the 2020 COVID period, the odds of mortality for a patient who had a fracture repair and flu/COVID-like illness was 2.85 (CI:2.36,3.42) compared to those who had a fracture repair but no flu/COVID-like illness. Patients who did not receive a fracture repair and had flu/COVID-like illness had 2.26 times the odds of

Table 3. Odds Ratios and 95% Confidence Intervals for Odds of Mortality Associated with Receiving a Proximal Femoral Fracture Repair Compared to Not Receiving a Repair by Time Defined Cohorts, as Stratified by Flu/COVID-Like Status.

| Cohort/stratification | Odds Ratio Comparison | Total | Repair | Repair group deaths | No repair | No repair group deaths | Unadjusted OR (95% CI)b | Adjusted OR (95% CI)c | BIC selected OR (95% CI) |
|------------------------|-----------------------|-------|--------|---------------------|----------|-----------------------|--------------------------|------------------------|------------------------|
| 2019 - Total Sample    | PFF repair vs No PFF repair | 73,953 | 66,720 | 2,144               | 7233     | 993                   | 0.21 (0.19, 0.23)         | 0.22 (0.20, 0.23)       | 0.22 (0.20, 0.23)       |
| Flu/COVID-like illness | PFF repair vs No PFF repair | 2581   | 2,323  | 199                | 258      | 68                    | 0.26 (0.19, 0.36)         | 0.26 (0.19, 0.37)       | 0.27 (0.19, 0.37)       |
| No Flu/COVID-like illness | PFF repair vs No PFF repair | 71,372 | 64,397 | 1,945              | 6,975    | 925                   | 0.20 (0.19, 0.22)         | 0.21 (0.19, 0.23)       | 0.21 (0.19, 0.23)       |
| COVID period - Total Sample | PFF repair vs No PFF repair | 34,842 | 31,520 | 1,143              | 3,322    | 493                   | 0.22 (0.19, 0.24)         | 0.22 (0.20, 0.25)       | 0.22 (0.20, 0.25)       |
| Flu/COVID-like illness | PFF repair vs No PFF repair | 1,636  | 1,457  | 151                | 179      | 52                    | 0.28 (0.28, 0.41)         | 0.29 (0.20, 0.43)       | 0.29 (0.20, 0.42)       |
| No Flu/COVID-like illness | PFF repair vs No PFF repair | 33,206 | 30,063 | 992                | 3,143    | 441                   | 0.21 (0.19, 0.24)         | 0.21 (0.19, 0.24)       | 0.21 (0.19, 0.24)       |

aReference group (No hip fracture repair).
bRepresents mortality and COVID-status relationship only.
cAdjusted for gender, race, married, age, congestive heart failure (ELIX1), cardiac arrhythmia (ELIX2), valvular disease (ELIX3), pulmonary circulation disorders (ELIX4), peripheral vascular disorders (ELIX5), hypertension uncomplicated (ELIX6), hypertension complicated (ELIX7), diabetes uncomplicated (ELIX11), diabetes complicated (ELIX12), coagulopathy (ELIX22), obesity (ELIX23), cerebrovascular disease (CCI4), chronic pulmonary disease (CCI6), renal disease(CCI13), cancer (CCI14), tobacco use.
A Adjusted for gender, age, ELIX1, ELIX2, ELIX4, ELIX6, ELIX7, ELIX15, CCI6, CCI13, CCI14.
B Adjusted for age, ELIX1, CCI14.
C Adjusted for gender, age, ELIX1, ELIX2, ELIX4, ELIX6, ELIX7, ELIX15, CCI4, CCI6, CCI13, CCI14.
D Adjusted for gender, age, ELIX1, ELIX2, ELIX4, ELIX5, ELIX6, ELIX15, ELIX22, CCI6, CCI14.
E Adjusted for age, ELIX1.
F Adjusted for gender, age, ELIX1, ELIX2, ELIX4, ELIX6, ELIX15, ELIX22, CCI6, CCI14.
Table 4. Odds Ratios and 95% Confidence Intervals for Odds of Mortality Related to flu/COVID-Like Illness Compared to no flu/COVID-Like Illness by Time Defined Cohorts, and as Stratified by Proximal Femoral Fracture Repair and no Proximal Femoral Fracture Repair Patient Status.

| Cohort/stratification | Odds Ratio Comparisona | N   | COVID N | COVID deaths N | No COVID Nb | No COVID deaths N | Unadjusted OR (95% CI)b | Adjusted OR (95% CI)c | BIC Selected OR (95% CI) |
|------------------------|------------------------|-----|---------|---------------|-------------|------------------|-------------------------|------------------------|------------------------|
| 2019 - Total Sample    | Flu/COVID-like vs No Flu/COVID like | 73 953 | 2581    | 267           | 71 372      | 2870             | 2.75 (2.41, 3.14)       | 2.29 (1.90, 2.61)     | 2.29 (2.00, 2.62)A    |
| PFF Repair             | Flu/COVID-like vs No Flu/COVID like | 66 720 | 2323    | 199           | 64 397      | 1945             | 3.01 (2.58, 3.49)       | 2.47 (2.11, 2.88)     | 2.47 (2.11, 2.88)B    |
| No PFF Repair          | Flu/COVID-like vs No Flu/COVID like | 7233  | 258     | 68            | 6975        | 925              | 2.34 (1.75, 3.10)       | 2.04 (1.50, 2.75)     | 2.06 (1.52, 2.77)C    |
| COVID period - Total Sample | Flu/COVID-like vs No Flu/COVID like | 34 842 | 1636    | 203           | 33 206      | 1433             | 3.14 (2.68, 3.66)       | 2.67 (2.27, 3.13)     | 2.65 (2.25, 3.11)D    |
| PFF Repair             | Flu/COVID-like vs No Flu/COVID like | 31 520 | 1457    | 151           | 30 063      | 992              | 3.39 (2.82, 4.04)       | 2.85 (2.36, 3.42)     | 2.84 (2.35, 3.41)E    |
| No PFF Repair          | Flu/COVID-like vs No Flu/COVID like | 3322  | 179     | 52            | 3143        | 441              | 2.51 (1.78, 3.50)       | 2.26 (1.57, 3.21)     | 2.31 (1.61, 3.27)F    |

aReference=No COVID-like illness.
bRepresents mortality and COVID-like status relationship only.
cAdjusted for gender, race, married, age, congestive heart failure (ELIX1), cardiac arrhythmia (ELIX2), valvular disease (ELIX3), pulmonary circulation disorders (ELIX4), peripheral vascular disorders (ELIX5), hypertension uncomplicated (ELIX6), hypertension complicated (ELIX7), diabetes uncomplicated (ELIX11), diabetes complicated (ELIX12), coagulopathy (ELIX22), obesity (ELIX23), cerebrovascular disease (CCH), chronic pulmonary disease (CCI6), renal disease (CCI13), cancer (CCI14), tobacco use.

A Adjusted for gender, age, ELIX1, ELIX2, ELIX4, ELIX6, ELIX7, ELIX15, CCI6, CCI13, CCI14.
B Adjusted for gender, age, ELIX1, ELIX2, ELIX4, ELIX6, ELIX7, ELIX15, CCI4, CCI6, CCI13, CCI14.
C Adjusted for gender, age, ELIX1, ELIX6, ELIX7, ELIX15, ELIX23, CCI6, CCI13, CCI14.
D Adjusted for gender, age, ELIX1, ELIX2, ELIX4, ELIX5, ELIX6, ELIX15, ELIX22, CCI6, CCI14.
E Adjusted for age, ELIX1, ELIX4, ELIX5, ELIX6, ELIX22, CCI6, CCI14.
F Adjusted for age, ELIX3, ELIX15, CCI6, CCI13, CCI14.
mortality (CI:1.57,3.21) compared to those who did not receive a fracture repair and did not have flu/COVID-like illness.

Table 5 displays odds ratios and 95% confidence intervals for odds of mortality associated with flu/COVID-Like severity classification by time-defined cohort, and as stratified by proximal femoral fracture repair and no fracture repair patient status.

| Cohort                        | N     | Unadjusted OR (95% CI) | Fully adjusted OR (95% CI) | BIC selection OR (95% CI) |
|-------------------------------|-------|------------------------|-----------------------------|---------------------------|
| 2019 - Total Sample           |       |                        |                             |                           |
| No Flu/COVID-like             | 71    | Reference              | Reference                    | Reference                  |
| Mild/moderate                 | 1246  | 1.27 (0.97, 1.63)      | 1.23 (0.94, 1.58)           |                           |
| Severe                        | 483   | 3.65 (2.77, 4.72)      | 2.98 (2.25, 3.90)           | 3.02 (2.28, 3.95)         |
| Critical                      | 352   | 8.57 (6.71, 10.85)     | 5.89 (4.56, 7.56)           | 5.89 (4.55, 7.55)         |
| 2019 – PFF repair only        | 64    | Reference              | Reference                    | Reference                  |
| No Flu/COVID-like             | 1137  | 1.32 (0.97, 1.77)      | 1.28 (0.93, 1.71)           |                           |
| Mild/moderate                 | 424   | 3.62 (2.60, 4.92)      | 2.94 (2.09, 4.03)           | 2.98 (2.12, 4.08)         |
| Critical                      | 309   | 9.93 (7.56, 12.89)     | 6.55 (4.92, 8.61)           | 6.51 (4.89, 8.56)         |
| 2019 - No fracture repair only| 6975  | Reference              | Reference                    | Reference                  |
| No Flu/COVID-like             | 109   | 1.29 (0.75, 2.10)      | 1.25 (0.71, 2.06)           |                           |
| Mild/moderate                 | 59    | 3.61 (2.08, 6.12)      | 3.15 (0.75, 5.54)           | 3.31 (0.85, 5.79)         |
| Critical                      | 43    | 5.69 (3.08, 10.40)     | 4.49 (2.34, 8.56)           | 4.51 (2.37, 8.55)         |
| COVID period - Total Sample   | 33    | Reference              | Reference                    | Reference                  |
| No Flu/COVID-like             | 679   | 1.31 (0.93, 1.80)      | 1.19 (0.84, 1.65)           |                           |
| Mild/moderate                 | 284   | 5.33 (3.91, 7.12)      | 4.92 (3.57, 6.68)           | 4.82 (3.50, 6.54)         |
| Critical                      | 220   | 9.92 (7.38, 13.21)     | 6.88 (5.02, 9.34)           | 7.11 (5.20, 9.63)         |
| COVID period – PFF repair only| 30    | Reference              | Reference                    | Reference                  |
| No Flu/COVID-like             | 603   | 1.21 (0.78, 1.79)      | 1.13 (0.72, 1.67)           |                           |
| Mild/moderate                 | 247   | 6.00 (4.23, 8.33)      | 5.70 (3.96, 8.03)           | 5.53 (3.84, 7.78)         |
| Critical                      | 197   | 10.51 (7.55, 14.42)    | 6.93 (4.88, 9.73)           | 7.15 (5.04, 10.00)        |
| COVID period – No fracture repair only | 31    | Reference              | Reference                    | Reference                  |
| No Flu/COVID-like             | 76    | 1.38 (0.74, 2.42)      | 1.19 (0.62, 2.15)           |                           |
| Mild/moderate                 | 37    | 3.32 (1.63, 6.46)      | 2.91 (1.37, 5.93)           | 3.38 (1.60, 6.86)         |
| Critical                      | 23    | 14.00 (5.94, 36.61)    | 12.65 (5.10, 34.71)         | 13.79 (5.59, 37.63)       |

This table is a subgroup analysis, as such numbers for classification are smaller than total sample.

aRepresents mortality and COVID-like status relationship only.
bAdjusted for gender, race, married, age, congestive heart failure (ELIX1), cardiac arrhythmia (ELIX2), valvular disease (ELIX3), pulmonary circulation disorders (ELIX4), peripheral vascular disorders (ELIX5), hypertension uncomplicated (ELIX6), hypertension complicated (ELIX7), diabetes uncomplicated (ELIX11), diabetes complicated (ELIX12), coagulopathy (ELIX22), obesity (ELIX23), cerebrovascular disease (CC14), chronic pulmonary disease (CC16), renal disease(CCI13), cancer (CCI14), tobacco use.
A Adjusted for gender, age, ELIX1, ELIX2, ELIX4, ELIX6, ELIX7, ELIX15, CCI4, CCI6, CCI13, CCI14.
B Adjusted for gender, age, ELIX1, ELIX2, ELIX4, ELIX6, ELIX7, ELIX15, CCI4, CCI6, CCI13, CCI14.
C Adjusted for age, ELIX1, ELIX6, ELIX7, ELIX15, CCI6, CCI13, CCI14.
D Adjusted for gender, age, ELIX1, ELIX2, ELIX4, ELIX6, ELIX7, ELIX15, CCI4, CCI6, CCI13, CCI14.
E Adjusted for age, ELIX2, ELIX15, CCI6, CCI13, CCI14.

According to the NIH had 5.70 (CI:3.96,8.03) and 6.93 (CI:4.88,9.73) times the odds of mortality, respectively, compared to patients who did not have symptoms.

**Discussion**

Understanding how COVID, and potentially other infectious conditions, may impact outcomes in patients undergoing PFF repair surgery may be useful for managing the presence of disease in a similar manner that other
underlying conditions are considered prior to surgery. Given the potential for significant morbidity and mortality, it may not be appropriate to warrant abstinence from repair procedures even if a patient is SARS-CoV-2 positive. As shown within our study, the odds of mortality associated with receiving a PFF repair procedure were lower compared to those who did not receive a repair procedure and were similar for the 2019 cohort (OR:0.22, CI:0.20,0.23) and the COVID period cohort (OR:0.22, CI:0.20,0.25). Further, within those who received PFF repair procedure, the odds of mortality associated with flu/COVID-like illness compared to those who did not have flu/COVID-like illness were increased in both the 2019 (OR:2.47, CI:2.11,2.88) and COVID period (OR:2.85, CI:2.36,3.42) cohort. A similar pattern was observed for those who did not have a PFF repair, though these odds were slightly attenuated compared to the previous estimates from patients who received a repair procedure (2019 OR:2.04, CI:1.50,2.75; COVID Period OR:2.26, CI:1.57,3.21). This attenuation may have resulted from reasons that the patient was not recommended for surgery and may represent biases in selection. Since we were unable to assess reasons that patients did not receive surgery, no firm conclusions can be drawn from this information. However, it should be noted that due to the high risk for morbidity and mortality without timely intervention generally only patients deemed to be too high risk for surgery do not receive surgical intervention, which may explain the association observed here. 

While our study found that patients with PFF and mild/moderate COVID status have increased odds of mortality compared to patients with no COVID-like symptoms, in line with previous findings, our study lacks data on asymptomatic patients who may be captured in the no flu/COVID-like group. Regardless, even an asymptomatic case should be considered for its potential effect on patients undergoing PFF repair procedures to optimally manage the patient and needed healthcare resources including management and resource allocation. Further, while this study could not ascertain COVID testing status, the use of a proxy in this study may also demonstrate the potential need to consider not just COVID, but potentially any viral illness. This is supported by the similarity of estimates in the flu/COVID-like illness group for both 2019 and 2020 COVID time periods, though mortality was higher during the 2020 COVID period.

Kayani et al investigated the effects of COVID-19 status and post-operative complications in PFF patients and found that compared to COVID negative patients, COVID positive patients had significantly longer lengths of stay (13.8 days vs 6.7 days), more admissions to critical care (61.0% vs 18.2%), more complications (89.0% vs 35.0%), and increased mortality rates (30.5% vs 10.3%). Approximately half the patients who were included in the COVID positive group had negative swabs on admissions indicating that they may have contracted COVID during their stay. This study also found that positive patients who had 4 or more comorbidities had the greatest risk, a valuable finding given that hip fractures are common in the elderly population where a higher number of comorbidities is expected.

Hall et al also assessed the effects of COVID-19 status on PFF outcomes and found that among the 27 COVID-positive patients compared to the 290 COVID-negative patients, there was significantly lower 30-day survival (64.5% (CI:45.7,83.3) vs 91.7% (CI:88.2,94.8)), though the small sample size likely contributed to relative imprecision. Hall et al also noted the presence of asymptomatic carriers which should be considered. Results from Muñoz-Vives et al support an increase in mortality among PFF patients, noting that hospitals with more COVID cases had higher mortality rates. LeBrun et al also found that despite a similar number of comorbidities between groups, positive COVID status was associated with increased mortality in PFF patients.

This study has several limitations that should be considered alongside its results. First, this study was unable to directly confirm SARS-CoV-2 infection due to a lack of available testing data within PHD. Instead, flu/COVID-like symptoms were used as a proxy for SARS-CoV-2 infection. In the US, there was a shortcoming of testing availability during the earlier stages of COVID-19. Use of SARS-CoV-2 infection test positive cases only may have led to an overestimation of mortality as only the COVID-19 most severe cases received tests. Thus, a broad consideration of potential cases still confers benefit to this analysis and should be interpreted in light of this limitation. The early stages of COVID also lacked a specific diagnosis code to identify COVID patents further lending to potential missed cases if diagnosis alone was considered. Finally, due to the cross-sectional nature of the Premier database, patients that may have expired at home shortly after discharge are not captured within our mortality outcome, even while accounting for discharges to palliative care. It should be considered that as a result the associations presented here may be underestimated.

Conclusions

Patients with PFF represent emergent cases with high risk for mortality and morbidity. COVID status may influence mortality in patients sent for surgical repair of PFF, though regardless of COVID status, PFF repair procedures are associated with lower odds of mortality compared to those who did not receive them. It may be beneficial to consider COVID status, for management as a comorbidity. Further, due to the similarity of estimates in mortality from the 2019 and 2020 time periods, consideration of other viral illnesses such as the flu may also be warranted to ensure optimal patient and resource management.
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Supplemental Material
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References
1. Pujari R, Thommana MV, Mercedes BR, Serwat A. Therapeutic options for COVID-19: A review. Cureus 2020;12(9):e10480.
2. Menni C, Valdes AM, Freidin MB, et al. Real-time tracking of self-reported symptoms to predict potential COVID-19. Nat Med. 2020;26(7):1-4.
3. Fraser E. Long Term Respiratory Complications of Covid-19. British Medical Journal Publishing Group; 2020.
4. Mitrani RD, Dabas N, Goldberger JJ. COVID-19 cardiac injury: Implications for long-term surveillance and outcomes in survivors. Heart Rhythm. 2020;17:1984-1990.
5. Albitar O, Ballouze R, Ooi JP, Ghadzi SMS. Risk factors for mortality among COVID-19 patients. Diabetes Res Clin Pract. 2020;166:108293.
6. Bonanad C, García-Blas S, Tarazona-Santabalbina F, et al. The effect of age on mortality in patients with COVID-19: A meta-analysis with 611,583 subjects. J Am Med Dir Assoc. 2020;21(7):915-918.
7. Kanis J, Oden A, Johnell O, De Laet C, Jonsson B, Oglesby A. The components of excess mortality after hip fracture. Bone. 2003;32(5):468-473.
8. Guzon-Illescas O, Fernandez EP, Villarias NC, et al. Mortality after osteoporotic hip fracture: inci-dence, trends, and associated factors. J Orthop Surg Res. 2019;14(1):203.
9. Katsoulis M, Benetou V, Karapetyan T, et al. Excess mortality after hip fracture in elderly persons from Europe and the USA: The chances project. J Int Med. 2017;281(3):300-310.
10. Menéndez-Colino R, Alarcon T, Gotor P, et al. Base-line and pre-operative 1-year mortality risk factors in a cohort of 509 hip fracture patients consecutively admitted to a co-managed orthogeriatric unit (FONDA Cohort). Injury. 2018;49(3):656-661.
11. Nyholm AM, Gromov K, Palm H, et al. Time to surgery is associated with thirty-day and ninety-day mortality after proximal femoral fracture: A retrospective observational study on prospectively collected data from the Danish Fracture Database Collaborators. JBJS. 2015;97(16):1333-1339.
12. Bretherton C, Parker M. Early surgery for patients with a fracture of the hip decreases 30-day mortality. Bone & Joint J. 2015;97(1):104-108.
13. Anthony CA, Duchman KR, Bedard NA, et al. Hip fractures: Appropriate timing to operative intervention. J Arthroplasty. 2017;32(11):3314-3318.
14. Health NIf, Excellence C. Hip Fracture: Management. Clinical Guideline CG124. National Institute for Health and Care Excellence London; 2011.
15. Wang Z, Chen X, Yang L, Wang H, Jiang W, Liu Y. A new preoperative risk score for predicting mortality of elderly hip fracture patients: an external validation study. Aging Clin Exp Res. 2021:1-9.
16. Health NLo. Clinical Spectrum of SARS-CoV-2 Infection; 2020. https://www.covid19treatmentguidelines.nih.gov/overview/clinical-spectrum/
17. Sciences PA. Premier Healthcare Database White Paper: Data that Informs and Performs. NC: Premier Inc Charlotte; 2018.
18. US Department of Health and Human Services. Code of Federal Regulations. Public Welfare. https://www.hhs.gov/ohrp/sites/default/files/ohrp/policy/ohrpregulations.pdf (2011).
19. Menendez ME, Neuhaus V, van Dijk CN, Ring D. The Elixhauser comorbidity index outperforms the Charlson index in predicting inpatient death after orthopaedic surgery. Clin Ortho Related Res. 2014;472(9):2878-2886.
20. Center for Disease Control and Prevention. People with Certain Medical Conditions. COVID-19 (Coronavirus Disease); 2020.
21. Chowdhury MZI, Turin TC. Variable selection strategies and its importance in clinical prediction modelling. Family med commu heal 2020;8(1):e000262.
22. Sullivan NM, Blake LE, George M, Mears SC. Palliative care in the hip fracture patient. Geriatr ortho surge & rehabilita. 2019;10:2151459319849801.
23. Haslam L, DePaul V. Case study application of an ethical decision-making process for a fragility hip fracture patient. Canadian Geriatrics Journal. 2019;22(1):7.
24. Muñoz-Vives J, Jornet-Gibert M, Cámara-Cabrera J, et al. Mortality rates of patients with proximal femoral fracture in a worldwide pandemic: Preliminary results of the Spanish HIP-COVID observational study. J bone Joint surgery Am. 2020;102(13):e69.
25. Kayani B, Onochie E, Patil V, et al. The effects of COVID-19 on perioperative morbidity and mortality in patients with hip fractures: A multicentre cohort study. The bone & joint journal. 2020;102(9):1136-1145.
26. Hall AJ, Clement ND, Farrow L, et al. IMPACT-Scot report on COVID-19 and hip fractures: A multicentre study assessing mortality, predictors of early SARS-CoV-2 infection, and the effects of social lockdown on epidemiology. Bone & Joint J. 2020;102(9):1219-1228.
27. LeBrun DG, Konnaris MA, Ghahramani GC, et al. Hip fracture outcomes during the COVID-19 pandemic: Early results from New York. J Orthop Trauma. 2020;34(8):403-410.