Title

The association between surgical fixation of hip fractures within 24 hours and mortality: A systematic review and meta-analysis

Abstract

Aims

The aim of this study was to assess the effect of time to surgical intervention from admission on mortality and morbidity for patients with hip fractures.

Methods

MEDLINE and Embase were searched from inception to June 2020. Reference lists were manually assessed to identify additional papers.

Primary comparative research studies that recruited patients: (i) aged over 60 years, (ii) with non-pathological (iii) primary proximal femoral fractures (iv) treated surgically were included. Studies that did not include a group operated on within 24 hours or reported time to surgery in calendar days were excluded.

Two investigators extracted data on study characteristics, methods, and outcomes. The pre-defined primary outcome was thirty-day mortality. Secondary outcomes were complications and mortality at other time points. Relative risks (RRs) with 95% confidence intervals were aggregated and were grouped by study level characteristics.

Results

This review included 46 studies (1991-June 2020), comprising 521,857 hip fractures with 64,047 postoperative deaths. No randomized controlled trials were eligible for inclusion. In pooled analysis of 15 studies, RR (95% CI) of mortality at 30 days comparing time to surgery <24 vs >24 hrs was 0.86 (0.82-0.91; I^2 =69%; 95% CI 50, 81%; *p* for heterogeneity<0.01). The association was stronger in observational studies that did not adjust for confounders than those that adjusted for multiple covariates. In pooled analysis of 6 studies, the RR (95% CI) of mortality at 30 days comparing time to surgery <24 vs 24-36 hrs was 0.87 (0.81-0.93; I^2 =65%; 95% CI 16, 85%; *p* for heterogeneity=0.01).

Conclusions

This meta-analysis indicates reduced mortality for patients operated within 24 hrs compared with those operated on beyond 24 hrs or within 24-36 hrs. Where resources allow and there is not a specific reversible contraindication to early surgery, we recommend that hip fractures should be surgically treated within 24 hrs.

Main Text

Introduction

In the UK, approximately 98% of hip fractures are managed operatively.(1) Several variables influence the outcomes of patients following hip fracture surgery. Advanced age, reduced functional status and comorbidity are associated with adverse outcomes, but are beyond the control of surgeons.(2, 3) In contrast, earlier surgical treatment is, to some extent, a modifiable factor that may reduce mortality following hip fracture.(4, 5) An acceptable definition of ‘early surgery', however, is widely debated, varying from 6-72 hrs (hours).(6) As a result, national guidance on when to perform surgery following hip fracture varies. The British Orthopaedic Association and National Institute for Health and Care Excellence (NICE) in the UK advise operating on a planned trauma list on the day of, or the day after admission, i.e. within 36 hrs.(7, 8) By comparison, Swedish guidelines recommend repairing hip fractures within 24 hrs, while US guidelines recommend surgical repair within 48 hrs.(9, 10)

There is a need to clarify whether performing hip fracture surgery within 24 hrs confers any additional benefit to operating beyond 24 hrs. Changing national guidelines would present significant challenges to the consistent delivery of healthcare across the seven-day week, with potentially high associated up-front costs. As such, any alteration to future guidelines needs to be evidence based and cost effective.

A previous meta-analysis demonstrated improved survival at 1 year following hip fracture surgery performed within 24 hrs of admission.(5) Since then, several high-quality registry studies have been published.(11-14) An updated analysis of existing data is therefore required to review and inform guidelines for the management of hip fractures.

We performed a systematic review and meta-analysis, to assess the effect of time to hip fracture surgery performed within 24 hrs of admission compared to the beyond 24 hours and the secondary time point of 24-36 hrs.

Methods

Data sources and search strategy

This review was conducted according to PRISMA and MOOSE guidelines **(Supplementary Materials 1-2)**.(15, 16) A predefined protocol was registered in the prospective register of systematic reviews, PROSPERO (CRD42019127787).(17) MEDLINE and Embase were searched from inception to June 2020. The search strategy was constructed by combining MeSH search terms and keywords related to the population (e.g., “hip fracture”, “femoral fracture”) and intervention (e.g., “delay”, “time”, “surgery”), with input provided by an information specialist. It was restricted to human studies published in English language. Details of the search strategy are reported in **Supplementary Material 3**. Titles and abstracts of studies retrieved were screened independently by two of three reviewers (PW, CSJ, GD) to assess their potential for inclusion. Full texts were subsequently assessed for inclusion by at least two of three independent reviewers (PW, CSJ, GD). Discrepancies were resolved by discussion and where no consensus could be reached, the third reviewer was consulted. Reference lists of relevant review articles and included studies were manually assessed to identify additional papers. Where relevant information was not available within the manuscript, corresponding authors were contacted directly via email.

Eligibility criteria

All primary comparative research studies were eligible for inclusion. Case reports, letters and review articles were excluded. Studies that recruited patients: (i) aged over 60 years, (ii) with non-pathological (iii) primary proximal femoral fractures (iv) treated surgically were included. We included studies in which a small number of patients (<5%) lay outside of these criteria. The exposure of interest was surgery within 24 hrs of admission and/or injury. Studies that did not include a group operated on within 24 hrs or reported time to surgery in calendar days were excluded. The primary comparison of interest was delay-to-surgery of greater than 24 hrs. Where studies also reported outcomes of patients operated on between 24-36 hrs, these were also extracted for secondary analysis. Thirty-day mortality was chosen as the primary outcome as this is felt to be most directly influenced by perioperative factors in this population and is also the most common follow up period measured in reported studies.(18) Complications and mortality at other time points including inpatient, three months, four months, six months, one year, two years and three years were secondary outcomes. Studies involving periprosthetic fractures, or in which delay to surgery was directly attributed to anticoagulation effects were excluded.

Data extraction and quality assessment

Data were extracted by at least two of three independent reviewers (PW, CSJ, GD) into a data collection spreadsheet which was standardized for these purposes. Any disagreements were resolved by discussion with the third reviewer. Information on the following study characteristics was extracted: first author's name, year of publication, country of study, baseline years of recruitment, mean or median age, definition of time to surgery, sample size, operative time frame, average time to surgery, duration of follow-up, and outcome data including risk estimates. Quality assessment was completed for each study using the Newcastle Ottawa Scale (NOS).(19)

Statistical analyses

Relative risks (RRs) with 95% confidence intervals (CIs) were used as summary measures of associations between the exposure and risk of outcomes. Hazard ratios, rate ratios and odds ratios were assumed to approximate the same measure of RR based on the assumptions of rare outcomes and relatively short follow-up times.(20, 21) Multivariable adjusted risk estimates were used for pooling when reported, otherwise crude RRs were calculated from the raw counts extracted from studies. The primary comparison for time-to-surgery was <24 vs >24 hrs. Secondary time point of interest was <24 vs 24-36 hrs. The primary outcome for the analyses was mortality at 30 days. Random-effects meta-analysis was used as the primary method of analysis.(22) Additional sensitivity analyses were also conducted using a fixed-effects approach. Heterogeneity was assessed using the Cochrane χ^2 statistic and the I^2 statistic.(23) In pooled analyses involving 10 or more studies with substantial heterogeneity between studies, pre-defined study-level characteristics which may explain heterogeneity were explored using stratified analysis and random effects meta-regression. Publication bias was evaluated through funnel plots and Egger's regression symmetry tests.(24) The statistical analyses employed STATA release MP 16 (Stata Corp, College Station, Texas, USA).

Results

Study identification and selection

The search strategy and manual screening of relevant references lists identified a total of 4635 potentially eligible articles. Screening and reasons for exclusion are summarized in **Figure 1.** A total of 46 articles corresponding to 46 unique observational studies were finally included in the review.(11-14, 18, 25-64)

Study characteristics and quality

The publication dates of included articles ranged from 1991 to June 2020. A summary of the key characteristics of eligible studies is presented in **Table 1**. The only RCT of time to surgery performed to date was not eligible for inclusion as it randomised patients to surgery within or after 6 hours and did not report data at other time points. Relevant baseline characteristics and quality assessment scores of the individual studies are presented in (**Supplementary Material 4)**. The 46 studies involved 521,857 hip fractures with 64,047 recorded deaths following surgery. Overall, 27 studies were conducted in Europe (Austria, Denmark, Finland, Germany, Hungary, Ireland, Italy, Norway, Spain, Sweden, Turkey and UK), 14 in North America (USA and Canada), 4 in Asia (Japan, South Korea, and Taiwan), and 1 from Australasia (New Zealand). The average baseline age of participants in the included studies ranged from 69.0 to 94.2 years with a weighted mean age of 82.4 years. Methodological quality score of studies ranged from 3 to 9 with a median score of 7 **(Supplementary Material 5)**.

Time to surgery of <24 vs >24 hrs and outcomes

In pooled analysis of 19 studies (n =496,637), the RR (95% CI) of mortality at 30 days comparing time to surgery <24 vs >24 hrs was 0.86 (0.82-0.91; I^2 =69%; 95% CI 50, 81%; p for heterogeneity<0.01) (**Figure 2**). In subgroup analyses, none of the study-level characteristics explored explained the substantial heterogeneity between studies, except for degree of adjustment (p for meta-regression=0·001). The effect was unchanged in subgroup analyses of 16 studies that clearly defined time to surgery as the time from admission or diagnosis to surgery (RR 0.86, 0.81-0.91).(12, 13, 18, 30, 31, 40, 42, 47, 48, 51, 54, 56, 57, 59, 36, 64) The association was stronger in studies that did not adjust for confounders than those that adjusted for multiple covariates (RR 0.94, 0.89-0.99; **Figure 3**).

Comparing time to surgery <24 vs >24 hrs, the RR (95% CIs) for mortality at 1 year in pooled analysis of 19 studies (n =122,666) was 0.85 (0.80-0.90; I^2 =56%; 95% CI 27, 74%; *p* for heterogeneity=0.001) (**Figure 2**). Except for sample size (*p* for meta-regression=0·01) and marginal significant evidence of effect modification by degree of adjustment (*p* for meta-regression=0·07), none of the study level characteristics explained the heterogeneity between studies (**Figure 4**). In studies that adjusted for confounding factors, the association was attenuated at 1 year (RR 0.95, 0.84-1.08. **Figure 4)**.

The associations of time to surgery <24 vs >24 hrs and risk of mortality at other time points are reported in **Figure 5.** The RRs (95% CIs) were 0.82 (0.67-1.01; I^2 =30%; 95% CI 0, 66%; *p* for heterogeneity=0.16) for inpatients (11 studies); 0.80 (0.70-0.90; I^2 =79%; 95% CI 51, 91%; *p* for heterogeneity=0.001) at 3 months (5 studies); 0.79 (0.76-0.83; I^2 =0%; 95% CI 0, 0%; *p* for heterogeneity=0.49) at 4 months (2 studies); 0.70 (0.54-0.90; I^2 =76%; 95% CI 46, 89%; *p* for heterogeneity=0.001) at 6 months (6 studies); and 0.68 (0.37-1.27; I^2 =88%; 95% CI 67, 96%; *p* for heterogeneity<0.01) at 2 years (3 studies). The finding at 3 years was based on a single report, which showed a decrease in mortality risk.

The risk of other complications at 30 days comparing time to surgery <24 vs >24 hrs are portrayed in **Supplementary Material 6.** There were no differences in the risk of deep vein thrombosis (DVT, 2 studies), myocardial infarction (MI, 3 studies), urinary tract infection (UTI, 2 studies), reoperation (3 studies), readmission (3 studies), sepsis (2 studies), wound complications (2 studies), and other complications (4 studies): RRs (95% CIs) of 0.64 (0.38-1.09), 0.93 (0.68-1.27), 1.05 (0.95-1.15), 0.94 (0.82-1.07), 1.00 (0.88-1.13), 0.97 (0.82-1.15), 0.81 (0.63-1.05) and 0.95 (0.88-1.03) respectively. There was a decrease in the risk of pulmonary embolism (PE, 2 studies) and pneumonia (2 studies): RRs (95% CIs) of 0.61 (0.49-0.76) and 0.81 (0.74-0.89) respectively. Results from single reports showed no difference in the risk of venous thromboembolism (VTE), renal complications or other minor complications, but a decrease in the risk of respiratory complications.

Except for pneumonia, the risk of other complications at 1 year for time to surgery <24 vs >24 hrs were all based on single reports **(Supplementary Material 7)**. In pooled analysis of 2 studies, the RR (95% CI) of pneumonia was 0.88 (0.81-0.95). Whereas there were no differences in the risk of VTE, UTI, ulcers, DVT, reoperation, failure to recover to pre-morbid ambulation, avascular necrosis or other complications, the risk was decreased for PE and MI.

Time to surgery of <24 vs 24-36 hrs and mortality

In pooled analysis of 6 studies comparing time to surgery <24 vs 24-36 hrs, the RR (95% CI) of mortality at 30 days was 0.87 (0.81-0.93; I^2 =65%; 95% CI 16, 85%; *p* for heterogeneity=0.01) (**Figure 6**).(11, 13, 40, 42, 48, 51) In pooled analysis of 3 studies comparing time to surgery <24 vs 24-36 hrs, the RR (95% CIs) for mortality at one year was 0.91 (0.87-0.95; I^2 =0%; 95% CI 0, 90%; *p* for heterogeneity=0.93).(11, 14, 37) At three months, the RR (95% CI) of mortality in pooled analysis of two studies was 0.79 (0.69-0.90, **Supplementary Material 8)**.(40, 48)

Other subgroups

Comparing time to surgery <24 vs >24 hrs, the RR (95% CIs) for mortality at 30 days in ASA 1-2 and ASA 3 or more was 0.96 (0.80-1.17) and 0.92 (0.80-0.98) respectively **(Figure 7)**. The corresponding RR (95% CIs) for mortality at 1 year was 0.94 (0.85-1.03) and 0.94 (0.91-0.97) respectively **(Supplementary Material 9)**. Due to heterogeneity in endpoints between studies, there was insufficient data available to perform sub-group analysis by sex.

Publication bias

Funnel plots for risk of mortality at inpatient stay, 30 days and 1 year for time to surgery <24 vs >24 hrs which involved 10 or more studies were symmetrical on visual inspection, implying little evidence of small study effects or publication bias **(Supplementary Material 10)**. These were consistent with Egger's regression tests (*p*-values of 0.92, 0.36 and 0.08 respectively).

Discussion:

This systematic review and meta-analysis of 46 studies included 521,857 patients treated operatively for hip fracture. Results demonstrated a reduced risk of mortality for patients operated within 24 hrs of admission, compared to those operated beyond 24 hrs. This reduction in mortality was relatively consistent across included studies and at all study endpoints. In sensitivity analysis including maximally-adjusted data only, the effect of time to surgery was reduced but remained statistically significant at 30 days. Results further demonstrated a reduced risk of mortality for patients operated within 24 hrs of admission, compared to those operated at 24-36 hrs. The effect remained significant at both the 30 day and one year endpoints. These findings strengthen calls for a shift in national guidance, both in the UK and overseas.

Previous systematic reviews have demonstrated clear survival benefits of performing hip fracture surgery within 48 hrs of admission, compared with surgery performed beyond 48 hrs.(5, 65)

Advantages of operating within 24 hrs, however, have been less obvious. The most recent review on the topic by Chen et al. reported significantly improved survival for patients operated within 24 hours at one year (RR 0.68, 0.56-0.84), but not at 30 days (RR 1.05, 0.90-1.22).(5) Similarly, Klestil et al. also reported reduced mortality at one year for patients operated within 24 hrs (8 studies, RR 0.68, 0.56-0.84).(65) Further analysis using adjusted data, however, was inconclusive (3 studies, RR 0.82, 0.62-1.01). Since these reviews, significant contributions have been made to the published literature, including the addition of multiple large registry studies. Our analysis included an additional 20 studies reporting outcomes from 258,092 patients.(11-14, 18, 30, 37, 39, 42, 47-49, 54, 56-59, 61, 63, 64) In contrast to previous meta-analyses that investigated time to surgery, this study showed increased survival for patients operated within 24 hrs at both 30 days and one year. In subgroup analysis using only adjusted data, the benefit of earlier surgery remained significant at 30 days, but not at one year. We selected 30-day mortality as our primary outcome, as this is considered more sensitive to operative factors than one-year mortality in this population.(66-68) Following hip fracture surgery, mortality rates have been noted to decrease rapidly after an initial postoperative spike and become more reflective of patient comorbidity at one year.(66) It would therefore be expected that a causal relationship between early surgery and mortality would be strong at 30 days and wane with time. This effect is supported by our data which demonstrate an attenuated relationship at one year in studies that included multivariate analyses.

Uncertainty regarding optimal time to surgery has led to heterogeneity in guidelines internationally.(7-10) A drive towards earlier surgery would require considerable investment and reorganization of services in the short term, but may reduce costs in the medium to long term.(69) To our knowledge, this is the first review to demonstrate improved survival outcomes for patients operated within 24 hrs compared to those operated at 24-36 hrs. Given the high incidence of hip fractures and associated morbidity and mortality, small improvements in care have the potential to save many lives and significantly reduce healthcare system costs.

Certain demographics of patients may be particularly vulnerable to the negative effects of surgical delay.(12, 48, 59) Targeting high-risk patients for surgery within 24 hrs may offer some compromise to the challenges of a change in clinical guidance. Greve et al. demonstrated increased mortality at four months for comorbid (ASA 3-4) patients operated on beyond 24 hrs.(12) This association was stronger for women and those aged over 85. Similarly, Beaupre et al. reported that patients with increased age and Charlson Comorbidity Index (CCI) appeared particularly susceptible, whereas women were less affected.(48) In our study, pooled analyses of studies reporting mortality by ASA group, demonstrated a greater benefit of early surgery for patients with high ASA grades at both 30 days and 1 year. The number of studies included in these analyses however, were limited by infrequent reporting, heterogeneity in endpoints and variation in classification of factors such as comorbidity. Greater understanding of which patients are sensitive to delayed surgery may enable risk stratification and more targeted resource allocation.

Strengths and limitations

This study has several strengths. Our search strategy identified several studies that were not included in previous meta-analyses on this subject.(4, 5, 65) In contrast to previous reviews, we employed a strict definition for time to surgery. To meet criteria for inclusion, studies were required to state explicitly that time-to-surgery was measured in hours rather than calendar days. This is an important distinction. As Müller et al. noted, a patient who was admitted at 23:00 and operated two hours later, at 01:00 would, on the basis of calendar days, have waited one day.(58) By comparison, a patient admitted at 01:00 and operated at 23:00 the same day would be defined as having had surgery on day zero, despite waiting 22 hours for the procedure. Measuring time to surgery in hours avoids this lack of precision. Previous reviews on this subject have been less stringent in making this distinction and have included a number of studies reporting in calendar days.(70-72) To control for the important confounding effect of comorbidity, a comprehensive analysis of ASA sub-groups was completed and maximally-adjusted data was used for sensitivity analysis, when available. Where data was missing or incomplete, authors were contacted.(12, 13, 42, 56, 61). Data analysis for the present systematic review included an assessment of study quality, consideration of heterogeneity and an examination of publication bias. To our knowledge, this systematic review and meta-analysis was the first to compare a 24 hr target for time to surgery with the 36 hr target that currently dictates UK clinical practice.(7, 8)

Like any systematic review, this study was dependent on the quality of available primary data. All included studies were observational in design, and the majority were retrospective. Although maximally-adjusted data was used when available, this was frequently absent or available only for timeframes not captured in this study, e.g. <24 hrs vs 24-48 hrs. Furthermore, although this study focused on </> 24 hrs, it is possible that additional benefits may be seen if surgery is performed even earlier. For example, Nyholm et al. reported reduced mortality at 30 days for patients operated within 12 hours.(40) Heterogeneity exists in the definitions used and populations studied. For example, Leer-Salvensen clearly differentiated delay between injury, admission and surgery, while Mutulu provided no definition of time to surgery.(11, 39) Reason for operative delay was, in general, poorly reported. Included studies were also inconsistent in which confounders were controlled for. Medical comorbidities are increasingly recognized as potent confounders in the relationship between time to surgery and mortality.(12) Data for ASA subgroup analysis was frequently absent or incomplete. Several included studies controlled for comorbidities only in time to surgery groups that were beyond the scope of this review. In these cases, raw data were extracted. The influence of confounding factors must therefore be considered. It is plausible that patients who are deemed to be less fit for surgery could be delayed due to the perception that they could be optimized prior to surgery. Alternatively, surgeons may prioritize sicker patients on the basis that they have most to gain from early surgery. Such factors cannot be controlled for in the observational data included in this review. Large randomized studies are therefore required to account for this variation in contemporary practice and to understand the causal effect of time to surgery on outcomes.

Frequently, individual studies reported that the relationship between time to surgery and mortality was diminished or removed when confounders were adjusted for. Analysis of maximally adjusted mortality data suggests that the effect of time to surgery is less pronounced but remains significant at 30 days. However, higher risk patients may be more likely to experience delay to surgery. Additional confounders may not be accounted for in observational studies. The HIP ATTACK trial is, to our knowledge, the only randomized controlled trial (RCT) to have investigated the effect of time to surgery on mortality following hip fracture.(73) The study found that surgery performed within 6 hrs conferred no survival benefit compared to surgery performed after 6 hrs, although the risk of postoperative delirium was reduced. There are ethical and logistical challenges to conducting an RCT using a 24 hr cut-off. However, such challenges were common to HIP ATTACK, suggesting that an RCT reflective of variation in international standards could be delivered. Given the cost and resource implications of delivering an RCT that is large enough to examine time strata of interest and remains generalizable to clinical practice, a registry nested randomized trial design may be the most cost-effective way to further explore this important topic.

Finally, 45 of 46 included studies were conducted in high-income countries. One paper (Turkey, n =11) concerned work done in an upper-middle income setting. Generalizability of our findings is limited by significant delays that may exist between hip fracture and admission to hospital in low and lower-middle income countries.

Conclusions

This meta-analysis demonstrates reduced mortality for patients operated within 24 hrs compared with those operated on beyond 24 hrs or within 24-36 hrs. For some patients, medical optimization prior to surgery is essential, such as a reversible cause of a tachyarrhythmia. Where this is not the case, in the absence of directly relevant RCT evidence, we recommend that hip fractures should be surgically treated within 24 hrs.

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Tables

Table 1. Summary characteristics of the 46 eligible studies

Characteristics

Participants	
Total number of hip fractures	521,857
Total number of mortality cases	64,047
Study characteristics	
Location	Number of studies (Number of hip fractures)
Europe	27 (421,624)
North America	14 (98,991)
Asia	4 (1,104)
Australasia	1 (138)
Median (IQR) study quality score for observational studies	7 (6-8)
Study level participant characteristics	
Weighted mean age (min-max), years	82.4 (69.0-94.2)
Median (IQR) % males	27.0% (21.5-29.9)

IQR, interquartile range; SD, standard deviation

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Figure Captions

Figure 1: PRISMA flowchart. TTS: Time to surgery

Figure 2: Risk of mortality at 30 days and 1 year for time-to-surgery <24 vs >24 hrs (D+L= random effects model, I-V= fixed effects model)

Figure 3: Risk of mortality at 30 days for time-to-surgery <24 vs >24 hrs, grouped according to study level characteristics

Figure 4: Risk of mortality at 1 year for time-to-surgery <24 vs >24 hrs, grouped according to study level characteristics

Figure 5: Risk of mortality at other time points for time-to-surgery <24 vs >24 hrs (D+L= random effects model, I-V= fixed effects model)

Figure 6: Risk of mortality at 30 days and 1 year for time-to-surgery <24 vs 24-36 hrs (D+L= random effects model, I-V= fixed effects model)

Figure 7: Risk of mortality at 30 days in ASA subgroups for time-to-surgery <24 vs >24 hrs. CI, confidence interval (bars); RR, relative risk. D+L, random effects model; I-V, fixed effects model; ASALo, ASA 1-2; ASAHi, pooled ASA 3-4 and ASA 3-5