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Mortality Following Post-Operative Periprosthetic Fracture of the Femur after Total Hip Replacement: Meta-analysis of 35 cohort studies including 4841 patients.

Abstract:

Introduction: Post-operative periprosthetic fracture of the femur (POPFF) is associated with increased mortality. There is a lack of general estimates of mortality following POPFF and a need for higher-level evidence in this area. The aim of this study was to estimate mortality following POPFF mortality using data reported in cohort studies from the last decade.

Materials and Methods: Literature search was conducted using Medline and EMBASE. Primary outcome was all-cause mortality during time as an inpatient, within 30-days, within 90-days and within one year of POPFF. Mortality (95% CI [confidence interval]) was estimated using metaregression.

Results: 4841 patients from 35 cohort studies were included. Study quality was generally low. Weighted mean follow-up was 2.3 years and the most common POPFF was Vancouver B. Pooled mortality as an inpatient was 2.4% (95% CI 1.6% to 3.4%). Pooled mortality within 30 days was 3.3% (95% CI 2.0% to 5.0%). Pooled mortality within 90 days was 4.8% (95% CI 3.6% to 6.1%). Pooled mortality within one year was 13.4% (95% CI 11.9% to 14.8%). Mortality following POPFF was like that of Neck of femur fracture (NOF) up to 30 days, but better at one year.

Conclusion: Mortality is like that experienced by patients following NOF up to 30 days, but better at one year, which may represent the lower underlying risk of death in the POPFF cohort. These results may form the basis for evaluation of services treating POPFF in the future.

Word count: 238

Key words: Hip arthroplasty, Periprosthetic fracture, Hip, Femur, Mortality

Introduction

Improvements in survival of total hip replacements (THR) due to a reduction in common failure modes has led to a shift in focus onto previously less common failure modes, such as post-operative periprosthetic femoral fracture (POPFF). The cumulative incidence of POPFF is between 2.1% for cemented stems and 7.7% for cementless stems at 20 years (1-3). A vast majority of patients require major surgery which is associated with large volume blood loss and an increased risk of post-operative mortality (4). Once complete the patient must then endure a substantial risk of reoperation which is reported to be as high as 23% (5). The overall mortality following POPFF approaches that of hip fracture, which affects a similar cohort of frail patients (6-8). Estimated mean life expectancy for patients following POPFF is just 71 months (9).

Estimates of mortality following POPFF may serve as a useful metric for treatment success and every effort should be made to improve patient survival. Current estimates of mortality are generally limited to analyses of single center cohorts or larger registry-based studies. Mortality from single center cohort studies may not represent mortality in other health systems with different patient populations, since mortality may change with increasing patient age and comorbidity (4, 10-12), treatment method (13, 14), pre-operative delays (6, 11) and fracture type (6). Registry based estimates of mortality may also be limited to capturing cases of POPFF which are revised (15), which may not accurately represent all patients with POPFF, who are managed with fixation or without surgery at all. Meta-analysis of recent studies to combine cohort data into a larger international multi-center group, may be a useful way of understanding mortality in the context of modern surgical practice and setting benchmarks on which services can be evaluated.

The aim of this study is to estimate mortality rate following POPFF after THR from cohort studies published in the last decade.

Methods

Data source:

A meta-analysis of death rates following POPFF after total hip replacement reported in peer-reviewed cohort studies from the last decade was performed.

Systematic review and meta-analysis of cohort studies:

The study methodology was peer-reviewed and registered on the PROSPERO (id: CRD42020170819). The literature search was conducted using the online databases Medline and EMBASE. Articles were identified using a combination of keyword searches describing periprosthetic fracture of the femur, hip replacement and mortality. Results were combined with searches for Mesh terms (Appendix 1).

Citation searching was performed for all full text manuscripts to identify manuscripts which were not found in initial searches. Inclusion criteria for cohort studies included: Articles written in English language, available in full text, published between January 2010 and January 2020, human studies reporting mortality of cohorts which contain only patients with POPFF following primary THR.

We excluded conference abstracts, manuscripts which reported on the same cohort twice and systematic reviews to prevent duplication of observation. Abstracts and the full texts were screened by two authors (ON and AA) independently and disagreements at each stage were settled by consensus. Risk of bias/quality of studies was assessed using criteria developed by Wylde et al. independently by two authors (ON and AA) (16). Where available extracted data included: Title, authors, year of publication, number in cohort, average age of cohort, average co-morbidity score of cohort, frequency of Vancouver grades in cohort(17), frequency of treatment methods in cohort, average follow-up, follow-up range, number lost to follow up, number died, survival/ mortality of cohort (with confidence intervals), number of reoperations and time of reoperations. Where available, survival curves published as figures were digitized manually to extract data points (18). Data was extracted by three authors (ON, AA and JL).

Statistical analysis:

The primary exposure was the diagnosis of POPFF, and the primary outcome measure was all-cause mortality during a specified follow-up time. The time periods during which deaths were reported included: Inpatient deaths, all deaths within 30 days of POPFF, all deaths within 90 days of POPFF and all deaths within one year of POPFF. Study and patient level statistics were estimated using mean values weighted by number of cases. Mortality was estimated by dividing the total number of patients during a given time (excluding loss to follow-up) by the number of patients. Where reported, number of patients who died was derived from the Kaplan–Meier estimates of patient survival. Unadjusted estimates of mortality for each time with 95% confidence intervals was estimated using a fixed effects model (inverse-variance method). The included studies were assessed for heterogeneity based on cohort characteristics and inclusion criteria. Robust estimates of mortality rates were calculated using meta-regression with adjustment for mean age of patients, patient sex, treatment method and fracture type. Adjusted estimates were calculated with associated 95% confidence intervals. To understand the mortality rates in context of normal orthopedic practice, meta-analysis results were compared against the mean values for survival following neck of femur fracture (NOF) as reported in a recent systematic review of international fragility fracture registries (19). All data analysis was completed using R (version 4.0.0, Vienna Austria, 2019).

Results

Our search resulted in 727 unique references from database and citation searches. After title and abstract screening, 639 records were excluded, and 88 manuscripts underwent full text review (Figure 1). After full-text review 35 papers were included in the meta-analysis.

Data quality assessment:

Despite a low number of patients being lost to follow-up, the quality of cohort studies was generally low with most studies reporting only from a single center with half of studies explicitly reporting consecutive patients (Table 1).

Table 1 Description of study quality in accordance with criteria set out by Wylde *et al.*, 2017.

Author, date (reference)	**n**	**Representativeness (multicenter adequate)**	**Percentage follow up**	**Minimization of potential confounding (multivariable analysis adequate)**	**Inclusion of consecutive patients (yes - adequate)**
Amenabar and Vera, 2015 (20)	76	inadequate	adequate	inadequate	inadequate
Biggi et al., 2019 (21)	235	inadequate	adequate	inadequate	adequate
Boylan et al., 2018 (10)	1655	adequate	adequate	adequate	inadequate
Cassidy et al., 2018 (22)	9	adequate	adequate	inadequate	inadequate
Chakrabarti et al., 2019 (23)	32	inadequate	adequate	inadequate	adequate
Chatziagorou et al., 2019 (24)	632	adequate	adequate	inadequate	adequate
Cohen et al., 2018 (13)	71	inadequate	adequate	inadequate	inadequate
Colman et al., 2014 (25)	97	inadequate	adequate	inadequate	adequate
Dargan et al., 2014 (26)	27	inadequate	adequate	inadequate	adequate
Ehlinger and Bonnomet, 2014 (27)	234	adequate	adequate	inadequate	adequate
El-Bakoury et al., 2017 (28)	27	inadequate	adequate	adequate	inadequate
Finlayson et al., 2019 (29)	189	inadequate	adequate	adequate	adequate
Font-Vizcarra et al., 2010 (30)	21	inadequate	adequate	inadequate	adequate
Fuchtmeier et al., 2015 (31)	121	inadequate	adequate	inadequate	adequate
Gavanier et al., 2017 (32)	45	adequate	adequate	inadequate	inadequate
Gitajn et al., 2017 (4)	203	adequate	adequate	adequate	adequate
Griffiths et al., 2013 (11)	60	inadequate	adequate	inadequate	inadequate
Jennison and Yarlagadda, 2018 (33)	29	inadequate	adequate	inadequate	adequate
Jennison and Yarlagadda, 2020 (34)	173	inadequate	adequate	inadequate	adequate
Johnson-Lynn et al., 2016 (35)	82	adequate	adequate	inadequate	adequate
Langenhan et al., 2012 (36)	52	inadequate	adequate	adequate	adequate
Mardian et al., 2015 (9)	67	inadequate	adequate	adequate	inadequate
Moloney et al., 2014 (37)	58	adequate	adequate	inadequate	adequate
Munro et al., 2014 (38)	55	inadequate	adequate	inadequate	adequate
Pavone et al., 2019 (39)	38	inadequate	adequate	inadequate	inadequate
Perez-Prieto et al., 2015 (40)	21	inadequate	adequate	inadequate	inadequate
Phillips et al., 2013 (41)	79	inadequate	adequate	adequate	adequate
Shields et al., 2014 (42)	70	inadequate	adequate	inadequate	inadequate
Spina and Scalvi, 2018 (43)	39	inadequate	adequate	inadequate	adequate
Spina et al., 2014 (44)	61	inadequate	adequate	inadequate	inadequate
Suarez-Huerta et al., 2015 (45)	17	inadequate	adequate	inadequate	inadequate
Thaler et al., 2019 (46)	40	inadequate	adequate	inadequate	adequate
Trieb et al., 2016 (47)	34	inadequate	adequate	inadequate	adequate
van Laarhoven et al., 2020 (48)	86	adequate	inadequate	inadequate	adequate
Zheng et al., 2020 (49)	106	inadequate	adequate	adequate	adequate

Included studies:

35 cohorts included a total of 4841 patients who were diagnosed with POPFF following THR. Weighted mean follow-up was 2.3 years and ranged from 0 to 23 years after POPFF. The most common POPFF Vancouver class was type B (69.4%) and B2 (30.5%) sub classification, specifically. Most patients were treated with ORIF (Table 2). Reoperation was reported in 21 studies (2102 patients) and the weighted mean reoperation rate was 13.7% of POPFF cases. Few studies reported detailed outcomes for patients who were conservatively managed. Zheng reported a high mortality in a group of 11 patients treated non-operatively following POPFF (49).

Ten studies (1293 patients) reported in-patient mortality, 19 studies (2928 patients) reported 30-day mortality, 17 studies (1374 patients) reported 90-day mortality and 24 studies (4100 patients) reported one-year mortality. Patient level characteristics derived from reported data are displayed in Table 2. The studies were heterogeneous and included a range of ages, fracture types and treatment methods.

Table 2 Descriptive statistics for studies included in systematic review and meta-analysis. *Note:* ASA indicates American Society of Anesthesiologists, ORIF is open reduction and internal fixation.

Variable	***Statistic***	**All cohorts**	**Inpatient mortality**	**30-day mortality**	**90-day mortality**	**One-year mortality**
Number of cohorts	*n*	35	10	19	17	24
Publication year	*range*	4841	1293	2928	1374	4100
Patients	*n*	2010-2020	2012-2020	2010-2020	2012-2020	2012-2020
Age in years	*weighted mean*	77.8	76.3	78	77	77.7
Female patients	*%*	69.4	75.8	67.8	63.3	70.5
ASA	*weighted mean*	2.7	2.8	2.7	2.5	2.8
Vancouver A	*%*	2.5	2.4	3.5	4.7	2.6
Vancouver B1	*%*	23.0	8.5	31	32.7	23.9
Vancouver B2	*%*	30.5	12.6	40.6	43	25.4
Vancouver B3	*%*	15.9	22.5	9	11.2	16.7
Vancouver C	*%*	26.9	53.5	12.8	7.7	31.3
Treatment:						
Revision	*%*	43.5	32.5	40.8	52.6	37.7
ORIF	*%*	55.7	65	54.2	47	61.4
Follow up (years)	*weighted mean*	2.3	4.2	1.7	2.5	2.5
Follow up range in years		0.0-23.0	0-23.0	0-23	0-13.9	0-13.9

In-patient mortality:

10 Studies reported inpatient mortality. These studies included 1293 patients with a weighted mean age of 76.3 years, of which 75.8% were female and included a large proportion of Vancouver C POPFF (Figure 2). For ten studies with complete data (1293 patients), the adjusted mortality rate (95% CI) was 2.4% (95% CI 1.6% to 3.4%).

30-day mortality:

19 Studies reporting 30-day mortality included 2928 patients with a weighted mean age of 78.0 years, 67.8 % were female and most cases were Vancouver B2 POPFF (40.6%) (Figure 3). For 19 studies with complete data (2928 patients), the adjusted mortality rate (95% CI) was 3.3% (95% CI 2.0% to 5.0%).

90-day mortality:

17 studies reporting 90-day mortality included 1374 patients with a weighted mean age of 77.0 years, 63.3 % were female and most cases were Vancouver B2 POPFF (43.0%) (Figure 4). For 17 studies with complete data (1374 patients), the adjusted mortality rate (95% CI) was 4.8% (95% CI 3.6% to 6.1%).

One-year mortality:

24 studies reporting one-year mortality had a weighted mean age of 77.7 years, 70.5% were female and most cases were Vancouver C POPFF (31.3%) (Figure 5). For 22 studies with complete data (2375 patients), the adjusted mortality rate (95% CI) was 13.4% (95% CI 11.9% to 14.8%).

Data extracted from a recent review of national hip fracture registries demonstrated a mean percentage inpatient mortality of 4.6%, 30-day mortality of 6.5% and one year mortality of 24.0% (19). In comparison to international data on mortality following NOF reported in registries (19), in-patient mortality was similar but mortality following POPFF appeared to be better up to one year following fracture (Figure 6).

Discussion

This study gives the first estimate of mortality following POPFF around a primary THR from international cohort studies from the last decade. This study estimated an adjusted mortality rate of 3.3% within 30 days of POPFF, which increased to 13% at one year. Overall, the mortality rate following POPFF was better than that for fractured NOF as reported by international hip fracture registries (19). The findings of this study may be used in the formation of benchmarks representing the likely estimates of mortality following POPFF.

The demographics of the included studies are like those reported in large scale registry analyses (50-52). Many comparisons have been drawn between patients with POPFF and those with hip fracture, with authors making frequent comparisons between the two groups. Patients with POPFF have a co-morbidity profile which is reported to be significantly better than that of patients with fractured neck of femur (6, 8, 10). After adjustment for the comparative difference in comorbidities, there was no significant difference in the mortality risk between the two groups at 30 days and at one year (10). Differences in mortality rate may also be accounted for by longer delays until surgery in comparison to patients with native hip fractures, which is likely to be due to the added requirement of subspecialist surgeons and specialist equipment (10). In general, POPFF surgery takes longer than native hip fracture surgery and following surgery there is greater major and minor complications, rate of return to theatre and requirement for blood transfusion (8). These factors may contribute to significant risk of mortality after POPFF and surgeons should seek to streamline these approaches to reduce the effects of delays to surgery, intraoperative blood loss and return to the operating room on patient mortality.

Early mortality following POPFF represents a combined effect of injury and treatment. As one might expect, deaths closely following POPFF probably have greater likelihood of a causal relationship with POPFF and its treatment, whereas later deaths are more likely to represent the comorbidity profile of patients with POPFF. In a large Swedish registry study the mortality risk increased dramatically at 14 days after POPFF and returned to a level slightly higher than that of a comparable patient without fracture (53). In this study, the greatest estimated increase in mortality also occurred in the immediate post-operative period with a 30-day mortality rate of 3.3%. This might suggest that the physiological hit of the POPFF injury and surgery are key to patient survival in the immediate peri-operative period. Patients with greater co-morbidities might be expected to tolerate this insult less well. Perhaps unsurprisingly, worse ASA, Deyo comorbidity score and Charlson Comorbidity Score are all associated with increased mortality risk following treatment for POPFF (4, 10). Likewise, age greater than 85 years old at the time of POPFF is associated with a nine fold increase in mortality risk at one year and dependent functional status are associated with a fivefold increased mortality risk at one year (8). These results follow a similar trend to those from a large German cohort where increased mortality was associated with patients over the age of 85 and a history of cardiac disease (12). Larger well controlled prospective studies are required to investigate the effect of surgical delay and risk factors on patient outcomes following POPFF.

90-day mortality from the analyzed studies was 4.7%, which may in part be attributable to the added physiological load of re-operations occurring because of failed treatment. In this study approximately 1 in 7 patients in studies reporting reoperation underwent further surgery, which is similar to rates reported for all both hip and knee implant POPFF (54). Although re-operation only affects a proportion of patients, it poses a significant risk to a frail population and should be avoided. Common causes of reoperation are non-union, infection and stem loosening (24). Re-operations may be avoided through increased use of revision techniques (54) and modern locking plates (24). However, high quality prospective studies in this area are limited and prevent the formation of evidence-based guidelines which may reduce reoperation rates. This emphasizes the need for further investigation with focused quality improvement and studies to demonstrate the most effective surgical POPFF treatment methods.

In the UK data on POPFF admissions will be collected prospectively alongside data already collected for NOF (55). This approach is likely to improve the outcomes of patients with POPFF and the results of this study may be used as a benchmark from which to assess the performance of POPFF management in the future.

Limitations:

The studies included were of poor quality and were heterogeneous. Given that most papers published in the orthopedic literature are retrospective in nature, this was unavoidable, and the results represent a pooling of published evidence for patients with a range of POPFF classification and treatment methods. This limitation increases the risk of reporting and publication bias and the true mortality rate for patients with POPFF may differ. Further study using robust hospital derived datasets may improve the estimates reported in this paper.

The studies included in this analysis include cohorts from many different countries and represent an interesting global perspective on mortality following POPFF. However, aggregation of international results is likely to be subject to confounding factors due to local and national practices and racial and or ethnic differences between papers. The estimates for mortality in this paper were adjusted according to features of the reported cohorts but adjustment of all relevant features such as comorbidity scores was not possible due to varied reporting practices. Specifically, we were not able to identify comorbidities which are associated with an increased risk of death. The cause of death is not consistently reported in studies describing POPFF cohorts, which limits further investigation. Future studies may benefit from unified reporting practices using simple measures such as pre-operative ASA grading. Given this limitation, mortality estimates should be treated with caution and may serve as a useful guide to mortality following POPFF.

Direct contrast with NOF mortality is an interesting comparison but due to the aggregated nature of the data, this analysis does not serve as a precise comparison and direct comparisons should be made in suitably designed studies, which allow for measurement and adjustment of co-morbidity risk factors. The estimates in this study are likely to reflect the mortality risk factors of the included patient population and should be quoted with reference to these. Application of these estimates in patient discussions should be caveated with reference to the patient co-morbidities in each case.

Some cohorts included all admissions with POPFF, which may include patients which do not require surgery where mortality is likely to be low, and patients who are not fit for surgery, where the associated mortality may be high (49). This irregularity in reporting is likely to reduce the accuracy of the estimated mortality in this study.

Conclusion:

This study combines the reported mortality for patients with POPFF from studies published in the last decade. Mortality was three percent at 30 days, five percent at 90 days and 13% at one year. Mortality following POPFF is significant and may in part be due to patient age, comorbidities, and a large rate of reoperation. These results may be used to create more accurate estimates of the mortality after POPFF and help guide treatment decisions. We recommend further research into predictive factors of early mortality after POPFF, as well as looking into treatment options which offer a lower risk of reoperation.

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