




Original Article

Is it really advantageous to operate proximal femoral fractures within 48 h from diagnosis? – A multicentric retrospective study exploiting COVID pandemic-related delays in time to surgery

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ABSTRACT

Objectives: Hip fractures in the elderly are common injuries that need timely surgical management. Since the beginning of the pandemic, patients with a proximal femoral fracture (PFF) experienced a delay in time to surgery. The primary aim of this study was to evaluate a possible variation in mortality in patients with PFF when comparing COVID-19 negative versus positive.

Methods: This is a multicentric and retrospective study including 3232 patients with PFF who underwent surgical management. The variables taken into account were age, gender, the time elapsed between arrival at the emergency room and intervention, pre-operative American Society of Anesthesiology score, pre-operative cardiovascular and respiratory disease, and 10-day/1-month/6-month mortality. For 2020, we had an additional column, "COVID-19 swab positivity."

Results: COVID-19 infection represents an independent mortality risk factor in patients with PFFs. Despite the delay in time-to-surgery occurring in 2020, no statistically significant variation in terms of mortality was detected. Within our sample, a statistically significant difference was not detected in terms of mortality at 6 months, in patients operated within and beyond 48 h, as well as no difference between those operated within or after 12/24/72 h. The mortality rate among subjects with PFF who tested positive for COVID-19 was statistically significantly higher than in patients with PFF who tested. COVID-19 positivity resulted in an independent factor for mortality after PFF.

Conclusion: Despite the most recent literature recommending operating PFF patients as soon as possible, no significant difference in mortality was found among patients operated before or after 48 h from diagnosis.

Keywords: COVID-19 pandemic, Elderly, Fracture, Proximal femur, Time to surgery

INTRODUCTION

The outbreak of severe acute respiratory syndrome coronavirus, SARS-CoV-2, also known as 2019 novel coronavirus or 2019-nCoV disease (COVID-19) in China at the end of 2019, started a worldwide pandemic that is still a major public health issue.^[1] Health system resources of the most European countries have been redeployed to manage the epidemic crisis. Despite the reallocation of resources in favor of infectious disease departments and intensive care units, patients with hip fractures have continued to present at the Emergency Departments and require urgent medical care.^[2]

Hip fractures in the elderly are common injuries that need prompt surgical management to allow immediate post-operative mobilization to expedite rehabilitation and early supported discharge.^[3] Since the beginning of the pandemic, hospitals had to be reorganized to avoid viral transmission and provide health-care continuity at the same time.^[4,5] Especially during the 1st months of the pandemic, the treatment of proximal femoral fractures (PFF) was still a surgical priority in the context of hospital disorganization.

In a recent meta-analysis, Patralkh *et al.* concluded that the mortality risk is markedly increased in hip fractures with concomitant COVID-19 compared to those non-infected.^[6] They stated that this increased risk persisted in those managed surgically and concluded that this could be explained by the sum of inflammation induced by the fracture, inflammation exacerbated by surgery, and further virus-induced inflammation, leading to a cytokine storm.

Before the COVID-19 outbreak, the orthopedic and traumatology departments in Europe were organized by

national guidelines that favored early fixation/hemiarthroplasty of hip fractures and a short hospitalization period. However, since mid-January 2020, because of the COVID-19 spread, clinical practice has been guided by principles conceived to protect patients and healthcare workers, often causing treatment delays and failure to operate within 48 h.^[7]

The primary aim of the multicentric study was to investigate the mortality among COVID-19 positive patients compared to COVID-19 negative patients in 2020 in patients with PFF. Furthermore, the study aimed to evaluate whether different pre-operative timing and pandemic-related treatment delays were associated with a statistically significant change in mortality in the general population and in patients with specific comorbidities.

MATERIALS AND METHODS

This study is a multicentric, retrospective, observational, and epidemiological study involving 23 hospitals in six countries (Italy, Spain, Portugal, Czech Republic, Greece, and England). Before commencing recruitment, we obtained ethical approval from the Local Committee, and the relevant health authorities approved the protocol.

Eligible patients were the ones diagnosed with a PFF (femoral head, subcapital, midcervical, basicervical, and pertrochanteric) and undergoing surgery.

The data obtained have been anonymized by the aggregation method. Patients were grouped into two large clusters "patients with femur fractures operated in 2019" and "patients with femur fractures operated in 2020." For each of the two clusters, the dichotomous qualitative variables of "gender," "COVID-19 swab positivity," "pre-operative

heart disease,” “pre-operative respiratory disease,” “10-day mortality,” “1-month mortality,” “6-month mortality,” and the non-dichotomous qualitative variable “pre-operative American Society of Anesthesiology (ASA)” were presented in the study as discrete and pooled quantitative variables.

Each hospital team collected its own data and sent it to San Raffaele Hospital for final elaboration. Tables were referred to PFFs occurring from February 16 to May 16, in 2019–2020. The same variables were collected for both years: Initials of the patient’s first and last name, date of birth, gender (Male or female), the time elapsed between arrival at the emergency room and intervention, expressed in hours; pre-operative ASA (1–4), pre-operative cardiovascular disease (yes or no), pre-operative respiratory disease (yes or no), 10-days mortality (yes or no), 1-month mortality (yes or no), and 6-months mortality (yes or no). For 2020, we had an additional column, “COVID-19 swab positivity (positive or negative).”

The variable “time expressed in hours elapsed between arrival at the emergency room and intervention” was transformed into a dichotomous variable by setting cutoff at 12 h, 24 h, 48 h, and 72 h.

The primary outcome of the study was a change in mortality among COVID-19 positive patients compared to COVID-19 negative patients in 2020. Secondary outcomes were: To evaluate a statistically significant change in 6 months mortality as a result of possible delayed surgery determined by COVID-19 emergency status. To highlight whether different pre-operative timings (before or after 12 h, before or after 24 h, before or after 48 h, and before or after 72 h) are associated with a statistically significant change in mortality.

Statistical analysis has been performed at San Raffaele Hospital using SPSS version 28.0.0.0 (190).

For the primary and secondary outcomes, we used the Chi-square test and Fisher’s exact test to test the association between variables, referred to as significant if $P < 0.01$, and odds ratio to quantify the strength of the association.

RESULTS

We collected a total of 3232 cases of PFFs, 1603 (49.6%) in 2019 and 1629 (50.4%) in 2020. Of the aforementioned patients, 1492 (46.2%) reported cardiovascular comorbidities, 645 (20.2%) respiratory, and 855 (26.4%) an ASA greater than or equal to 3 despite having no cardiovascular or respiratory comorbidities. There was a 10-day mortality of 3.1% (100 cases), a 1-month cumulative mortality of 7.5% (242 cases), and a 6-month cumulative mortality of 19.3% (625 cases).

The mean age of patients was 84.39 years (\pm SD 11.203), the median age was 86 years with an interquartile range of

12 years. The mean pre-operative time was 48.25 h \pm SD 5.867 h; the median pre-operative time was 38 h with an interquartile range of 29 h.

The 2020 population was represented by 71.8% females and 28.2% males and in 2019 by 70.55% females and 29.45% males. In 2020, 735 (45.1%) patients reported cardiovascular comorbidities, 335 (20.6%) respiratory comorbidities, and 443 (11.47%) an ASA greater than or equal to 3 (without respiratory and cardiac comorbidities).

In 2019, 757 (47.2%) patients reported cardiovascular comorbidities, 319 (19.9%) respiratory comorbidities, and 412 (25.7%) an ASA greater than or equal to 3 (without respiratory and cardiac comorbidities).

The mean age in 2020 was 83.34 years (\pm SD 9.781), the median age was 86 with an interquartile range of 11. In 2019, the mean age was 84.95 years (\pm SD 12.478), the median age is 87 with an interquartile range of 13.

In 2020, there were 941 (57.8%) patients operated on within 48 h and there was a 10-day mortality of 3.3% (54 cases), 1-month cumulative mortality was 8% (130 cases), and a 6-month cumulative mortality of 19.6% (319 cases). In 2019, there were 1066 (66.5%) patients operated within 48 h and the 10-day mortality was 2.9% (46 cases), 1-month cumulative mortality 7% (112 cases), and 6-month cumulative mortality 19.1% (306 cases).

Considering the time interval between 10 days and 1-month, mortality in 2020 was 76 (4.82%) out of 1575 patients; mortality between 1-month and 6 months was 189 (12.61%) out of 1499 patients. Considering the time interval between 10 days and 1-month, mortality in 2019 was 66 (4.24%) out of 1557 patients; mortality between 1-month and 6 months was 194 (13.01%) out of 1491 patients.

Three thousand one hundred and thirty-two survived in the first 10 days after surgery for PFF, which occurred for 1949 (62%) individuals within 48 h and for 1183 (38%) individuals after 48 h. One hundred (3.09%) patients died in the first 10 days after operation, whose 58 (58%) operated within the first 48 h after fracture and 42 (42%) after 48 h.

Two thousand nine hundred and ninety patients survived 1 month after surgery, which occurred for 1869 (63%) patients within 48 h and for 1121 (37%) people after 48 h. Two hundred and forty-two (7.48%) patients died in the 1st month after operation whose 138 (57%) operated within the first 48 h after fracture and 104 (43%) after 48 h.

Two thousand six hundred and seven patients survived in the 6 months after operation for PFF, which occurred for 1627 (62%) persons within 48 h and 980 (38%) persons after 48 h. In the same observation period, 625 patients died after the operation, of which 380 (61%) operated within the first 48 h of fracture and 245 (39%) after 48 h [Figure 1].

Primary outcome

The higher mortality of subjects with PFF who tested positive for COVID-19 compared to the mortality of patients with PFF who tested negative for COVID-19 was statistically significant, with an odds ratio of 4.126 (2.107–8.081) for 10-day mortality, 6.622 (4.227–10.374) for 1-month mortality, and 4.782 (3.236–7.067) for 6-month mortality.

Secondary outcomes

The rate of patients operated within 48 h in the period of interest during 2019 was significantly higher than in the same period in 2020 (1066, 65% vs. 941, 57.8%) with an odds ratio of 1.451 (1.258–1.674), although this was not associated with a statistically significant change in mortality [Table 1].

Moreover, taking into account the whole sample, there was no statistically significant difference at 10-day, 1-month, and 6-month mortality of patients undergoing surgery before 48 h compared with patients operated after 48 h. The same result was obtained for the groups defined by 12-, 24-, and 48-h preparatory time cutoffs.

DISCUSSION

Data collected and presented in this study reflect those reported in the literature, with regards to incidence and mortality.^[8-10] More specifically, PFF incidence in males (37.16%) has been revealed to be lower than in females (62.84%), and the overall mortality rate at 6 months was 19.3%. In addition, it was confirmed that PFFs did not decrease in incidence (1629 cases in the period from February to May 2020 vs. 1603 cases in the same period in 2019) despite the lockdown; it makes sense thinking that these are fragility fractures, caused by low energy traumas, typically happening within houses.

The present study was planned to investigate mortality in COVID-19 positive patients with associated PFFs, to evaluate any possible association between surgery-delay due to the health emergency and mortality. As known, it has been confirmed that COVID-19 infection represents an independent mortality risk factor in patients with PFFs.^[11-13]

Table 1: The rate of patients operated within 48 h in the period of interest during 2019 was significantly higher than in the same period in 2020, it was not associated with a statistically significant change in mortality at 10 days, 1-month, and 6 months.

	Death in 2019	Death in 2020	Cumulative
10 days	46	54	100
1 month	112	130	242
6 months	306	319	625
Total	464	503	967

Subjects who tested positive for COVID-19 had significantly higher 6-month mortality from PFF than COVID-19 negative patients. As a matter of fact, COVID-19 infection generates an inflammatory response, an increase in pro-inflammatory cytokines (IL-2, IL-6, and TNF- α), and an endothelial dysfunction that facilitates microangiopathy and clot formation. Clinically, this can expose patients to pulmonary embolism and exacerbate virus-related hypoxia.^[14,15] The COVID-19 infection has been associated with disseminated intravascular coagulation as well, characterized by high D-dimer levels, fibrinogen level increase, and International Normalized Ratio and Prothrombin time decrease.^[16]

Concerning PFF time-to-surgery during the 1st months of pandemic compared to the same months in 2019, it was found that the number of patients treated beyond 48 h was statistically higher. Although surgery delays during 2020, no statistically significant change in PFF mortality was detected when compared to 2019 mortality.

It is, hence, possible to affirm that during the time interval February–May 2020, the state of pandemic provoked a statistically significant delay in time to surgery for those patients with PFF due to reduction of available operating rooms, decrease in orthopedic and anesthesiology personnel, and mostly due to the swab results waiting.

The contrast between the need to consider patients as a potentially contagious source until proved negative and the scarce number of centers entitled to analyze swabs has dramatically prolonged pre-operative time. However, despite the delay in time-to-surgery occurring in 2020, in our study, no statistically significant variation in terms of mortality was detected between the periods in question.

Nowadays, American Academy guidelines claim with a moderate, not strong, evidence, and to operate PFF

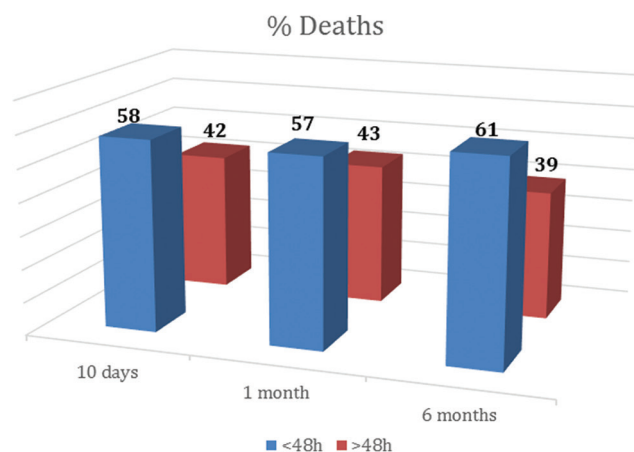


Figure 1: The death percentage at 10 days, 1 month, and 6 months, if the operation took place within or beyond 48 h from the diagnosis.

within 48 h.^[17] The study “HIP ATTACK,” involving 69 hospitals from 17 different countries, for a total amount of 2970 patients, has recently evaluated if surgery within 6 h had different outcomes in mortality when compared to standard timing (24 h).^[18] It was noticed that operating patients within 6 h are not always a significant advantage in terms of survival, and in reverse, can increase the risk of severe complications.

Within our sample (3232 patients), a statistically significant difference was not detected in terms of mortality at 6 months, in patients operated before and beyond 48 h, as well as no difference between operated before or after 12/24/72 h. Similar results were obtained considering exclusively patients with cardiovascular comorbidities ($n = 1492$), although our study cannot correlate mortality, stratified according to the pre-operative time, to individual cardiovascular diseases.

However, it has been noticed that in patients who had their surgery beyond 72 h, mortality did not correlate with cardiovascular comorbidities and respiratory diseases. This implies that probably, a thorough study of the frail patients could bring more benefit in terms of mortality, when compared to early surgery. The ideal situation would be to study frail patients adequately and operate them within 48 h, but this is not always possible. In these cases, we do believe that hospital quality standards should not have priority on patient welfare; patients should be operated in the best possible conditions. The 48 h cutoff should not be put in practice for every patient as required by hospital quality standards but taking into account that some frail patients could take advantage from an early surgery whereas some others from a deep study of comorbidities.^[17]

As described in many articles in the past,^[19,20] to operate PFF within 48 h improved health-care standards, especially for frail patients, and allowed to lower mortality: Not more than 10–15 years ago, these patients were often surgically treated many days after the event, altering a delicate and unstable homeostasis irreversibly. In recent years, especially in some realities, we have observed the opposite phenomenon: To keep hospital quality-standards elevated and operate within 48 h, some useful investigations have been neglected.

The main limitation of the study was collecting data during the 1st month of pandemic; we tried to simplify the data to be collected since the study is multicentric.

CONCLUSION

Nowadays, we have a greater awareness about the different frailties and each patient deserves the best possible treatment. In most cases, the 48 h standard should be implemented because it improves the quality of life, reduces delirium, reduces pain, removes any risk of developing skin sores, and allows upright position, with tremendous advantages for patients.

In some patients with specific comorbidities, operation within 6–12 h may be indicated. However, in other specific cases of frailty, the thorough study of the patient is mandatory and a pre-operative wait within 72 h does not cause a significant increase in mortality. More studies are needed to further investigate perioperative timing that could possibly improve survival in patients with specific comorbidities, especially cardiovascular, defining new treatment standards and custom-made protocols to individualize for each patient.

RECOMMENDATIONS

The 48 h cutoff should not be put in practice for every patient as required by hospital quality standards but taking into account that some frail patients could take advantage from an early surgery whereas some others from a deep study of comorbidities.

AUTHORS' CONTRIBUTION

The authors testify that all persons designated as the authors qualify for authorship and have checked the article for plagiarism; all authors helped in data acquisition, revised the paper, and approved the final version; GP conceived and designed the study, GB and AI collected and organized data and drafted the article.

ETHICAL APPROVAL

This study received ethical approval from the Ethics Committee of Scientific Institute San Raffaele Hospital on May 14, 2021, protocol number NOF COVID 19V.1.2.

Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

DECLARATION OF PATIENT CONSENT

The authors certify that they have obtained all appropriate patients consent forms. In the form, the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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CONFLICTS OF INTEREST

There are no conflicts of interest.

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