Periprosthetic Femoral Fractures around Primary Total Hip Replacements

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Intellectual property and publication statement

The candidate confirms that the work submitted is their own, except where work which has formed part of jointly authored publications has been included. The contribution of the candidate and the other authors to this work has been explicitly indicated below. The candidate confirms that appropriate credit has been given within the thesis where reference has been made to the work of others.

The work in Chapter Two of the thesis has appeared in publication as follows:

King SW, **Lamb JN**, Cage ES, Pandit H. *Periprosthetic femoral fractures following total hip and total knee arthroplasty*. **Maturitas** 117:1-5, Nov 2018.

The candidate performed literature search and review, contributed to manuscript writing, review and editing.

HP supervised and led the project, ES assisted in literature review and manuscript writing and SK performed a large amount of manuscript writing and editing.

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The candidate was responsible for data application, study inception, data preparation (cleaning and processing), data analysis and interpretation, manuscript writing, review, editing and submission.

HP led the project and provided guidance on data application, assistance in interpretation of results, review, editing and assistance in writing the manuscript. RW gave advice on statistical approaches, interpretation of results and manuscript writing and review. AJ was involved in the initial data application, statistical approaches and data processing. GM assisted in data application, approaches to data analysis and manuscript review. AR gave guidance in the project design, manuscript review and editing.

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Abstract

Post-operative periprosthetic femoral fractures (POPFF) increase morbidity and mortality, and premature failure of hip replacements. POPFF is most likely after cementless femoral stem implantation and are caused by intraoperative and post-operative injury. Prevention of POPFF may be possible by modifying implant selection, design and use.

Propensity matched survival analysis of 4831 intraoperative periprosthetic femoral fractures (IOPFF) from the National Joint Registry of England, Wales and the Isle of Man (NJR) identified increased risk of POPFF revision and mortality when compared to propensity matched controls. IOPFF risk-factor modelling using 793977 primary total hip replacements identified that cementless femoral implants doubled the risk of any IOPFF, but particularly calcar and shaft fractures. A novel design-linked analysis of 349161 cementless hip replacements from the NJR identified stem features which were associated with increased risk of POPFF within 90-days, including: collarless design, mineralised and porous coatings, and triple-tapered stem bodies.

A novel manual segmentation method to analyse POPFF fracture patterns was developed and used to analyse a series of 125 cases from four large UK centres. This analysis demonstrated that POPFF within 90 days occurred almost exclusively around the femoral stem, probably as a result of rotational and axial forces. Experimental simulation of early POPFF in paired cadaveric femurs established that the force required to fracture was increased when a calcar collar was present. Further testing revealed that the increased fracture resistance during simulation was dependent on calcar-collar contact and was most likely when the initial separation was 1 mm or less.

A strong relationship between femoral implant design and risk of subsequent POPFF exists. The ability to associate specific design features with clinical outcomes and ratify the findings with experimental methods will help to develop this field further and improve implant use and design for future generations of patients with hip replacement.

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List of Abbreviations

ACC	Anterior calcar collar distance
ANOVA	Analysis of variance
AO	Arbeitsgemeinschaft für Osteosynthesefragen
AP	Anteroposterior
ASA	American Society of Anaesthesiologists grade
ASL	Aseptic stem loosening
AVN	Avascular necrosis of the hip
BMI	Body mass index
CCC	Calcar collar contact
CGS	Computer guided surgery
CI	Confidence interval
CT	Computed tomography
DM	Dual mobility
G	Torsional modulus
GRIT	Grit blasted or roughened
GT	Greater tuberosity
HR	Hazard ratio
IOPFF	Intraoperative periprosthetic femoral fracture
IQR	Interquartile range
J	Polar moment of inertia
LT	Lesser tuberosity
MIN	Mineralised with hydroxyapatite or calcium phosphate
NHS	National Health Service
NJR	National Joint Registry of England, Wales, Northern Ireland and the Isle of Man
NOF	Neck of femur fracture
OA	Osteoarthritis
OR	Odds ratio
ORIF	Open reduction and internal fixation
PCC	Posterior calcar collar distance

PCF	Pounds per cubic foot
POPFF	Post-operative periprosthetic femoral fracture
POR	Non-mineralised porous finish
PPI	Pixels per inch
PTS	Polished taper femoral stems
RR	Relative risk
SD	Standard deviation
SHAR	Swedish Hip Arthroplasty Registry
SMD	Standardised mean difference
THR	Total hip replacement
UCS	Universal classification system
UK	The United Kingdom
USA	United States of America

Chapter 1 Introduction

1.1 Justification of the subject matter

Since the first recognisable total hip replacements (THR) performed by Sir John Charnley in the 1960's (Gomez and Morcuende, 2005), the success of the THR has relied upon the dependable pain relief afforded to patients with hip pain (Patterson and Brown, 1972; Todd et al., 1972). The clinical effectiveness and implant survival of the THR has improved steadily over time as a result of successive improvements in the technology and surgical technique (Learmonth et al., 2007). Modern THR is a highly cost-effective operation for end-stage arthritis (Fordham et al., 2012; Jenkins et al., 2013) and the majority of THRs can now be expected to last 20 years (Evans et al., 2019). This benefits recipients of THR in the older orthopaedic cohort but also allows the use of THR to a broader cross section of younger and more demanding patients with end-stage hip arthritis.

Improvements in survival of 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). POPFF occur as a result of intraoperative fracture or injuries such as a fall from standing height or a stumble (Abdel et al., 2016b; Lindahl et al., 2006a; Yoon et al., 2016; Lindahl et al., 2005) and a majority occur in the early post-operative period, particularly after cementless stem implantation (Gromov et al., 2017; Yoon et al., 2016; Capello et al., 2014). At five years the incidence of POPFF is approximately 1% and cumulative incidence of POPFF between 2.1% for cemented stems and 7.7% for cementless stems at 20 years (Abdel et al., 2016b; Meek et al., 2011; Chatziagorou et al., 2018). In Australia, where THR have been predominantly performed using cementless THR, POPFF is now the most common cause of revision following THR (AOANJRR, 2019). POPFF incidence is predicted to increase over the next 30 years as a result of an ageing population (Pivec et al., 2015).

Once POPFF has occurred, a vast majority of patients require major surgery which is associated with large volume blood loss and an increased risk of post-operative mortality (Gitajn, I.L. et al., 2017). Once complete the patient must then endure a substantial risk of reoperation which is reported to be as high as 23% (Lindahl et al., 2006b). The overall mortality following POPFF approaches that of hip fracture, which affects a similar cohort of frail patients (Bhattacharyya et al., 2007; Griffiths et al., 2013b; Haughom et al., 2018).

Practical considerations may affect the likelihood of successful treatment. Successful treatments may be best performed by high volume surgeons with a subspecialist interest in hip revision surgery (Katz, Jeffrey N. et al., 2003). This may necessitate the referral and transfer of a patient to a hospital capable of providing appropriate care. In addition, evidence suggests that the delay between POPFF and surgery is associated with patient mortality following POPFF (Griffiths et al., 2013b). Specialist centres are also under increased pressure since surgical treatment for POPFF is the most costly single stage revision procedure (Vanhegan et al., 2012). These factors contribute to a uniquely intense burden on health care systems. Given the poor outcomes of treatments for POPFF and the demands placed on the healthcare providers, prevention of POPFF is perhaps the best strategy to reduce patient harm.

Many clinical studies have attempted to quantify the risk of POPFF associated with various patient, surgical, implant and other variables to identify possible targets for prevention strategies. Patient factors associated with increasing risk of POPFF include increasing age at primary THR (Thien et al., 2014; Meek et al., 2011; Watts et al., 2015; Cook et al., 2008; Berend, K.R. et al., 2016; Palan et al., 2016; Broden et al., 2015; Chatziagorou et al., 2019b), increasing American Society of Anesthesiologists grade (ASA) (Singh, J.A. et al., 2013), standardised co-morbidity scores (Singh, J.A. et al., 2013), osteoporosis (Lindberg-Larsen et al., 2017), heart disease, peptic ulcer disease (Singh, J.A. and Lewallen, 2012), non-osteoarthritis indications (Chatziagorou et al., 2019b; Lindberg-Larsen et al., 2017; Watts et al., 2015; Thien et al., 2014) and Dorr type C morphology when using predominantly cementless stems (Gromov et al., 2017). The effect of patient sex on POPFF risk is mixed and has been reported to increase with female sex (Singh, J.A. et al., 2013; Meek et al., 2011; Gromov et al., 2017; Berend, M.E. et al., 2006; Lindberg-Larsen et al., 2017) and male sex (Chatziagorou et al., 2019b; Palan et al., 2016).

Given that a majority of POPFF occur within the first year following surgery there is little scope to optimise patient co-morbidities. A more obvious target is surgical methods and implants. Direct anterior and Hardinge approaches have been associated with greater incidence of intraoperative periprosthetic femoral fracture (IOPFF) (Berend, M.E. et al., 2006; Hendel et al., 2002; Hartford et al., 2018) and anterior approach with greater incidence of POPFF (Panichkul et al., 2016; Meneghini et al., 2017). Given that IOPFF is associated with increased risk of subsequent POPFF (Abdel et al., 2016b; Watts et al., 2015; Abdel et al., 2016a) and a proportion of POPFF are due to IOPFF, a strategy to prevent POPFF should go hand in hand with a similar approach to IOPFF. IOPFF are however, a heterogeneous group and each anatomical subtype is likely to have an esoteric aetiology. Currently, it is not clear which IOPFF are most likely to lead to POPFF and thus where the efforts to prevent IOPFF should be focused.

Worldwide the use of cementless implants is increasing (Wyatt et al., 2014) due to benefits in shorter operating time and reduced incidence of aseptic loosening, particularly in younger patients (Hailer et al., 2010). Cementless stem fixation is associated with a higher risk of POPFF (Singh, J.A. et al., 2013; Abdel et al., 2016b; Thien et al., 2014; Berend, M.E. et al., 2006; Lindberg-Larsen et al., 2017) and IOPFF (Abdel et al., 2016b; Abdel et al., 2014; Nowak et al., 2012; Abdel et al., 2016a; Berry, 1999). The increased risk of IOPFF is possibly associated with the forceful rasping which is necessary to generate appropriate press-fit required for cementless stem function (Jasty et al., 1994). The mechanism linking cementless stems to POPFF is unclear. Since a majority of POPFF occur within the first six months, intraoperative injury and the press fit biomechanical environment prior to osseointegration may contribute. The risk of POPFF around cementless stems varies by stem brand (Thien et al., 2014). Brand comparison is not always useful since the design of a stem can differ significantly under the same branding. A recent systematic review using the stem design groups proposed by the Mont group (Khanuja et al., 2011) concluded that single wedge and double wedge-shaped stems are associated with a threefold increase in the risk of POPFF (Carli et al., 2017). The Mont group classification system groups stems which are broadly similar in some general design feature, but each grouping contains a constellation of specific design features. Since the underlying contribution of each design feature to risk of POPFF is unknown, analysis of clinical data based on classification systems will inevitably group stems which are not similar in POPFF risk profile and introduce unknown bias. A better approach may be to perform more in-depth modelling of the components which make up each femoral stem to establish the specific risk factors of each design feature for POPFF.

The relationship between stem design characteristics and POPFF risk has been investigated to some extent using biomechanical testing of cemented stems

(Morishima et al., 2014; Ginsel et al., 2015) and cementless stems (Jones, C. et al., 2015; Bishop et al., 2010; Jakubowitz et al., 2009a; Jakubowitz et al., 2009b; Kannan et al., 2014; Olsen et al., 2010). This approach allows corroboration of hypotheses derived from retrospective clinical data, which is an important step towards the inference of causation. Results of biomechanical studies are difficult to interpret because comparisons are made between stems where multiple design differences exist or because of heterogeneous methodology and outcomes measures. The major drawback of biomechanical testing is that the most likely mechanisms of POPFF are unknown so that the simulation method of POPFF in vitro is difficult to validate. Current research attempts to mimic fracture patterns seen in real POPFF cases with a subjective comparison of similarity (Ginsel et al., 2015; Morishima et al., 2014). Such approaches are in part due to the lack of a reproducible method to quantify fractures which occur in POPFF and compare them to those which occur in laboratory simulations.

POPFF represents an important complication of low energy injuries in older frail patients. Patients often require major surgery and are at a significantly increased risk of death and complications. The overall economic impact of POPFF treatment is considerable and the demand for such treatment is likely to grow in the future. Patient related risk factors are reasonably well understood but are largely non-modifiable owing to the early onset of POPFF following THR and the inherent nature of most known risk factors. Modification of implants and surgical technique used in THR appear to be a reasonable choice for risk reduction following THR. The available evidence on which to make modifications is poor. To advance science in this area a new approach is required to gain insight into the effect of specific implant designs on the risk of POPFF. New methods should aim to define the risk associated with implant design features using clinical data. Hypotheses regarding common POPFF mechanisms should also be developed, so that hypotheses can be corroborated with biomechanical testing, which accurately simulate common POPFF mechanisms.

1.2 Hypothesis and overarching aim of the thesis

The hypotheses explored in this thesis are:

Risk of POPFF is increased following IOPFF and the risk is dependent on the anatomical structure which is subject to IOPFF.

Risk of POPFF is dependent on the design of the cementless femoral stem used in primary THR.

This thesis describes a program of work which explores the contribution of IOPFF and cementless femoral implant design to the occurrence of POPFF in the context of patient, surgical and implant related risk factors. This thesis aims to develop evidence-based hypotheses to explain the relationship between IOPFF and POPFF and which design features of cementless femoral implants are associated with increased POPFF risk using statistical models derived from large datasets. The likely mechanisms of injury leading to POPFF will be estimated using radiographic analysis and Hypotheses will then be tested using valid biomechanical analyses.

Chapter 2 Literature review

The content of this chapter has been used in part or whole in the following publications:

King SW, **Lamb JN**, Cage ES, Pandit H. *Periprosthetic femoral fractures following total hip and total knee arthroplasty*. **Maturitas** 117:1-5, Nov 2018.

Ramavath A, Palan J, **Lamb JN**, Pandit HG, Jain S. *Postoperative periprosthetic femoral fracture around total hip replacements: current concepts and clinical outcomes.* **EFORT Open Reviews**. ISSN 2396-7544 (In Press).

2.1 Defining periprosthetic fractures of the femur

For the purposes of this review post-operative periprosthetic femoral fractures (POPFF) will be used to describe fractures of the femur which are recognised following hip replacement surgery. POPFF can take a variety of forms, some of which have no existential consequences for the patient and some with very grave consequences indeed. This chapter will focus almost entirely on POPFF which most significantly affect the health of patients with hip replacement. For clarity this review will focus on Vancouver grade B and C fractures unless there is sufficient evidence of an effect on patient's health to discuss other fractures in detail (Figure 2-1).

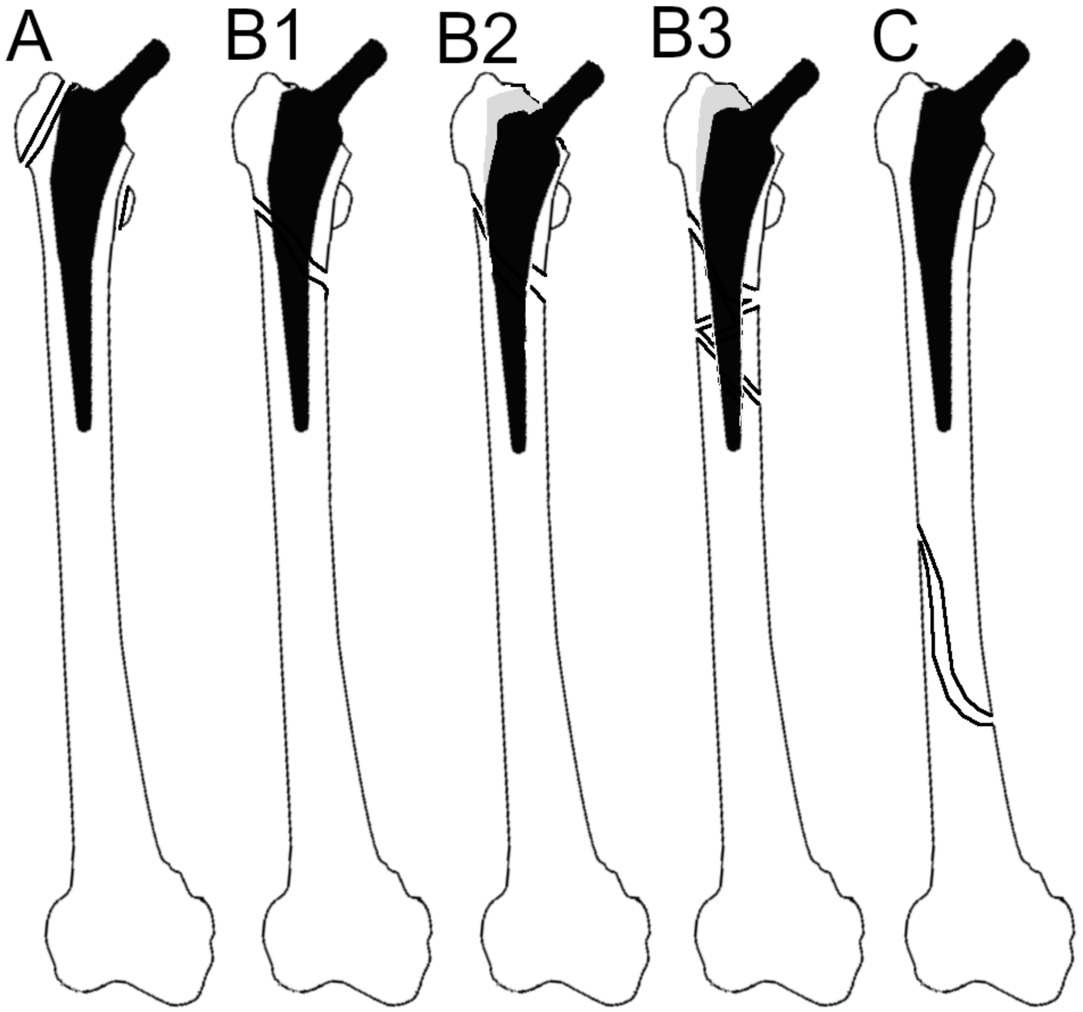


Figure 2-1 Vancouver classification system. Labels indicate Vancouver class: A is greater tuberosity or lesser tuberosity avulsion fracture, class B1 indicates fracture at level of stem with a well-fixed stem, B2 indicates fracture at level of the stem with loose stem, B3 indicates a fracture at the level of the stem with a loose stem and poor quality bone and C indicates fracture below the level of the stem.

2.2 The typical patient population

The mean age of a patient with POPFF is 74.0 to 83.0 years (Cox et al., 2016; Ehlinger et al., 2015; Katz, J. N. et al., 2014; Lindahl et al., 2005; Chatziagorou et al., 2019a; Shields et al., 2014). The majority of patients with POPFF in the literature are females (Cox et al., 2016; Katz, J. N. et al., 2014; Sarvilinna et al., 2003; Ehlinger et al., 2015; Chatziagorou et al., 2019a; Shields et al., 2014). In two retrospective studies from the United States of America (USA), 43 to 69% of patients lived in their own accommodation, 19% in retirement home and 12% in an institution (Ehlinger et al., 2015; Shields et al., 2014). In the United Kingdom (UK), 87 – 96 % of POPFF patients were reported to live in their own home (Dutton et al., 2018; Ruiz et al., 2000). Patients with POPFF had a pre-fracture Parker mobility score of three to five out of nine, which represents a severe to moderate restriction in indoor and outdoor mobility (Shields et al., 2014; Kuiper and Huiskes, 1997). This information depicts a group of patients who are commonly female, elderly and have a significant reduction in pre-injury mobility. These features are likely to reduce the capacity of patients to endure lengthy surgery, reoperation and further reductions to mobility caused by POPFF.

2.3 Incidence

Total volume of periprosthetic fractures undergoing treatment with revision under the jurisdiction of the NJR (National Joint Registry of England, Wales, Northern Ireland and the Isle of Man) is estimated to be at least 750 cases a year (National Joint Registry, 2019). The overall burden, including estimated cases treated with fixation and no surgery, is likely to reach over a thousand cases annually, using estimates from the Swedish National Arthroplasty Register (Chatziagorou et al., 2018). In the USA during the first 11 months of 2013, there were an estimated 4456 cases of POPFF (Reeves et al., 2019). The exact incidence of POPFF is difficult to establish as the reported cohorts are heterogeneous and incidence tends to increase in older frailer patients and with cementless stem use (Lindahl, 2007). In high risk patients, the incidence of POPFF has been reported to be as high as 7.4% with a cementless stem and as low as 0.9% with a cemented stem at a median of five years follow-up (Inngul and Enocson, 2015). The most accurate figures from large national registries, which include all POPFF, estimate the incidence of new POPFF between 0.7% and 3% (Meek et al., 2011; Chatziagorou et al., 2018; Gromov et al., 2017; Katz, J. N. et al., 2014; Singh, J. et al., 2016; Springer et al., 2019).

POPFF incidence is concentrated in the early post-operative period (Gromov et al., 2017; Thien et al., 2014; Broden et al., 2015) and this effect is greatest following cementless stem implantation where the risk of POPFF within the first 30 days post-operatively is ten times that of cemented stems (Abdel et al., 2016b). Late POPFF have also been reported to increase dramatically after ten years following cementless stem implantation (Peitgen et al., 2019; Abdel et al., 2016b). The cumulative probability of POPFF has been reported to increase exponentially to 13.2% at 29 years, becoming the most important long-term complication following cementless THR (Peitgen et al., 2019). Fractures in the third decade tend to occur in patients who have had their primary procedure at a young age and have the greatest risk of wear related osteolysis and loosening, which may be a predisposing factor (Peitgen et al., 2019; Berry, 2003). Simulated femoral implant loosening has been shown to reduce the resistance to fracture in biomechanical POPFF models (Harris et al., 2010).

The Swedish and New Zealand arthroplasty registries reported that the proportion of first time reoperations and revisions performed for POPFF has increased over time (Rolfson, 2017; New Zealand Orthopaedic Association, 2019). The increase in POPFF incidence in Swedish patients has been attributed to an increase in POPFF incidence in patients over 80 years old (Chatziagorou et al., 2018). Analysis of international registry data has predicted an average increase in POPFF incidence of 4.6% every decade over the next 30 years, largely because of an expected increase in older patients with THR (Pivec et al., 2015).

2.4 Aetiology

POPFF are thought to originate from intraoperative injury or new injury which occurs post-operatively. New injuries are typically caused by a fall from standing or sitting in approximately three quarters of cases (Lindahl et al., 2005; Abdel et al., 2016b; Gromov et al., 2017; Innmann et al., 2018), approximately one tenth of fractures are reported to occur spontaneously (Gromov et al., 2017; Lindahl et al., 2005) and a similar proportion as a result of major trauma (Lindahl et al., 2005). This pattern of injury is different to that experienced by native hip fracture patients where 98% of fractures occur as a result of a fall (Parkkari et al., 1999). Most hip fractures occur following sideways fall with direct impact on the hip (Parkkari et al., 1999). Given the superficial difference in aetiology between POPFF and native hip fractures it might seem that the mechanisms and vulnerabilities of the implanted proximal femur are different to that of the non-implanted femur. Indeed, a biomechanical in vitro study comparing a native femur with a femur implanted with a cemented femoral stem, demonstrated that femoral stem implantation reduces the stiffness and failure load of the femur in a medial-lateral bending configuration by up to a third (Rupprecht et al., 2015). This suggests that the presence of a femoral implant changes the mechanical properties of the native femur and suggests that mechanisms of injury for POPFF may not be like those leading to native hip fracture.

POPFF can also be caused by intraoperative injury. A recent study using routine post-operative computed tomography (CT) discovered occult IOPFF after cementless THR in 11.5% of cases (Yun et al., 2019). Fractures occurred without knowledge of the operating surgeon and without significant difference in symptoms between those with and without fracture. This observation gives clear evidence that intraoperative injuries can and do occur during uneventful hip replacement operations with cementless stems.

The mechanism for intraoperative injuries is likely to follow that of IOPFF in general, which is well documented. One of the earliest report of intraoperative fracture mechanism is from 1975, fractures were reported to occur during 'reaming the canal, seating the femoral component, or manipulating the femur' (Scott et al., 1975). An almost identical analysis comes recently from a large single centre series where IOPFF are noted to result primarily from component placement then canal preparation and trial reduction (Abdel et al., 2016b).

The aetiology of POPFF in a population is likely to be a varying combination of intraoperative injury, weakening of the femur-implant construct and new post-operative injury. It is possible that there are common risk factors for each of these aetiological origins, which would possibly simplify approaches to the prevention of POPFF overall.

2.5 Mortality and morbidity

2.5.1 Mortality in general

POPFF is associated with a large increase in mortality. In a large national USA study, in-hospital mortality was 2.6% for an average length of stay of just eight days following POPFF (Cox et al., 2016). In this sample of over 4500 cases, 70% were treated with open reduction and internal fixation (ORIF), 27% with revision surgery and the remainder treated conservatively or with implant removal only. In English studies, where the mean length of stay was 34.9 days (range 4–136), in patient mortality was 11% (Johnson-Lynn et al., 2016). The trend continues over longer follow up periods with 30 days mortality estimated at 2.7% in another large American database study of over 500 POPFFs. Estimated mortality was 14% at three months and 18% at one year from a large American geriatric fracture registry study (Shields et al., 2014). Causes of death included: respiratory failure, sepsis, unclear, pulmonary embolism, and cancer. Deaths between three and 12 months were caused by cancer, congestive heart failure and coronary artery disease. Other studies have reported one year mortality between 11 and 23% (Bhattacharyya et al., 2007; Lyons et al., 2018; Mardian et al., 2017; Gitajn, I.L. et al., 2017; Sayegh et al., 2011). A large retrospective German report estimated mean life expectancy for patients following POPFF is just 71 months (95% confidence interval [CI] 62 to 79).

2.5.2 Mortality comparisons

To put this mortality into context, Griffiths and colleagues estimated that the mortality of patients with POPFF was eight fold greater than for patients undergoing aseptic THR revision cases at six months (7.3% versus 0.9%) (Griffiths et al., 2013a). This might suggest that significant differences exist between patients with POPFF and other elective revision causes. It is reasonable to equate the population of patients with POPFF to those with native hip fracture since both patient groups tend to be older on average and have a propensity to fall and fracture. Patients with POPFF have a co-morbidity profile which is reported to be significantly better than that of patients with fractured neck of femur (Bhattacharyya et al., 2007; Boylan et al., 2018). However, after adjustment for the comparative difference in comorbidities, there is no significant difference in the risk of dying between the two groups at 30 days and at one year (Boylan et al., 2018). An American study found that patient with POPFF experienced a longer delay until theatre in comparison to patients with native hip fractures, which is likely to be due to the added requirement of subspecialist surgeons and specialist equipment (Boylan et al., 2018). POPFF surgery takes longer than native hip fracture surgery and following surgery there are greater major and minor complications, rate of return to theatre and requirement for blood transfusion (Haughom et al., 2018).

2.5.3 Mortality risk factors

Increased risk of dying may arise from risk related to the patient, the injury and the surgery. 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 risk of dying increased dramatically at 14 days after POPFF and returned to a level slightly higher than that of a comparable patient without fracture (Lindahl et al., 2007). 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 risk of dying following treatment for POPFF (Gitajn, I.L. et al., 2017; Boylan et al., 2018). Likewise, age greater than 85 years old at the time of POPFF is associated with a nine fold increase in risk of dying at one year and dependent functional status are associated with a fivefold increased risk of dying at one year (Haughom et al., 2018). 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 (Mardian et al., 2017). Larger well controlled prospective studies are required to investigate the effect of surgical delay and risk factors on patient outcomes following POPFF.

Delay to surgery beyond 48 hours has been shown to increase the risk of dying following native hip fracture (Klestil et al., 2018). A similar relationship could be expected with patient awaiting surgery for POPFF, however the results are mixed. A delay of between two and three days has been associated with an increase in mortality, complications and a poor outcome (Bhattacharyya et al., 2007; Griffiths et al., 2013a). Other similar studies have failed to show any relationship between delay to surgery and outcomes (Gitajn, I.L. et al., 2017; Johnson-Lynn et al., 2016; Boylan et al., 2018). Most of the current evidence regarding delay to theatre and mortality originates from the USA, where the delay to theatre may be just one to two days. Findings may be quite different when comparing the outcomes of patients who may be waiting greater than three to four days for surgery in the National Health Service (NHS) (Johnson-Lynn et al., 2016). In addition, investigating delay to theatre and the associated morbidity is prone to confounding because patients who are less fit for theatre may require delay for optimisation prior to surgery. This would have the effect of artificially increasing mortality in patients whose surgery appears to be delayed.

The relative morbidity and outcomes for treatment approaches has been the subject of much interest. Gitajn *et al*. conducted a retrospective comparison of treatment and outcomes between POPFF treated by revision THR or fixation. There was a longer delay to surgery (4.0 vs. 2.3 days), larger estimated blood loss (1236 vs. 627 cc), and more red blood cells transfused (5.1 vs. 3.0 units) for those treated with revision. There was a small non-significant patient survival benefit for those treated with revision at one and five years post POPFF. In a similar comparison using a large database from the USA, Reeves and colleagues found a much lower 90-day mortality rate associated with fixation versus revision treatments for POPFF (2.3% versus 4.3%). A clinical retrospective study from Marseille, France, also found a patient survival advantage at a mean of 3.5 years in patients treated with fixation versus revision (88.6% surviving versus 51.1%). The authors noted that there was no difference in complications and that nine of the 12 deaths in the fixation group were related to ‘decubitus complications’ (Cohen et al., 2018). Like much traditional clinical practice, the standard rehabilitation advice for patients undergoing fixation was partial weight-bearing for three months post-operatively. Boylan and colleagues compared treatment methods with adjustment for covariates including age, sex, ethnicity, co-morbidity score and delay to operation and found lower mortality for fixation at 30 days and six months post-operatively but no long-lasting benefit at one year post-operatively. On the surface these results appear to be more robust and it would also make sense that a well-adjusted study would find only a short-term change in mortality associated with a short-term exposure. It is difficult to understand the true effect of surgery since the patients are not randomly assigned to treatment groups and so the group allocation is prone to bias, which is likely to prevent a fair comparison between groups. The results of these studies are also difficult to extrapolate to modern practice where patients are more likely to undergo fixation with modern locking plates which can allow immediate full weight bearing and perhaps reduce ‘decubitus complications’ to some extent.

Investigators have also tried to control for the confounding effect of fracture type on by comparing outcomes of within and between different fracture subtypes. Griffiths and colleagues found no difference in mortality between different treatments for Vancouver B type fractures and between Vancouver B type and C type fractures (Griffiths et al., 2013a). Others have found greater mortality associated with Vancouver B type fractures (Bhattacharyya et al., 2007). Within this subgroup mortality was doubled for patients undergoing fixation rather than revision after adjustment for available covariates.

One area which is not well reported is the effect of conservative management. Conservative management may be implemented in two broad situations: when the fractured femur is deemed to be stable enough without operative intervention to allow conservative management or when the patient is not thought to be fit enough for surgical intervention. Lee *et al* reported a case series of 19 patients with conservatively managed minimally displaced Vancouver grade B periprosthetic fractures around cementless femoral stems (Lee et al., 2017). Authors defined minimal displacement as less than 5 mm on plain radiographs. 17 of the 19 cases healed between two and six months after fracture. All patients received Teriparatide injections during the course of conservative management. Of the 19 cases, 11 were Vancouver grade B1 and seven were B2. Two patients were noted to have stem subsidence on plan radiographs and underwent surgery. Lee *et al.* also reported that none of the conservatively managed stems showed signs of radiographic loosening up to a mean follow-up of 26 months (range 12 to 74 months). However, mobility changed by between one and two grades on the Koval mobility score (Koval and Zuckerman, 1994). Other small case series have reported successful non operative treatment with a stable implants (Toth et al., 2017; van der Wal et al., 2005). Whilst this evidence is far from robust, it suggests that minimally displaced fractures which occur in the absence of stem subsidence may be managed conservatively. However, careful regular clinical and radiographic follow up is necessary to identify cases where the stem becomes unstable and operative intervention in required. Conservative management of patients unfit for surgery is an under-reported topic. A Chinese study reported a single centre retrospective series which estimated the mortality associated with conservatively managed POPFF to be as high as 36.4% at one year (Zheng et al., 2020). There is a large confounding affect since patients deemed unfit for surgery were allocated non-operative treatment. Given what is known about the risk of dying associated with failure to treat neck of femur fracture, it is unlikely that conservative management of POPFF will give a satisfactory result.

2.5.4 Morbidity

The outcomes following treatment for POPFF are poor and are worse than outcomes following other THR revision indications. Young and colleagues compared the outcomes of 232 patients who underwent POPFF revision versus revision for femoral component loosening in an observational cohort from the New Zealand Joint Registry and found a higher rate of re-revision in the POPFF group versus revision for loosening of the femoral component (7.3 vs. 2.6%) (Young et al., 2008). The most common cause of re-revision in the POPFF group was dislocation (7 patients), followed by re-fracture (3), loosening of the acetabulum (2) or stem (2), infection, implant failure, and pain (1 each). Oxford hip score (OHS) at six months was worse in patients revised for POPFF versus controls (29 versus 24 points). Unfortunately, the response rate for OHS was poor, complete data for POPFF was 57% and controls was 76%. The results represent an interesting insight, which is supported by subjective clinical experience given the poor outcomes reported in non-comparative cohort studies.

Griffiths and colleagues reported complication rates following POPFF surgery at 30 days between 45% and 63% (Griffiths et al., 2013b; Haughom et al., 2018). 13% to 14% of these were reported as major complications. Young and colleagues reported that all mortality was associated with a major complication. Interestingly, the authors reported blood transfusion as a minor complication of surgery, which accounts for a large proportion of the reported minor complications at 30 days. Haughom et al reported a return to theatre rate within 30 days of 7.8% (Haughom et al., 2018).

Over a longer follow-up mean period of 45 months Mardian and colleagues reported similarly poor outcomes for a German cohort of 118 patients (Mardian et al., 2015). Complications occurred in 25.4% of patients but were only recorded if related specifically to the implanted hip replacement. 13.4% of patients experienced infection, 9% hardware failure, 1.5% non-union and re-fracture was reported in 1.5%. Overall complication rates were higher than those reported in a similar North- American cohort (13% reoperation at 38 months mean follow-up) (Gitajn, I.L. et al., 2017). Although observational in nature and thus unable to offer conclusive evidence, neither study found a difference in complication rates between patients treated with revision or fixation surgery.

Quality of life and outcome reports in POPFF cohorts are rare but demonstrate poorer outcomes in patients with POPFF. Mardian et al reported worse pain and lower physical function than a normal German cohort (Mardian et al., 2015). Almost half of patients needed a walking aid following surgery and a quarter could not mobilise even with assistance. A fall in mobility following POPFF surgery was also reported from a French Cohort study, where the Parker mobility score fell by over two points at one year post-operatively (Cohen et al., 2018). 41% of these patients also reported home adaptations were required to maintain mobility around the house. Harris hip score assessment demonstrated 18% of patients had excellent outcome, 15% good, 25% fair and 42% poor outcome. Neither quality of life, mobility nor Harris Hip scores were significantly different by fracture type or by mode of treatment. These results are a valuable insight into a vulnerable patient group and demonstrate generally poor function for a large proportion of patients undergoing POPFF surgery. However, results from observational studies like these must be interpreted with caution since there is no control or adjustment for confounding factors.

2.6 Health economics

A reasonable view on the scale of the problem posed by POPFF can be gained through an appreciation of the costs associated with POPFF treatment incurred by hospitals and healthcare providers. To allow comparison between studies, costs are estimated to the nearest whole single denomination at prices for December 2019 using inflation estimates supplied by national banking and statistics bureaus (Bank of England, 2020; statistics).

Estimates of the cost of IOPFF are sparse. The only published estimates of IOPFF costs are from a study of national health claims data in the USA collected between 2010 and 2016. The cost of patients with IOPFF were estimated and compared to a group of non IOPFF patients using a mixed matching method. The study found that the 90-day costs were significantly greater for patients with IOPFF than those without ($36,809.53 versus $25,949.05). The increase in costs was greater still at one year ($45,889.07 versus $32,527.68). Greater costs were a product of greater service use in and out of hospital in almost every domain apart from hospice use and outpatient clinic appointments (Chitnis et al., 2019).

Costs for POPFF are typically greater than the additional cost of IOPFF over and above the cost of primary surgery. In an NHS study from 1999 to 2009 in a large single centre over 80% of POPFF costs come from the cost associated with hospital stay and bed usage, Theatre costs made up 6%, implants and investigations 7%. The mean length of stay was 39 days and cost of hospital treatment ranged from £925 to £335,486 with a median cost of £27,892 (Phillips, J.R. et al., 2013). In a later study from two large NHS centres between 2006 to 2014, the mean length of stay was 43 days with an associated mean inpatient cost of £42,396 (Jones, A.R. et al., 2016). In another NHS study from a large single centre, which compared inpatient costs of revision procedures, POPFF revision was the most expensive single stage procedure (Vanhegan et al., 2012). To put these costs into context, POPFF treatment is between three and ten-times more expensive than inpatient treatment for acute myocardial infarction (£3,291), Stroke (£5,242) and Coronary artery bypass surgery (£13,370) (Gaughan et al., 2012). Evidence from the NHS would suggest that the cost of POPFF is large and that there is a large variation in the cost of treating POPFF across the NHS, which may well be a function of variation in length of inpatient stay.

In the USA, POPFF may account for 1.5% of unplanned emergency department visits within 30 days of having undergone THR, and 5% of resulting admissions (Saleh et al., 2019). Beyond 30 days, POPFF may account for a sixth of all unplanned emergency department visits following THR and half of all reoperations following THR (Luzzi et al., 2018). Inpatient costs of POPFF are estimated by large single centre studies to be between $29,225 to $42,730 (Luzzi et al., 2018; Hevesi et al., 2019) and by large national hospital costs dataset at $115,162 (Cox et al., 2016) with a mean length of stay of just eight days. 90-day costs in the USA have been estimated between $60,066 and $64,348 (Phillips, J.L.H. et al., 2019; Chitnis et al., 2019) and 365 days costs have been estimated at $73 335 (Chitnis et al., 2019). Costs for POPFF patients were almost triple the costs for a well-matched THR cohort without POPFF at both 90 and 365 days (Chitnis et al., 2019). Hospitalisation costs for revision THR for POPFF were 33% to 48% higher than for all other aseptic revision THRs (Hevesi et al., 2019). The length of stay for patients with POPFF in the USA appears to be far shorter than in the NHS. It could therefore be assumed that in the USA, a large proportion of costs appear to be related to non-hospital stay costs.

Cost is reported to vary by treatment methods in the NHS. Non-operative management is reported to cost a mean of £26 189 (Phillips, J.R. et al., 2011) while the cost of revision surgery is reported to be between £41 876 (Phillips, J.R. et al., 2011) and £35 739 (Phillips, J.R. et al., 2011). ORIF alone is reported to cost between £33 357 (Jones, A.R. et al., 2016) and £37 361 (Phillips, J.R. et al., 2011). A study from the USA also found that ORIF cost less than revision surgery as a treatment for POPFF (Shields et al., 2014). In a single centre study from Ireland, POPFF cases which were treated with revision had the longest length of stay and were most expensive in comparison to other treatment methods for POPFF (Lyons et al., 2018). An NHS study reported that Vancouver ‘C’ fractures had the largest in hospital costs at £45 163, despite the most common treatment being for this class of fractures being ORIF, which is likely to be the least expensive mode of treatment (Jones, A.R. et al., 2016). This may well be because Vancouver C fractures occur more frequently in an older patient population (Chatziagorou et al., 2018), who may have greater health needs and longer hospitals stays. These reports are difficult to interpret since there is a large confounding effect of patient co-morbidities, treatment and rehabilitation restrictions. Further studies using matching or other methods may provide further useful answers which may help to unpick the true cost of treatment approaches to POPFF.

A crude estimate of the total annual cost of POPFF inpatient care in the NHS can be estimated from the product of average cost and estimated incidence per year. A sensible estimate of total POPFF cases occurring in the UK based on total annual revision burden reported in the NJR (~700 pa) might be 1000 cases (National Joint Registry, 2019). Using a mean weighted by cases numbers from two NHS studies reporting average inpatient costs (Phillips, J.R. et al., 2013; Jones, A.R. et al., 2016) gives an estimate of inpatient of cost of £33 423 per patient. The resulting estimate for total inpatient costs for POPFF annually in the UK based on 1000 annual cases is £33.4 million. This estimate is limited by a small and possibly outdated POPFF study population and an uncertain real POPFF incidence in the UK. The real costs, including social care and rehabilitation, are likely to be far higher.

To put total costs into perspective one can compare costs to those occurring as a result of hospital admissions for acute myocardial infarction. In the UK, 446 744 hospital episodes with a diagnosis of acute myocardial infarction in the NHS (Asaria et al., 2017) at a cost of £3 291 per episode (Gaughan et al., 2012) gives a total cost of £1.47 billion, which is approximately 44 times the total cost of POPFF treatment in the UK. Prevention in this group is potentially costly since the population at risk is large. Since

POPFF occurs in a much smaller group of patients, who can be identified by the presence of THR and other risk factors, large cost savings through targeted prevention measures are possible.

2.7 Morbidity, Mortality and health economics conclusions

The overall picture of mortality associated with POPFF is dire, with a significantly increased risk of dying for most patients. The overall impression from the current evidence on mortality risk factors is that POPFF and POPFF treatment is associated with a very large physiological stress which is likely to increase the risk of death, particularly in those with the least capacity to cope with such demands. Analysis of evidence relating to risk factors indicates that the risk of dying after POPFF may be amenable to reduction by patient and pathway optimisation, much like the approach undertaken for neck of femur fractures in the UK. The current evidence suggests that the outcomes following POPFF treatment are not predictable and often involve significant reductions in patient mobility, function, quality of life and an increase in the likelihood of further complications and major surgery.

The costs associated with POPFF are large and most costs in the NHS are associated with prolonged length of stay. There is limited recent evidence to document current trends in patient length of stay when using modern approaches which may allow early weight bearing and mobilisation. Future work should aim to describe the current state of practice within the NHS with a view to identifying areas where cost savings may be most achievable.

Given the poor and unreliable outcomes following POPFF and the large associated cost there is a need to look closely at factors which may be adjusted to prevent the occurrence of POPFF in the first instance. A detailed analysis of risk factors associated with POPFF is necessary to understand where the focus of future work should be placed for maximum likely patient benefit. Further evidence relating to the best treatment methods and patient pathways is required to reduce the risk of harm to those patients in whom prevention is not possible or fails.

2.8 Risk factors for periprosthetic fracture of the femur

2.8.1 Patient risk factors

The impact of age has been widely studied and the majority of evidence suggests that the risk of POPFF increases with increasing age at primary THR (Thien et al., 2014; Meek et al., 2011; Watts et al., 2015; Cook et al., 2008; Berend, K.R. et al., 2016; Palan et al., 2016; Broden et al., 2015; Chatziagorou et al., 2019b), however this effect has not always been demonstrated (Katz, J. N. et al., 2014; Gromov et al., 2017), particularly when accounting for other confounding factors (Singh, J.A. et al., 2013). The effect of ageing on POPFF appears to affect both men and women (Wangen et al., 2017). It has been noted in a large registry study that the risk of POPFF increases more rapidly with increasing age in women than in men (Thien et al., 2014; Berend, M.E. et al., 2006), which may in part be attributable to menopause related osteopenia (Osterhoff et al., 2016). Age and gender are also closely related to femoral morphology with older patients, females and patients with low body mass more likely to have a 'stove pipe' shaped femur with thinner diaphyseal cortices (Dorr C morphology, Figure 2-2) (Dorr et al., 1993). Morphological changes to the femur may have a direct effect on the strength of the femur and explain much of the 'ageing' and 'gender' effects. Age related increase in POPFF risk in both men and women has also been seen in populations which have undergone THR using both cementless and cemented stems (Thien et al., 2014). Age related effects may also be the result of increased risk of falls in older patients undergoing lower limb joint replacement (Lo et al., 2019). Age is a useful surrogate for a multitude of physiological measures which have a strong association with risk of POPFF, it is likely that age could be used as a useful tool to identify patients with the greatest risk of POPFF, particularly when detailed information regarding falls risk and femoral morphology are not available.

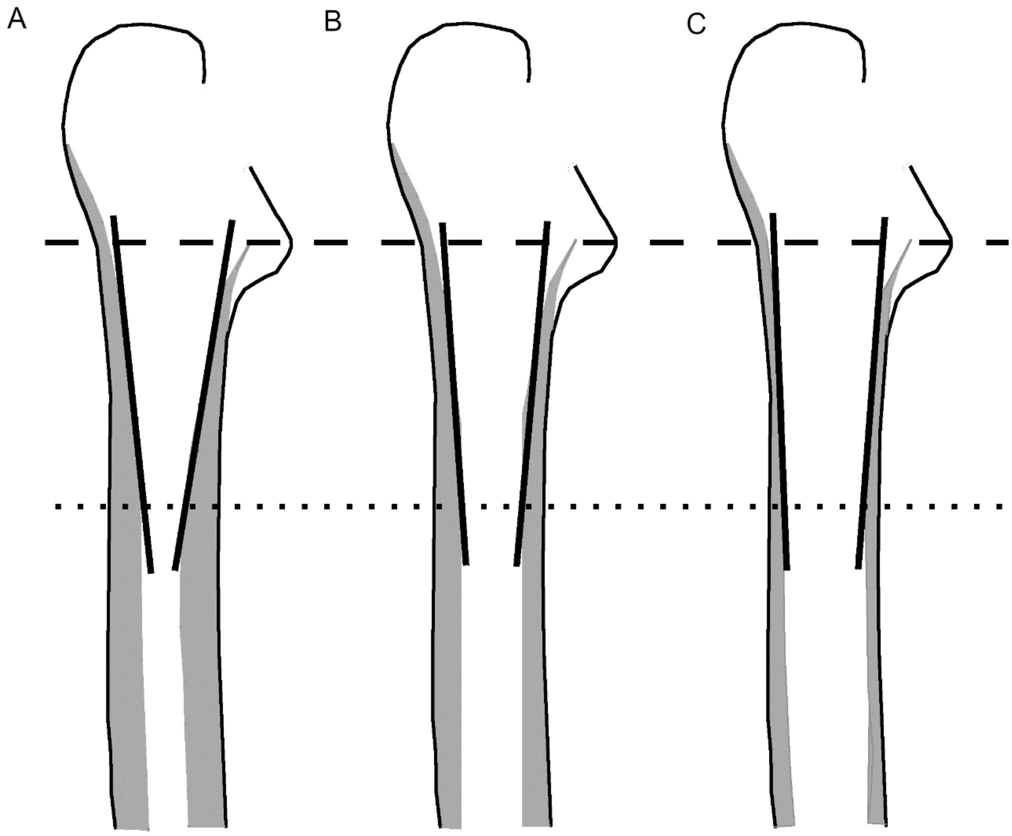


Figure 2-2 Femoral morphology classifications according to Dorr (Dorr et al., 1993). Lettering indicates Door classification grade.

The relationship between patient sex and POPFF risk appears mixed with studies showing greater risk in women (Singh, J.A. et al., 2013; Meek et al., 2011; Gromov et al., 2017; Berend, M.E. et al., 2006; Lindberg-Larsen et al., 2017), greater risk for men (Chatziagorou et al., 2019b; Palan et al., 2016) and no effect of sex (Watts et al., 2015; Broden et al., 2015; Katz, J. N. et al., 2014; Cook et al., 2008; Sarvilinna et al., 2003). A meta-analysis of comparative cohort studies reporting POPFF found a higher incidence of POPFF in women than men (0.25% versus 0.18%) (Deng, Y. et al., 2019). The reason for this mixed picture is likely to be down to the cohort heterogeneity since there appears to be a confounding effect of stem fixation. Men may be at higher risk of POPFF with cemented stems and women at higher risk with cementless stems (Thien et al., 2014). It may be that for a POPFF to occur around a cemented stem the stem must first break the cement, which may be a body weight dependent phenomenon and thus occur more readily in male THR patients. Early POPFF risk in men may also be partly affected by an increased risk of falling during an inpatient stay in male patients, which has been demonstrated by a recent meta-analysis (Lo et al., 2019).

Comorbidity in general and a range of specific medical comorbidities have been associated with a change in POPFF risk. Increasing ASA has been associated with increased POPFF incidence (Singh, J.A. et al., 2013) but the relationship is not consistent (Palan et al., 2016; Broden et al., 2015). Standardised co-morbidity scores have been associated with POPFF risk (Singh, J.A. et al., 2013) with increased risk associated specifically with osteoporosis (Lindberg-Larsen et al., 2017), heart disease and peptic ulcer disease (Singh, J.A. and Lewallen, 2012). Body mass index (BMI) has not been shown to be a useful predictor of POPFF risk (Singh, J.A. et al., 2013; Watts et al., 2015; Gromov et al., 2017; Berend, K.R. et al., 2016). The reason for increased risk of POPFF in patients with greater co-morbidity grading is likely to be multi-modal. A recent systematic review and meta-analysis found that patients with electrolyte or fluid imbalances, coagulopathy and surgery related complications are more likely to fall in the post-operative period (Lo et al., 2019). Indications for surgery other than osteoarthritis are associated with an increase in POPFF risk (Chatziagorou et al., 2019b; Lindberg-Larsen et al., 2017) with the greatest risk associated with avascular necrosis of the hip and femoral neck fracture (Watts et al., 2015; Thien et al., 2014). A meta-analysis of cohort studies demonstrated that a history of total knee replacement may increase the odds of falls in the early post-operative period by a factor of six (Lo et al., 2019). Such studies lack adjustment for other confounders and should be interpreted with caution. In addition, one might expect that increasing co-morbidities are associated with a reduction in mobility and some theoretical increase in disuse osteopenia, which may increase the risk of POPFF.

Bone morphology has not been consistently associated with POPFF risk through direct standardised measures although Dorr type C morphology has been associated with an increased risk of POPFF when using predominantly cementless stems (Gromov et al., 2017). Bigart et al. compared preoperative radiographic measurements between Vancouver B2 POPFF cases and controls matched for stem design, gender, age, and body mass index (Bigart et al.). POPFF cases had a small but statistically significantly reduced native neck shaft angle (3.2 degrees mean difference), a less conical type femur (canal calcar ratio, canal flare index) and thinner diaphyseal cortices but a similar diameter (canal bone ratio). Similar results were reported from a smaller matched cohort study of six POPFFs (Cooper and Rodriguez, 2010).

Canal calcar ratio and flare index both describe the size of diaphysis relative to the metaphysis on the anteroposterior (AP) view. In Bigart et al.'s study, where the external measurements of the metaphysis and diaphysis did not differ, the ratios serve to estimate a derivative of the relative endosteal thickness of the diaphysis and to a lesser extent, the metaphysis. The basic principles governing tube parameters and strength may be understood in part through a mechanical example of a simple tube. In a hollow tube with a fixed diameter and constant length, stiffness in torsion is equal to the product of G (torsional modulus) and J (polar moment of inertia). G is a constant related to the mechanical properties of the material from which the tube is constructed, and J is proportional to the difference between the external and internal wall diameter. Decreasing wall thickness by a factor of k, will also decrease rigidity and strength by a factor of k. However, if the diameter increases by k and wall thickness does not change, the rigidity increases by a factor of k^3 and strength increases by k^2. This over simplified model of course does not account for a host of real-life constraints including a change in properties of bone with ageing and the application of forces through both external muscle structures and an internal implant. It can be seen in principle that a decrease in femoral wall thickness may proportionally decrease the rigidity and strength of the femur and lead to a reduction in the force required to fracture.

Bigart's results suggest that cases with POPFF had a more varus neck and Dorr C morphology. It is possible that the authors found that the femur of patients with POPFF tended to have an 'older' physiological appearance, independent of patient age, which suggests that a main effect of ageing on POPFF risk is a change in femoral morphology. Interestingly, the preoperative radiographic measures of canal calcar ratio are all well within the Dorr A category from Dorr et al.'s original paper (Dorr et al., 1993) and represent quite a small difference in morphology. The authors did not estimate the increased absolute or relative risk of fracture based on these findings, which unfortunately makes the measured radiographic differences hard to interpret clinically. The study did not show any differences in post-operative radiographic measurements (canal fill and stem position), however a result in this regard is difficult to interpret given that different implants have been used. It would appear that risk of POPFF following cementless stem implantation may be associated with femurs which have a less conical shape, thinner diaphyseal femoral cortex relative to diameter and more varus femoral necks.

Patient ethnicity has not been shown to be associated with risk of POPFF specifically, although, a meta-analysis of risk factors for falls in patients undergoing lower limb joint replacement identified an increased risk of inpatient falls in Black and Hispanic patients (Lo et al., 2019). Further in-depth study of the relationship between ethnicity and POPFF risk is needed to ascertain whether ethnicity can be used to focus future preventative strategies

2.8.2 Surgical risk factors

Surgical approach has not been shown to have a consistent effect on the risk of POPFF (Broden et al., 2015; Chatziagorou et al., 2019b; Berend, M.E. et al., 2006). It is likely that there is confounding with stem design and other factors particularly when comparing techniques over large time scales.

IOPFF has been shown to increase the risk of subsequent POPFF event (Abdel et al., 2016b; Watts et al., 2015), which may be because of common risk factors like female sex, increasing age, poor bone quality and cementless stem fixation (Berend, M.E. et al., 2006; Hendel et al., 2002; Hartford et al., 2018; Abdel et al., 2016b; Nowak et al., 2012; Ricioli et al., 2015; Miettinen et al., 2016; Davidson et al., 2008). In addition, POPFF are commonly thought to result from unknown or known intraoperative injury. Although, 11% of patients may suffer from occult IOPFF without noticeable change in clinical picture (Yun et al., 2019), The link between intraoperative and postoperative POPFF is not well defined.

Stem alignment has not been shown to affect the incidence of POPFF (Gromov et al., 2017). It would seem logical that an increase in varus alignment of the stem might increase the stem offset and thus the effective moment arm through which the body weight may impart forces on the femur necessary to fracture. As an example, if we take a hypothetical stem of length 150mm from shoulder to tip and assume varus malalignment occurs about the centre of the stem length, we can calculate the approximate increase in perpendicular offset from the femoral axis by the product of tan (*varus angle*) and half the stem length. For a varus angle of five degrees the increase in offset is 6.6mm and for 10 degrees the increase is 13.2mm. This may have the effect of significantly increasing the offset by 16% and 33% respectively based on a well aligned stem offset of 40mm. This might have the effect of proportionally increasing rotational and bending moments acting on the proximal femur if all other factors are held constant.

The precise measurement of alignment can be difficult in practice however, and no well controlled trials have been completed either clinically or experimentally to investigate this.

Implant under-sizing in the proximal femur has been associated with an increased risk of POPFF with polished tapered cemented stems in both clinical (Mints et al., 2018) and biomechanical studies using composite femurs in axial loading simulations (Ginsel et al., 2015). Smaller body stems may offer less rotational stability of a stem during POPFF, which may lead to a mismatch of the proximal femur's anteroposterior diameter and the stem's medial-lateral dimensions, leading to an increase in cortical strains and femoral fracture. A similar pattern is possible with a cementless stem, but recent evidence has shown no difference in canal fill parameters between matched cohorts with and without POPFF (Bigart et al.). No experimental testing has been published to test this hypothesis in cementless stems.

Femoral neck resection has been thought to influence rotational stability as early as 1986, with a call to end extensive neck resection by the late Mr Michael Freeman (Freeman, 1986). Improved rotational stability was subsequently demonstrated using small scale cadaveric biomechanical models (Tanner et al., 1988; Carlson et al., 1988; Whiteside et al., 1995). It is likely that neck resection plays an important role in the risk of POPFF, potentially as a protection against torsional type POPFF. It is important that neck cut be controlled in cadaveric studies for this reason. Freeman points out that in clinical practice the risk of rotational instability must be carefully balanced against the risk of impingement related stiffness and instability, which is perhaps why this approach has not received much attention.

Revision surgery is associated with an increased risk of POPFF (Deng, Y. et al., 2019). This may be because of the differences in patient characteristics in people undergoing revision THR surgery versus primary THR surgery, implant design and usage, bone morphology and quality, mobility and risk of falling (Lo et al., 2019).

2.8.3 Implant related risk factors

2.8.3.1 Stem risk factors

Cementless stem fixation is associated with a higher risk of POPFF (Singh, J.A. et al., 2013; Abdel et al., 2016b; Thien et al., 2014; Berend, M.E. et al., 2006; Lindberg-Larsen et al., 2017). The mechanism is unclear but since a majority of cementless stem fractures occur within the first six months, intraoperative injury and the press fit stem environment may contribute. POPFF is likely to occur when the cortical strain exceeds the fracture strain of the implanted femur. Cortical strains are developed during cementless stem implantation as a function of forceful preparation and implantation of the proximal femur necessary to generate primary stability. However, adequate primary stability to allow osseointegration of the femoral stem is a careful balance between development of interference fit at the stem-implant interface and preventing excessive cortical strains which may precipitate IOPFF or POPFF in the early post-operative period (Abdul-Kadir et al., 2008). Following implantation, the proximal femoral cortical strains may be easily exceeded during a stumble, trip or fall and precipitate a POPFF. Design features which reduce the chance of high cortical strains are likely to be protective.

Analysis of the contribution of implant design on POPFF risk using clinical data is rare. Cementless stem design appears to have a large effect, with greatest risk posed by blade-type stems (Carli et al., 2017) and those with an exaggerated proximal taper (Watts et al., 2015). Current approaches to analysis of implant related risk factors using clinical data appear to either compare risk of fracture between different stem brands (Van Eynde et al., 2010; Thien et al., 2014; Christensen et al., 2019) and or between different overall stem design classifications (Carli et al., 2017). Comparison based on stem design is flawed since the design of cementless stems can differ significantly under the same brand name, such as presence or absence of a collar, or the surface coating, which can reduce the precision of any subsequent assessment. Comparison of femoral implants on the basis of implant design classification system (as proposed by the Mont group (Khanuja et al., 2011)) can also introduce bias since there is no strict adherence to design groupings by manufacturers and thus each group is poorly defined and lacks precision. In addition, groupings created in North America may not be easily applicable to implants used in the UK and beyond. A more robust approach would be to make valid comparisons between groups where only the variable of choice differs. Unfortunately, such an approach is rare in orthopaedic clinical research owing much to cost and impracticality. Orthopaedic research is largely based on retrospective case series, where control over confounding factors is limited. Another approach is to control for confounding factors through statistical adjustment. Such an approach is analogous to identifying key features of a person which can be measured (i.e. height, weight, eye colour etc.) and assessing statistical relationships with health outcomes, which is commonplace in epidemiological research. Such an approach might estimate the risk associated with each individual stem design feature (surface finish, stem shape etc.), whilst attempting to control for other known factors. This approach might give engineers and surgeons the ability to analyse the relationship between implant design and clinical outcomes with greater precision.

The link between specific cementless implant design features and POPFF risk has been more frequently investigated using biomechanical testing methods rather than larger clinical studies. Stem length has been investigated and a mixture of hypotheses have been developed (Bishop et al., 2010; Jones, C. et al., 2015; Jakubowitz et al., 2009b). A study evaluating the Silent hip (DePuy, Warsaw, IN, USA) demonstrated that decreasing implant size was associated with an increase in peak cortical strains and a decreasing fracture load in an axial loading experimental model (Bishop et al., 2010). The Silent hip is a ‘stemless’ metaphyseal stem. Shortening and size reduction of the metaphyseal implant are likely to have very different effects to shortening the femoral stem in a traditional femoral implant. In a separate study the Mayo hip (Zimmer, Warsaw, IN, USA) was compared to the CLS Sportorno stem (Zimmer, Warsaw, IN, USA) using a quasi-static loading method akin to walking loads. The shorter, Mayo, stem was not associated with a higher risk of POPFF. The effect of stem length is difficult to interpret in this setting since there are multiple differences in design variables between the compared stems which are not controlled for. In addition, the quasi-static loading regimen is not representative of a fall where the rate of loading may be much larger. Bone is viscoelastic and the mechanical properties may change under different loading conditions and thus, quasi static loading may not be representative (Jakubowitz and Seeger, 2015). A more realistic loading rate was used to compare standard length hydroxyapatite coated Furlong stems (Joint Replacement Industries, Sheffield, UK) to a shorter Furlong Evolution stems (Joint Replacement Industries, Sheffield, UK) in a composite bone model with torsional loading (Jones, C. et al., 2015). The authors found that the fracture torque and angular displacement was greater in the shorter stem and concluded that the reduced torsional stiffness was protective around shorter stems in torsional fractures. Whilst the implants are broadly similar in design apart from stem length, there are important differences in stem shape and collar shape which may also make direct comparison difficult. Additionally, it is unlikely that a purely rotational loading pattern is representative of a majority of POPFF occurring in vivo.

The effect of a calcar collar on primary stability has been investigated (Demey et al., 2011; Whiteside et al., 1988). A collared Corail stem (DePuy, Warsaw IN, USA) was compared to an otherwise identical collared version using separate quasi-static axial and torsional loading regimens by the Artro group in France. The implications for POPFF may be seen indirectly since the fresh frozen femoral specimens were loaded until fracture. Collared stems had greater stability and a higher fracture force in both axial and rotational loading scenarios. This is in line with older studies which investigated the effect of a collar when they were more a more popular feature on femoral stems (Whiteside et al., 1988; Markolf et al., 1980). It is likely that a medial calcar collar can prevent axial and rotational displacement leading to fracture around a pre-osseointegrated cementless stem model. These findings are supported by data analysis of large-scale data recorded in the NJR. An unpublished white paper reveals a larger proportion of Corail collarless stems revised for POPFF versus Corail collared stems (Mantel and Leopold, 2017) although the analysis relies on raw data comparison and lacks adjustment for potential confounding factors. Despite the short comings of biomechanical testing and the lack of detail in the analysis of clinical data, this evidence highlights an important design feature which merits further analysis.

Proximal femoral cortical stress can be changed by altering stem surface coating and coating distribution. Surface coating may only affect the transfer of loads which are primarily transferred by shear stresses at the implant-bone interface, which may make surface coating more important in the modulation of axial rather than bending forces (Keaveny, Tony M., 1994). Fully coated cementless stems versus proximally coated stems may result in more femoral cortical strain concentrated around the stem tip during axial loading (Skinner et al., 1994; Keaveny, Tony M., 1994; Gillies et al., 2002). Other investigators proposed a protection against POPFF when stems had a thicker, high-friction proximal surface coating versus a grit-blasted surface finish under axial loading conditions (Miles et al., 2015). It might seem fair to assume that a higher friction surface might induce greater interference fit and stability within the proximal femur and thus limit the ‘log splitting’ action by the femoral stem. However, Implants which generate high circumferential strains in the stiff proximal femoral metaphysis may precipitate failure (Otani et al., 1993). Similarly, implant coating depth can affect the cortical strains generated during implantation (Abdul-Kadir et al., 2008). A finite element analysis performed using a Zweimuller stem (ZimmerBiomet, Warsaw IN, USA) estimated that the ideal interference fit was 50 micrometres. At this point the stability would be enough for osseointegration during normal activities but not lead to excessive femoral cortical strains. Whilst this is useful information in a purely technical sense, generation of interference fit is poorly understood and impossible to specify during normal implantation (Abdul-Kadir et al., 2008). This makes investigation difficult in a clinical setting. It is clear however that surface finish, distribution of surface finish and stem interference may all be important factors in transfer of load to the proximal femur, generation of residual hoop stresses and prevention of stem movement which may cause a log splitting action to the proximal femur.

Much like the implant’s surface finish, surface shape can have a large effect on the generation of proximal femoral cortical strains in the implanted femur. Surface grooves can increase the contact surface at the bone-implant interface by as much as 25% (Vidalain et al., 2011). This can have the effect of both increasing the friction generated at the implant-bone interface and to reduce the stress concentration.

Longitudinal ridges have also been shown to improve rotational stability to anteriorly applied loads in cadaveric models (Tanner et al., 1988) and proximal surface grooves have shown to affect the stress transmission across the bone-implant interface in finite element analysis models (Rawal and Bhatnagar, 2012). Finite element analysis modelling has also estimated greater peak stresses associated with stems which have sharp edges occurring on the long lines of quadrangular prostheses and also along surface ridges (Hu et al., 2010). The authors make a large leap to infer an increased risk of POPFF from their results, which represent quasi static modelling of stair climbing. In the absence of robust clinical or biomechanical evidence it is difficult to draw similar conclusions. There is clear evidence to suggest that the surface shape of implants may affect the transfer of load from the implant to the proximal femur. As a result, it would seem sensible to assume that implant surface shape may also affect the risk of POPFF in the early post-operative press-fit scenario.

2.8.3.2 Non-stem implant risk factors

The evidence regarding the effect of other implants within the whole THR construct on the risk of POPFF is sparse. One study exists which uses a retrospective analysis of patients with ceramic on ceramic (CoC) bearings in one hip and ceramic on polyethylene (CoP) bearings in the contralateral hip over a period of 15 to 40 years (Hernigou et al., 2018). The stem was a cemented collared titanium stem in all cases. The odds of POPFF in the CoP group was higher than in the CoC group (Odds ratio [OR] 34.1, 95% CI 4.6 to 252.7). Most fractures occurred after the seventh follow up year and might suggest that fracture due to wear related osteolysis plays an important role in late fractures. The authors also reported an increase in femoral canal expansion, cortical thinning and osteolysis over follow up in CoP hips versus CoC hips. Such changes may have theoretically reduced the strength of the femur and may have increased the likelihood of subsequent POPFF, particularly since the link between osteolysis and increased POPFF risk has been made in the literature previously (Berry, 2003).

An association between acetabular cup design and the odds of POPFF has been made by a French group who compared the rate of revision for POPFF and dislocation in those patients with and without a dual mobility (DM) cup (Sappey-Marinier et al., 2019). The authors found that the odds of POPFF were 12-fold greater with a DM cup versus a standard cup, after adjusting for bone morphology, stem fixation and co-morbidity score. Interpretation of these results are difficult since the decision to use a DM cup is presumably not random and may introduce confounding by indication in this observational non-randomised study. For a POPFF to occur there must be sufficient bending, rotational and axial force. This can only occur if the bone is held solidly between a minimum of two points. This might occur when the hip joint is fixed by muscle action, capsule tension or impingement. Conversely femoral strains induced by fixation of the hip joint may be reduced by subluxation or dislocation. It might be possible then that DM cups lead to a reduction in subluxation and dislocation but increase the effective transmission of forces to the femur which may increase the likelihood of POPFF, although such hypotheses are yet untested. Since the current evidence on non-stem implant related risk of POPFF is sparse but may show significant effects, it is prudent to include the effect of all implants in any investigation of implant related POPFF risk.

2.9 Fracture classification

POPFF can be classified according to a range of systems, on which an understanding of POPFF can be built. Early methods to classify POPFF typically relied on small single surgeon series and classified fractures according to anatomical location (Parrish and Jones, 1964) or a combination of anatomical location and specific fracture patterns (Whittaker et al., 1974; Bethea et al., 1982; Mont, Michael A. and Maar, 1994; Johansson et al., 1981). Mont and Maar stated that a statistical analysis of fracture treatments and outcomes was impossible due to the small number of cases in each series, cohort heterogeneity and non-standard reporting (Mont, Michael A. and Maar, 1994). The pooled results include treatment with traction and spica casting through to long stem revision and fixation, which may not be applicable to modern practice. However, the identification of the need for standardised approaches and pooling of results to allow study of a relatively rare complication following hip replacement was well ahead of its time.

Following these approaches, which mixed fracture morphology, location and recommendations for treatment, a more treatment-based classification was introduced. The Vancouver classification system is now the most widely used classification system for POPFF (Duncan and Masri, 1995). The Vancouver system classifies POPFF, according to fracture location and implant stability, into groups which guide treatment methods. This classification system attempts to classify fractures based on the potential for the implants involved to continue functioning. Type A are avulsion fractures of the greater (Ag) and lesser trochanter (Al, Figure 2-1). Type B fractures occur at the level of the femoral implant and are further subdivided into fractures with a stable stem (B.1), an unstable stem (B.2), and fractures with an unstable stem and bone loss or comminution (B.3). Type C fractures occur well clear of the femoral implant, although the definition of `well clear` is not well-defined.

Incidences of fracture in each Vancouver class are difficult to assess as large series with complete records which include radiographic analysis are rare. Abdel and colleagues reported that approximately 10% POPFFs included fractures of more than one class. Of the remainder, approximately one third of POPFF occurred in the greater and lesser trochanter, a half of fractures were type B and the rest were type C (Abdel et al., 2016b). Type A fractures are typically treated conservatively with restricted weight bearing and rest unless significant displacement occurs (Abdel et al., 2015; Tsiridis et al., 2003). Type B.1 and C fractures are broadly treated with fracture fixation and types B.2 and B.3 with revision and fixation (Abdel et al., 2015; Tsiridis et al., 2003).

Various amendments to the Vancouver classification have been proposed. The Coventry classification system classified POPFF into broadly 'happy'- and 'unhappy'-hips. Happy-hips had no sign of pre-fracture loosening should be treated with a form of fixation, whilst unhappy-hips should be treated with revision (Ninan et al., 2007). Capello and colleagues recognised an early fracture type which occurred typically within the first two months after implantation. This fracture type was described as a clam-shell type, which involved the lesser trochanter and a significant position of the femoral shaft adjacent to the implant (Capello et al., 2014). A modified classification system was proposed, but the original Vancouver creators refuted the need for a modification as the new fracture could be classified as a B2 (Van Houwelingen and Duncan, 2011). Frenzel *et al.* proposed a novel and complex classification system which included information regarding fracture location, pattern, bone quality, implant duration in situ and implant stability (Frenzel et al., 2015). This system has not been validated however and is perhaps too complex to be widely used in clinical practice at present. The Vancouver classification system was incorporated into the unified classification system (UCS) for periprosthetic fractures (Duncan and Haddad, 2014). The UCS also includes classification of periprosthetic fractures of all anatomical locations including: Interprosthetic fractures, fractures of pairs of bones (e.g. tibia and fibula) and fractures of joint surface facing a hemiarthroplasty articulation.

In order to understand how to modify risk of POPFF due to implant design we must first understand how the femoral implant breaks the femur. This is important for two reasons. Firstly, understanding the mechanism of fracture helps us to understand common mechanical vulnerabilities of the femur-implant construct. For example, if an implant has a higher than expected fracture frequency with a fracture caused by rotation, an increase in rotational stability may lead to a reduction in fracture frequency. Secondly, if we are to test design improvements, we must understand how to construct tests which accurately replicate the mechanisms which implant designs must resist. Whilst the Vancouver classification system and the UCS are widely used and have proven validity and reproducibility as a treatment aid (Rayan et al., 2008; Naqvi et al., 2012; Brady et al., 2000; Huang et al., 2016), the Vancouver system and UCS do not help to identify fracture mechanism. A new method which seeks to classify POPFF by mechanism is required to achieve these goals. Fracture patterns can be viewed as a force footprint, which summarises the trajectory of a fracture forces through a bone. Detailed analysis of fracture patterns may provide an insight into common fracture mechanisms for any particular stem or patient group and further develop our understanding of how femoral stems break the femur during a POPFF.

2.10 Fracture mechanism

Correlation of fracture mechanism from fracture patterns and *vice versa* is a common clinical approach in orthopaedics. Similar approaches are utilised by anthropologists and pathologists (Love and Wiersema, 2016). Early cadaveric work in native human femurs demonstrated the relationship between spiral fracture patterns and torsional load, the propensity for spiral fractures to occur in the proximal femur, and comminution levels which were dependent on fracture impact energy (Tyler A. Kress, 1995). Spiral fractures typically occur at 45 degrees to the long axis of the femur. The two opposing ends of the spiral fracture line are often connected by a straight section (Figure 2-3). Compression in the long axis of a long bone may to lead to oblique fracture patterns which result from failure in shear at approximately 45 degrees to the loading direction. Spiral fractures can be specifically identified and differentiated from oblique fractures using these criteria. Bending deformation is thought to produce either a transverse fracture with or without a `butterfly` fragment. A butterfly fragment results from bending loads leading to a fracture starting on the tensile side and radiating at 45 degrees to perpendicular to the long axis of the bone (Gitajn, I. and Rodriguez, 2011). These descriptions are the basis of the Arbeitsgemeinschaft für Osteosynthesefragen (AO) type groupings of fracture patterns which classify native bone fracture types into oblique and transverse and spiral groups (Meinberg et al., 2018). The validity of fracture classification using AO methods is well established and has a good level of reliability both within and between assessors for fracture type specifically (percent agreement 78 to 80%, kappa 0.64 to 0.81 [substantial to near perfect agreement]) (Meling et al., 2012; Knutsson et al., 2019). Real world mechanisms such as falls and stumbles may produce a distribution of these patterns secondary to bending, axial loading and torsion.

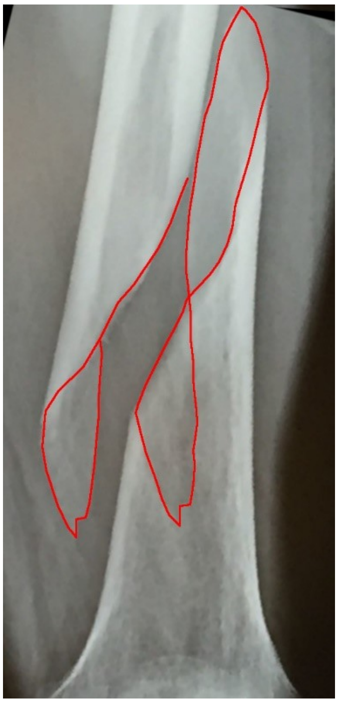


Figure 2-3 Typical spiral fracture pattern in the distal femoral diaphysis. Note that the cortical edges always cross in a spiral fracture and the cleavage plane is approximately 45 degrees to the femoral diaphyseal axis when viewed in-plane.

POPFF fracture mechanism in an implanted femur may be quite different and research on the subject is sparse. Clinical studies have identified that the majority of periprosthetic fracture patterns around the femoral stem are some combination of spiral and oblique fracture types (Abdel et al., 2016b; Fenelon et al., 2019). Much of the useful insight has come from biomechanical studies, where the relationship between mechanism and fracture type can be explored. Rupprecht and colleagues investigated POPFF fracture mechanisms in tissue stripped fresh frozen cadaveric femurs with a polished tapered cemented stem and found that rotational loads caused proximal fractures around the stem, side-bending loads caused fractures at the stem tip and anteroposterior bending loads caused fractures at the supracondylar level (Rupprecht et al., 2011). Fractures around the stem have been recreated with rotational loading mechanisms in other studies using polished taper stems and non-osseointegrated cementless femoral stems (Ginsel et al., 2015; Morishima et al., 2014; Jones, C. et al., 2015). In biomechanical studies using ‘normal walking’ orientation with axial loads (near vertical femur, vertical loading on femoral head), fractures occurred in a longitudinal pattern around a non-osseointegrated femoral stem and the location of the fracture varied between trials (Jakubowitz et al., 2009a; Jakubowitz et al., 2009b). Axial loading of a cementless stem are likely to give typical IOPFF patterns such as calcar cracks, which tend to be longitudinal (Abdel et al., 2016b). In addition to these types of fracture is the ‘log splitter’ or ‘metaphyseal split’ type fracture where the metaphysis splits around a femoral stem (Phillips, J. et al., 2012). This fracture differs from a linear or spiral fracture because the metaphysis is split into at least two separate parts and neither are in continuity with the femoral shaft. Metaphyseal split fractures are likely to be caused by axial loads which cause the stem to forcefully subside into the proximal metaphysis and may occur when the loads required to fracture are greater. Demey and colleagues described the generation of linear fractures around collarless stems at axial loads of approximately six Kilonewtons and metaphyseal split fractures around collared stems, where the fracture force was approximately double (Demey et al., 2011). Metaphyseal split fractures may be a special linear fracture type with comminution due to large amounts of fracture energy. Given the lack of understanding relating to the specific mechanisms leading to this fracture, it is useful to categorise this fracture type as a separate entity.

Atypical fracture patterns tend to occur perpendicular to the long axis of the femur and are associated with chronic bending deformation around the level of the stem tip. Atypical fractures are analogous to stress fractures and are associated with an increase in cortical thickness and progressive horizontal fracture. Anecdotally, such fracture patterns occur more frequently around older composite beam implants after many years of loosening. Atypical fractures associated with other stem types are more common in association with bisphosphonate usage, particularly in younger patients (Leclerc et al., 2019; Lee et al., 2018; Robinson Jde et al., 2016).

Clinical data on POPFF fracture patterns is typically descriptive in a nature and limited to subjective descriptions of ‘simple’, ‘complex’, ‘transverse’ and ‘oblique’ (Fenelon et al., 2019; Meinberg et al., 2018). It appears that both fracture location along the femur and fracture type are an important measurable variable of fracture pattern which may be linked to mechanism. This research also demonstrates that there is currently no objective method available for accurately recording of POPFF fracture position or type which may allow comparison of fracture mechanisms between implants in clinical data and validation of experimental methods.

2.11 Treatment methods

The treatment of POPFF in general is well established in most cases and a full review and discussion of treatment methods is outside the focus of this thesis. It is important to understand the treatment trends for periprosthetic fractures, and how subsequent data is collected, since it affects the data available for research. The most used treatment algorithm is based on the Vancouver classification system, as previously described. Vancouver A fractures are generally treated with non-operative management unless the avulsed fragment is significantly displaced (Abdel et al., 2015; Tsiridis et al., 2009). Vancouver B fractures can theoretically be treated conservatively, with ORIF or with revision surgery with or without supplementary fixation. Vancouver C fractures are treated with conservative management or ORIF. Data regarding all treatment methods is widely available in the form of small single centre cohort studies (Khan, T. et al., 2017), however, the quality and homogeneity of such studies is low which restricts the pooling of these data using standard meta-analysis methods (Deng, Y. et al., 2019). Large-scale high-quality data is available for all revision surgery for POPFF by the NJR. In general the NJR data has a low proportion of missing data and is able to follow patients without significant geographical restrictions (Porter, M., 2017). One major restriction of this dataset is the lack of POPFF which are treated by ORIF or managed conservatively, since only revision operations are recorded. Other options are available and data is theoretically available on all NHS admissions and thus all POPFFs admitted to NHS hospitals from Hospital Episode Statistics data provided by NHS Digital but lacks hospital, surgeon and implant information, which restricts the usefulness as an isolated data source for orthopaedic analysis. Additionally, the effect of missing information regarding procedures performed in non-NHS hospitals on large scale POPFF research has not been evaluated. It is possible to link NJR and NHS digital data sources in order to combine the richness of NJR and NHS data, but this has not yet been attempted.

Meta-analysis of case series data found that over 86% of cases of POPFF were treated with revision surgery (Khan, T. et al., 2017). These results are similar to those reported for the Swedish hip arthroplasty registry (SHAR), which found that only 10% of all POPFF occurring after cementless stem implantation were treated with ORIF. It is reasonable to assume that high quality registry data regarding POPFF treated by revision surgery only may be a useful data source for analysis of POPFF following cementless stemmed THR.

2.12 Summary

POPFF is a relatively uncommon surgical problem but is expected to become more common as the proportion of older patients with hip replacements in society increases. POPFF accounts for a large proportion of failures of THR internationally and is associated with increased patient mortality and disability despite the best available treatment. In the context of healthcare in general, POPFF is also associated with a relatively small number of hospital admissions (compared to myocardial infarction for instance) but a disproportionately large cost burden due to lengthy hospital stay, large cost of implants, theatre time but mostly associated loss of mobility and associated increase in health and social care requirements. The true cost of POPFF is likely to be much greater once increased social care and personal costs are properly estimated.

Given the poor outcomes for patients with POPFF, the need for focused prevention is quite clear. The scope for prevention is limited by the ability of carers to significantly change the risk profile of patients between a point where implantation is certain and the time of expected POPFF. This time frame is likely to be small with cementless stems, where the risk of POPFF is greatest and the time between implantation and POPFF may be less than six months.

2.12.1 Targets for prevention

Modifiable risk factors which are associated with large decreases in the risk of POPFF are obvious targets for deeper study and analysis. The target of study should ideally be a risk factor which is amenable to change and associated with a low incremental cost (cost of change of in activity). The key constraints on the modification of such risk factors are the short window of opportunity between the decision to treat hip disease with THR and POPFF, which can be as short as a few weeks (Gromov et al., 2017), and that the incidence is relatively low (Lindahl, 2007).

This review has described increased risks associated with co-morbidities which may not be easily manipulated in the short space of time available. Falls risk has not been well studied but is likely to be associated with POPFF, since the majority of POPFF follow a fall from a standing height. Interventions which reduce the risk of falls in a short space of time may be a useful tool to reduce the risk of POPFF (NHS, 2019). Multifactorial interventions are well-established and associated with a 35% reduction in falls risk in the elderly population. A relatively quick reduction in POPFF risk may be possible with targeting of patients at risk of falls at the point of referral for THR.

This review has identified a range of implant variables which may affect the risk of subsequent POPFF. Much of the current evidence suggests that most of the risk is associated with the presence of a cementless femoral stem, but the exact mechanism is not clear. Cementless stem THR can give outstanding clinical results, particularly in younger patients, where the need for long term survival is imperative. However, modern cementless stems are not designed to be fracture resistant. A deeper understanding of how the risk of POPFF increases with the use of cementless stems may lead to development in more appropriate product selection, implantation techniques and design. Retrospective analysis of current implant performance with reference to POPFF incidence, may help to develop hypotheses which can be developed into future methods to reduce POPFF incidence.

2.12.2 Gaps in the current literature

There is a clear association between the risk of intraoperative fracture and POPFF either through separate events in a population with common risk factors or through occult intraoperative fractures which are identified post-operatively (Yun et al., 2019). Thus, prevention of IOPFF may directly and indirectly reduce the risk of POPFF. However, the relationship between IOPFF and POPFF is not well defined and further work is required to define the risk factors for each subtype of IOPFF and explore the relationship between these subtypes and the risk of subsequent POPFF.

The association between implant design features and risk of POPFF is not well understood. IT is clear form this literature review that whilst cemented stem infer a lower risk of both IOPFF and POPFF, there are excellent reasons to use cementless stems in hip replacement surgery. It is also unlikely that the majority of surgeons around the world, who use cementless stems, will simply switch to a cemented stem to avoid a relatively small number of POPFF in the face of large perceived benefits of a cementless stem. Implant adaptation through implant selection or re-design may be a useful method of mitigating POPFF risk associated with cementless stems. Current evidence does not usefully attribute risk to specific design features, which can then be tested empirically. For an effective implant-based prevention strategy more robust and accurate measures are required to understand how the risk associated with cementless stems transpires.

A large underlying problem with the current POPFF literature is that there is no objective means of quantifying fracture patterns, which necessarily limits the understanding of POPFF mechanism and the mechanism by which an implant may increase the risk of POPFF. In turn this prevents objective validation of fracture mechanisms used in biomechanical testing.

2.13 Structure of the thesis, and specific aims

As established in the literature review, POPFF is a significant problem for patients undergoing THR and is associated with very poor outcomes both in the short and long term, and incurs large associated health care costs, despite the best current management techniques. As outlined, a sensible approach to reduce patient harm is to reduce the incidence of POPFF in patients undergoing THR. The first step in this approach is to establish as yet poorly understood risk factors for POPFF so that focused harm reduction strategies can be implemented.

Current knowledge of risk factors is limited to patient characteristics and to implant design in the very shallowest sense. The lack of knowledge regarding the risk associated with IOPFF and implant design features represent an important unmet need which this thesis will aim to fulfil. The overarching hypothesis being tested with this work is that the design features of a cementless stem influence the risk of subsequent periprosthetic femoral fracture.

This thesis describes a program of work which explores the contribution of cementless femoral implant design to the occurrence of POPFF in the context of other patient, surgical and implant related risk factors. This thesis aims to develop evidence-based hypotheses to explain which design features of cementless femoral implants are associated with increased POPFF risk using statistical models derived from large datasets. Hypotheses will then be tested using radiographic and biomechanical analyses.

The thesis will be comprised of six further chapters as follows:

Chapter Three - Understanding the relationship between IOPFF and POPFF using a large national joint registry.

This chapter is comprised of two bodies of work which both use a large national dataset to understand IOPFF and the relationship to POPFF. Firstly, the relationship between IOPFF and the risk of POPFF is described with reference to each particular anatomical subtype of IOPFF. Secondly, this chapter estimates the relative contribution of risk factors to the formation of IOPFF to understand whether POPFF related to IOPFF might be preventable.

Chapter Four: Understanding the relationship between femoral implant design and POPFF using a large national joint registry.

This chapter describes the creation of a design database, which was used to construct statistical models to understand the association between cementless femoral implant design features and the risk of periprosthetic fracture. Firstly, the construction of a large database using the NJR is described. Secondly, the estimated effect of femoral implant design on POPFF risk is reported.

Chapter Five: Development of a manual segmentation method to record and summarise POPFF fracture patterns.

This chapter describes the development of a method to quantify radiographic records of POPFF patterns and estimates the accuracy and repeatability of this method.

Chapter Six: Using radiographic records of POPFF to quantify POPFF mechanism and validate biomechanical methods.

The application of this method to a clinical dataset of POPFF occurring following hip replacement using a cementless femoral stem is then described. The fracture patterns are described to understand the spectrum of POPFF aetiology and to estimate the likely mechanism of POPFF, which can then be simulated experimentally.

Chapter Seven: Hypothesis testing using an in vitro biomechanical POPFF model.

This chapter describes the development and validation of an in vitro method of POPFF simulation using a paired cadaveric method. The relationship between femoral implant calcar collar and the risk of POPFF is tested to investigate the mechanism of action using a simulated POPFF model. Finally, the relationship between femoral implant calcar collar and the risk of POPFF is explored to investigate mechanism of action using a simulated POPFF model.

Chapter Eight: Summary, conclusions and future directions.

This chapter synthesises the evidence reported in the preceeding chapters to describe an overview of gaps in current knowledge and how the work in this thesis furthers the field of POPFF research. Limitations are identified and priorities for future research in this field are proposed.

Chapter 3 Intraoperative periprosthetic femoral fractures: a risk factor for post-operative periprosthetic fracture

This chapter will firstly report on a study to understand the relationship between IOPFF and subsequent implant and patient survival with specific reference to POPFF. This section forms the basis of the publication:

Lamb JN et al. *Patient and implant survival following intraoperative periprosthetic femoral fractures during primary total hip arthroplasty. An analysis from the National Joint Registry for England, Wales and the Isle of Man.* **Bone and Joint Journal** 101-B (10):1199-1208 01 Oct 2019.

The second section of this chapter describes a study which outlines risk factors for IOPFF. This study forms the basis of the publication:

Lamb JN, Matharu GS, Redmond A, Judge A, West RM, Pandit HG. *Risk factors for intraoperative periprosthetic femoral fractures during primary total hip arthroplasty. An analysis from the National Joint Registry for England and Wales and the Isle of Man.* **The Journal of Arthroplasty** 34 (12):3065-3073.e1 Dec 2019.

3.1 Patient and implant survival following intraoperative periprosthetic femoral fractures during primary total hip replacement.

3.1.1 Introduction

As noted in the chapter 2 THR is a highly successful procedure with a low complication rate. One significant complication is IOPFF, which can occur in the trochanteric region, calcar or femoral diaphysis (Masri et al., 2004). The incidence of IOPFF in primary THR ranges from 1–5% (Abdel et al., 2016b; Berry, 1999; Ricioli et al., 2015). Most IOPFF occur during canal preparation and stem implantation (Abdel et al., 2016b), when the circumferential strains of the proximal femur are highest (Elias et al., 2000), especially when the surgeon establishes implant stability through press-fit fixation with cementless implants (Jasty et al., 1994). Treatment of IOPFF is specific to fracture type and stability (Davidson et al., 2008). Calcar cracks are commonly treated with cerclage wires or cables (Berend, M.E. et al., 2006; Abdel et al., 2016b), shaft fractures with internal fixation and/or revision to a distally fixed stem (Abdel et al., 2016b) and unstable trochanteric fractures with wiring or plating (Abdel et al., 2016b; Tsiridis et al., 2009).

Case series have reported excellent outcomes with appropriately treated IOPFF (Berend, K.R. et al., 2004; Mont, M. A. et al., 1992). More recently however, IOPFF has been linked to an increased risk of post-operative POPFF and higher risk of revision (Miettinen et al., 2016; Berend, M.E. et al., 2006; Abdel et al., 2016b; Thillemann et al., 2008). It would seem reasonable to assume that different anatomical types of IOPFF might lead to different levels of risk of subsequent POPFF, given that each anatomical location will have a specific function with regards to load transfer and stem function. The relationship between type of IOPFF and risk of subsequent POPFF is not clearly established. It might also be reasonable to assume that any subsequent revision surgery also increases 30-day and 90-day mortality (Jones, M.D. et al., 2018), but the specific effect of IOPFF on mortality has not yet been estimated. In order to understand the cost to patients of IOPFF it is important to describe the risk of future revisions and the associated effect of further interventions on the risk of dying.

The purpose of this study was to estimate implant survival rates to an endpoint of revision surgery, with emphasis on POPFF compared to a matched cohort of patients undergoing uncomplicated primary THR using data from the NJR, the world's largest joint registry.

3.1.2 Methods

3.1.2.1 Dataset

The NJR records patient and surgical data for all THRs performed at hospitals in England and Wales since 2003; with overall missing data estimated at 5.8% (Porter, M, 2018). Surgeon-reported IOPFF, has been collected since 1st April 2004. This study investigated all primary stemmed THRs in the NJR from 1st April 2004 to 30th September 2016.

3.1.2.2 Participants

793976 THRs were eligible for analysis. Exclusions were; missing follow-up data (n = 15), cases from the Isle of Man (low numbers, n= 153) and where the bearing type was not a combination of metal on polyethylene (MoP), ceramic on polyethylene (CoP), ceramic on ceramic (CoC) or metal on metal (MoM) (n = 12 566). The resulting subset of data included 781 242 primary THRs. Institutional ethical approval was granted for this study.

3.1.2.3 Variables

All variables relating to patient age, sex, ASA grade (1-2 vs 3-5), year of surgery, side, surgical approach (anterolateral [Hardinge, anterolateral and lateral], trochanteric osteotomy, posterior, other), computer guided surgery (CGS), minimally invasive surgery, surgeon grade (consultant versus non-consultant), hospital type, indication, stem fixation type, bearing combination and type of thromboprophylaxis were included. IOPFF were reported as either ‘calcar crack’, ‘shaft fracture’, ‘shaft penetration’, ‘trochanteric fracture’ and text describing IOPFF in the free text field `other`. Cases were classified as calcar, trochanter or shaft fractures.

3.1.2.4 Outcomes

The primary outcomes were implant survival and patient survival. Implant survival was estimated until stem revision (all stem attributable revisions: Aseptic stem loosening [ASL], instability, POPFF, pain, infection, stem fracture, stem malalignment) and separately for revisions indicated for POPFF, instability, ASL and infection. Implants which were not revised during follow up were censored. Patient survival was estimated from primary surgery until death using pre-existing NJR data from the Office for National Statistics database, which provides data on all-cause patient mortality, using unique patient identifiers.

3.1.2.5 Statistical analysis

Comparisons of continuous variables which were not normally distributed were performed with a Mann-Whitney U test, and categorical variables were compared with Pearson’s chi-square tests. Since the dataset was large and multiple comparisons were made, a significance level of $p < 0.01$ was chosen. Survival analysis was performed using Kaplan Meier and Cox Proportional Hazards modelling. Direct comparison between patients with IOPFF would be biased by the difference in typical patient characteristics, so propensity score matching was used to balance the group of patients with IOPFF to those without a fracture on important available covariates so that a fairer comparison can be made. The proportional hazards assumptions were satisfied for all analyses. All analyses were performed using R (V 3.5.1, Vienna, Austria).

Influence of IOPFF on implant survival

Propensity scores were used to match patients who sustained IOPFF (IOPFF group) to similar patients without IOPFF (Control group) at a ratio of 1:10 with a 0.04 standard deviation (SD) calliper matching width. Propensity scores were generated using logistic regression and represented the probability that a patient sustained an IOPFF during primary THR. Variables used for matching were selected using a previously established model and included: age, gender, ASA grade, diagnosis, side of surgery, lead surgeon grade, organisation type, computer guided surgery, approach, stem fixation and bearing combination. Adequate balance of the IOPFF vs control group was assumed when the standardised mean difference (SMD) was <10% for each variable. Implant survival at up to 10-years was estimated using the Kaplan-Meier method and survival difference between IOPFF and controls was assessed using a log-rank test. Estimation of implant survival was assessed for each revision indication. Kaplan-Meier plots were assessed visually to identify the time period in which a difference in revision rate occurred between IOPFF and controls. The influence of IOPFF on implant survival during this period was assessed using univariate Cox regression models to estimate the adjusted hazard ratio with 95% CI (HR [95% CI]) of revision for those with IOPFF compared to controls. Multivariable Cox regression was utilised for subtypes of IOPFF, which were adjusted for age, gender, ASA score, indication for surgery, bearing combination and stem fixation to reduce confounding error.

Influence of IOPFF on patient survival

Unadjusted patient survival was estimated up to 10 years using the Kaplan-Meier method and compared between IOPFF and control groups using a log-rank test. Cases were coded according to whether the patient has an IOPFF and subsequent revision. Multivariable Cox regression models were used to assess the influence of IOPFF on mortality, which were adjusted for age, gender, ASA grade, indication for surgery, bearing combination, approach, stem fixation and thromboprophylaxis (Hunt et al., 2013).

3.1.3 Results

Following exclusions, the overall prevalence of IOPFF was 0.62% (4833/781 242). The prevalence of IOPFF during cementless stem implantation was 0.87% (2969/ 341 115) and for cemented stems was 0.42% (1864/ 440 127). Only two cases in the IOPFF group could not be appropriately matched. Matching was achieved at a ratio of close to 1:10 within the parameters of the matching algorithm. Matching resulted in 4831 hips in the IOPFF group and 48154 hips in the control group. Good balance between IOPFF and control groups was achieved (SMD <8.3%, Table 3-1). Median (IQR) follow-up time in IOPFF and control groups were similar (5.4 years [3.2 - 8.1] versus 5.5 years [3.2 - 8.3], p=0.305). Follow up ranged from 0.0 to 13.9 years in both groups. In the IOPFF group the prevalence of stem only revision in the five years following THR was significantly higher than in the control group (3.01% versus 2.01%, p<0.001).

Table 3-1 Description of balance between unmatched and matched cohorts. The table is continued on the following page

		Unmatched		SMD	Matched		SMD
Variable	*Level*	No IOPFF	IOPFF		No IOPFF	IOPFF	
n		776409	4833		48154	4831	
IOPFF subtype	*None (%)*	776409 (100.0)			48154 (100.0)		
	Calcar crack (%)		3018 (62.4)			3017 (62.5)	
	Shaft fracture (%)		340 (7.0)			340 (7.0)	
	Trochanteric fracture (%)		1475 (30.5)			1474 (30.5)	
Patient Gender	*Female (%)*	475029 (61.2)	3560 (73.7)	0.269*	35552 (73.8)	3558 (73.6)	0.004
Mean age	*years (range)*	69.25 (11 - 117)	68.26 (12 - 105)	0.083	68.27 (12 - 102)	68.25 (15 - 98)	0.001
Age group	*11 <50 (%)*	38225 (4.9)	390 (8.1)	0.161*	3282 (6.8)	390 (8.1)	0.083
	50 <60 (%)	95318 (12.3)	672 (13.9)		6570 (13.6)	672 (13.9)	
	60 <70 (%)	231378 (29.8)	1324 (27.4)		14300 (29.7)	1324 (27.4)	
	70 <80 (%)	279469 (36.0)	1543 (31.9)		15997 (33.2)	1543 (31.9)	
	80 <117 (%)	132019 (17.0)	904 (18.7)		8005 (16.6)	902 (18.7)	
Side	*Right (%)*	426349 (54.9)	2564 (53.1)	0.037	25716 (53.4)	2563 (53.1)	0.007
ASA grade	*1 - Fit and healthy (%)*	117874 (15.2)	729 (15.1)	0.158*	7086 (14.7)	729 (15.1)	0.017
	2 - Mild disease not incapacitating (%)	534690 (68.9)	3046 (63.0)		30718 (63.8)	3046 (63.1)	
	3 - Incapacitating systemic disease (%)	119598 (15.4)	1007 (20.8)		9842 (20.4)	1005 (20.8)	
	4 - Life threatening disease (%)	4129 (0.5)	49 (1.0)		482 (1.0)	49 (1.0)	
	5 - Expected to die within 24hrs (%)	118 (0.0)	2 (0.0)		26 (0.1)	2 (0.0)	
Indication	*Acute trauma including hip fracture (%)*	21685 (2.8)	146 (3.0)	0.276*	1426 (3.0)	146 (3.0)	0.022
	Avascular necrosis (%)	10293 (1.3)	123 (2.5)		1180 (2.5)	123 (2.5)	
	Previous trauma (%)	6974 (0.9)	168 (3.5)		1535 (3.2)	166 (3.4)	
	Inflammatory arthritis (%)	8394 (1.1)	99 (2.0)		993 (2.1)	99 (2.0)	
	Malignancy (%)	312 (0.0)	3 (0.1)		27 (0.1)	3 (0.1)	
	Osteoarthritis (%)	717258 (92.4)	4103 (84.9)		41082 (85.3)	4103 (84.9)	
	Other (%)	5651 (0.7)	68 (1.4)		660 (1.4)	68 (1.4)	
	Paediatric disease (%)	5185 (0.7)	108 (2.2)		1132 (2.4)	108 (2.2)	
	Previous arthrodesis (%)	236 (0.0)	2 (0.0)		17 (0.0)	2 (0.0)	
	Previous infection (%)	421 (0.1)	13 (0.3)		102 (0.2)	13 (0.3)	

Note: All results are total in group with percentage of variable total in parentheses apart from age which is also given as a mean with range. SMD is If SMD is <10% acceptable balance achieved. * is SMD >0.1. Standardised mean difference, ASA is American Society of Anesthesiologists grade (pre-operative), LMWH is Low molecular weight Heparin, TED is anti-embolism stockings.

Table 3-1 continued Description of balance between unmatched and matched cohorts.

Variable	Level	Unmatched No IOPFF	Unmatched IOPFF	SMD	Matched No IOPFF	Matched IOPFF	SMD
Approach	*Posterior (%)*	447506 (57.6)	2669 (55.2)	0.055	26541 (55.1)	2669 (55.2)	0.005
	Anterolateral (%)	292455 (37.7)	1923 (39.8)		19218 (39.9)	1921 (39.8)	
	Trochanteric osteotomy (%)	2986 (0.4)	13 (0.3)		121 (0.3)	13 (0.3)	
	Other (%)	33462 (4.3)	228 (4.7)		2274 (4.7)	228 (4.7)	
Surgeon grade	*Non consultant (%)*	134866 (17.4)	847 (17.5)	0.004	8582 (17.8)	847 (17.5)	0.008
Organisation Type	*National health service (%)*	529370 (68.2)	3726 (77.1)	0.204*	36959 (76.8)	3724 (77.1)	0.009
	Independent Hospital (%)	214471 (27.6)	984 (20.4)		9975 (20.7)	984 (20.4)	
	Treatment centre (%)	32568 (4.2)	123 (2.5)		1220 (2.5)	123 (2.5)	
Stem fixation	*Cementless (%)*	338158 (43.6)	2969 (61.4)	0.364*	29524 (61.3)	2967 (61.4)	0.002
Surgical technique	*Minimally invasive surgery (%)*	53589 (6.9)	336 (7.0)	0.002	3340 (6.9)	336 (7.0)	0.001
	Computer guided surgery (%)	20965 (2.7)	77 (1.6)	0.076	788 (1.6)	77 (1.6)	0.003
	Thromboprophylaxis						
	Aspirin (%)	93989 (12.1)	443 (9.2)	0.095	5187 (10.8)	443 (9.2)	0.053
	LMWH (%)	542559 (69.9)	3414 (70.6)	0.016	34048 (70.7)	3414 (70.7)	0.001
	Pent saccharide (%)	8785 (1.1)	62 (1.3)	0.014	512 (1.1)	62 (1.3)	0.02
	Warfarin (%)	9539 (1.2)	67 (1.4)	0.014	606 (1.3)	67 (1.4)	0.011
	Direct ThrombinInhibitor (%)	57713 (7.4)	415 (8.6)	0.042	3510 (7.3)	415 (8.6)	0.048
	Factor Xa Inhibitor (%)	36140 (4.7)	203 (4.2)	0.022	2118 (4.4)	203 (4.2)	0.01
	Other chemical prophylaxis (%)	53797 (6.9)	367 (7.6)	0.026	3569 (7.4)	365 (7.6)	0.005
	Foot pump (%)	204865 (26.4)	1212 (25.1)	0.03	12155 (25.2)	1212 (25.1)	0.004
	TED (%)	506125 (65.2)	3142 (65.0)	0.004	31412 (65.2)	3141 (65.0)	0.005
	Calf compression stocking (%)	304285 (39.2)	1987 (41.1)	0.039	19215 (39.9)	1986 (41.1)	0.025

Note: All results are total in group with percentage of variable total in parentheses apart from age which is also given as a mean with range. SMD is If SMD is <10% acceptable balance achieved. * is SMD >0.1. Standardised mean difference, ASA is American Society of Anesthesiologists grade (pre-operative), LMWH is Low molecular weight Heparin, TED is anti-embolism stockings.

3.1.3.1 Influence of IOPFF on implant survival

Ten-year implant survival for stem revision was significantly worse in the IOPFF group compared to controls (95.4% [94.5 – 96.2] versus 96.8% [96.6 – 97.1], p<0.001). The survival difference between IOPFF and controls became apparent within the first six months and divergence gradually increased up to 10 years (Figure 3-1). Relative hazard of stem revision in the first six months due to IOPFF versus no IOPFF was 2.6 (CI 2.0 – 3.4, p<0.001). Adjusted risk of stem revision within six months versus no IOPFF was greatest with trochanteric fracture (HR = 3.0 [CI 1.9 – 4.8], p<0.001) followed by shaft fracture (HR = 2.9 [CI 1.2 – 7.1], p=0.018) and calcar crack (HR = 2.4 [CI 1.7 – 3.3]. p<0.001) (Figure 3-6).

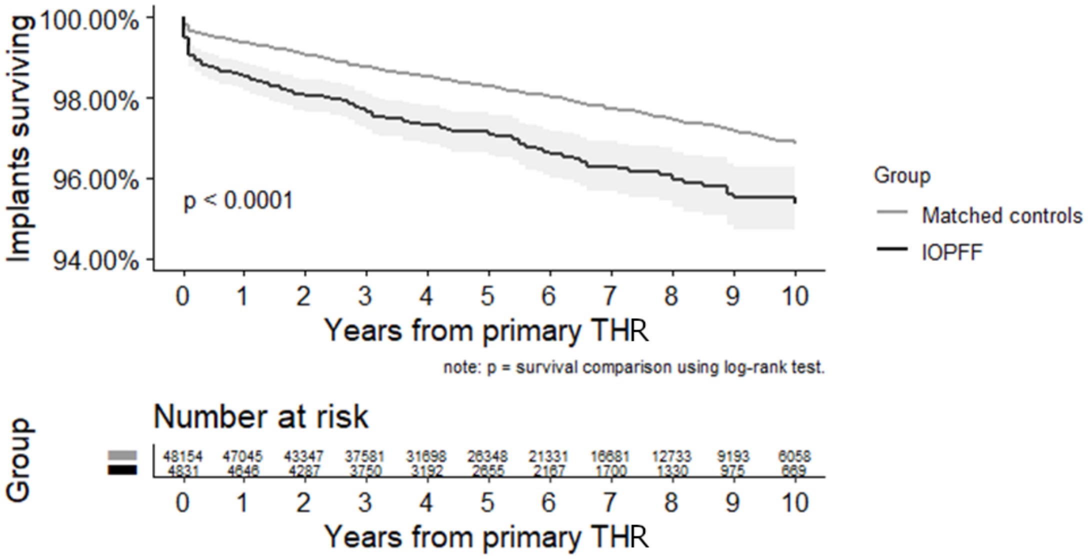


Figure 3-1 Femoral implant survival to all cause stem revision following THR with IOPFF versus matched controls over 10 years.

Ten-year implant survival until revision for ASL was significantly worse in the IOPFF group compared to controls (99.0% [CI 98.7 – 99.4] versus 99.3% (99.2 – 99.4), p=0.004). The implant survival difference between IOPFF and controls became apparent within the first six months and steadily increased to five years (Figure 3-2). Risk of revision in the first five years for aseptic loosening associated with any IOPFF versus no IOPFF was 2.1-fold (HR 2.1 [CI 1.3 – 3.2] p=0.001). The adjusted risk of stem revision for ASL within five years versus no IOPFF was greatest following shaft fracture (HR 7.2 [CI 2.9 – 17.7], p<0.001) followed by trochanteric fracture (HR 2.8 [CI 1.3 – 5.9], p=0.01) and least likely post calcar crack (HR 1.5 [CI 0.8 – 2.7], p=0.200) (Figure 3-6).

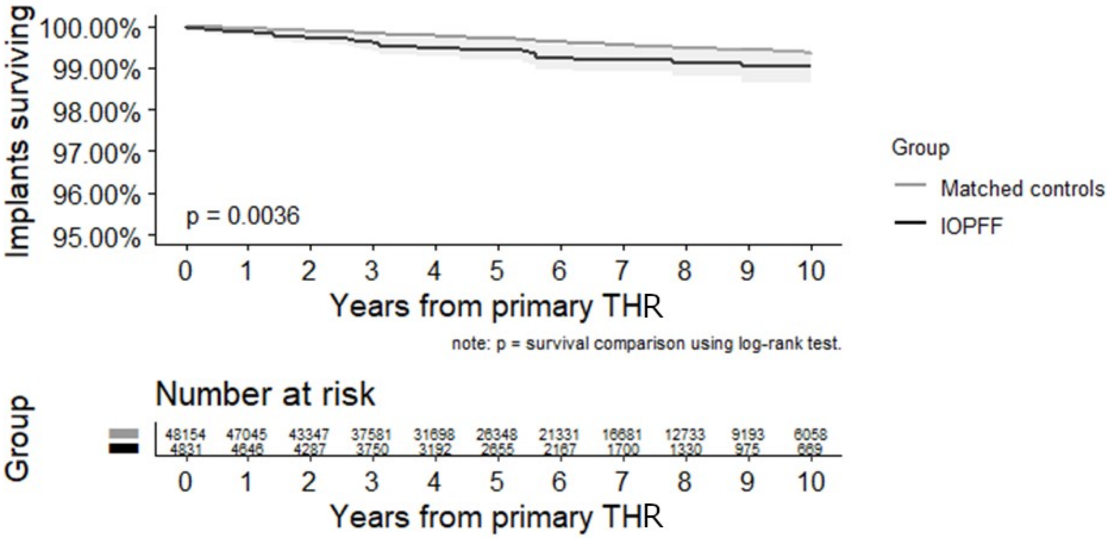


Figure 3-2 Femoral implant survival to revision for aseptic loosening following THR with IOPFF versus matched controls over 10 years.

Ten-year implant survival until stem revision for POPFF was significantly worse in the IOPFF group compared to controls (98.8% [98.4 – 99.2] versus 99.4% [99.3 – 99.5], p<0.001). The survival difference between IOPFF and controls became apparent within the first six months and maintained a similar trend up to ten years (Figure 3-3). The hazard ratio of revision for POPFF over six months for any IOPFF versus no IOPFF was 4.2 (CI 2.7 – 6.5, p<0.001). The adjusted HR of revision within six months for POPFF versus no IOPFF was greatest following shaft fracture (HR 4.4 [CI 1.1 – 18.1], p<0.039) then calcar crack (HR 4.3 [2.6 – 7.2], p<0.001) and finally trochanteric fracture (HR 3.6 [CI 1.6 – 8.3], p=0.003) (Figure 3-6).

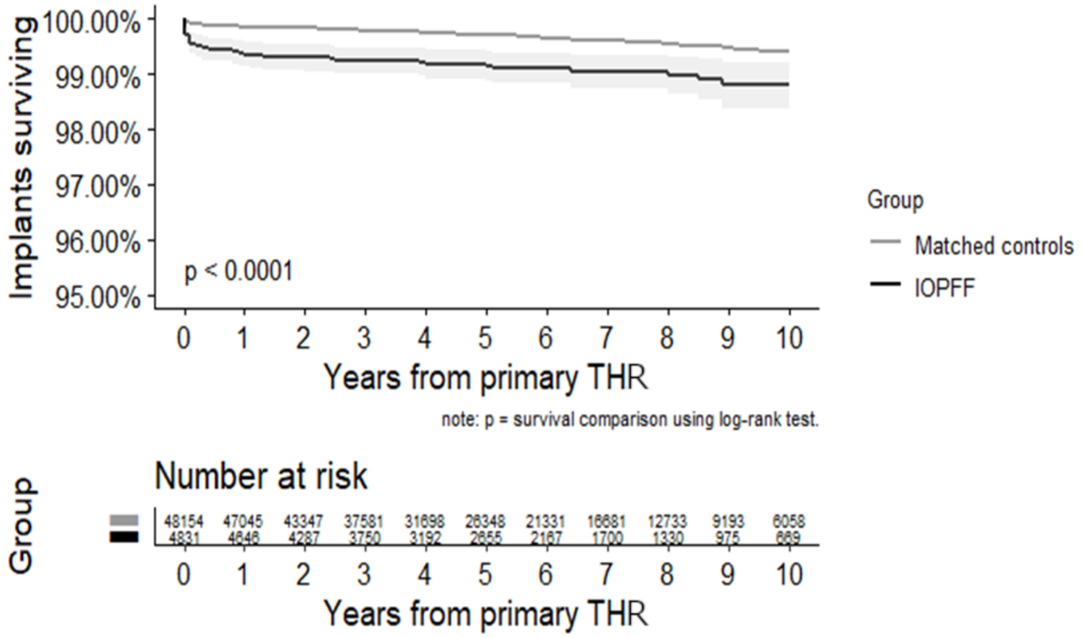


Figure 3-3 Femoral implant survival to revision for periprosthetic femoral fracture following THR with IOPFF versus matched controls over 10 years.

Ten-year implant survival to revision for instability was significantly worse in the IOPFF group compared to controls (98.7% (CI 98.3 – 99.2) versus 99.2% (99.1- 99.3), p<0.001). The survival difference between IOPFF and controls became apparent within the first six months and maintained a similar trend subsequently, up to ten years (Figure 3-4). Risk of revision for instability associated with IOPFF versus no IOPFF within six months was almost three-fold (HR 2.7 [CI 1.8 – 4.2] p<0.001). Adjusted risk of revision for instability versus no IOPFF within six months was greatest with trochanteric fractures (HR 3.6 [CI 1.8 – 6.9], p<0.001) then calcar cracks (HR 2.4 [CI 1.4 – 4.2], p=0.001) and then shaft fractures (HR 1.5 [CI 0.2 – 10.7], p=0.690) (Figure 3-6).

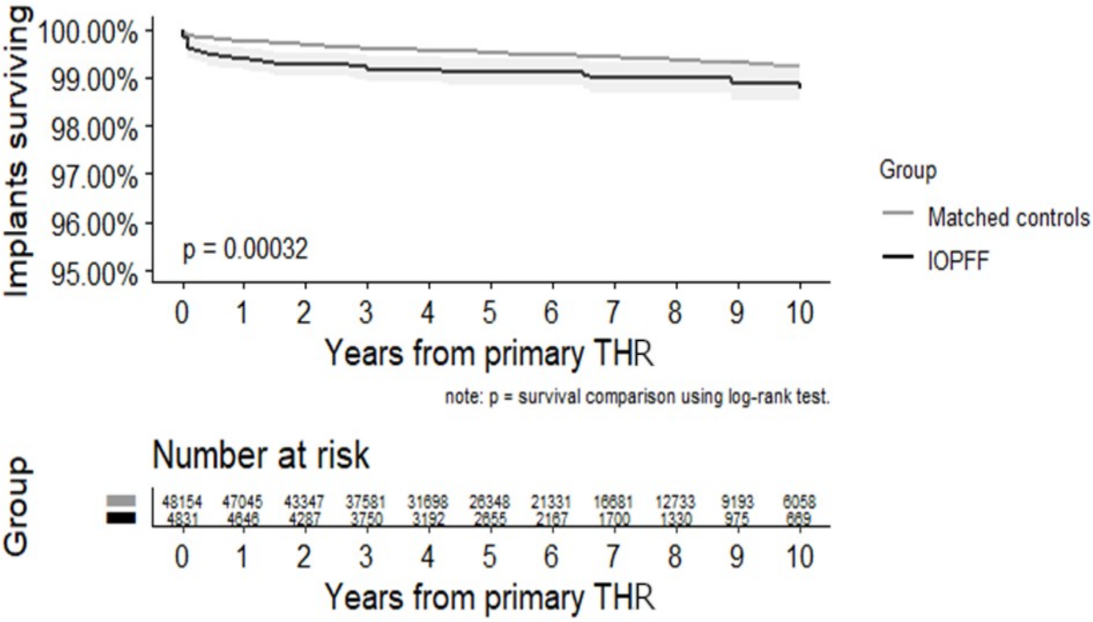


Figure 3-4 Femoral implant survival to revision for instability following THR with IOPFF versus matched controls over 10 years.

Ten-year implant survival for revision for infection was not significantly different in the IOPFF group compared to controls (99.2% (CI 98.8 – 99.6) versus 99.4% (99.3-99.5), p<0.20) (Figure 3-5). Risk of revision for instability associated with IOPFF versus no IOPFF was not statistically significant over the ten-year period (HR 1.3 [CI 0.9 – 2.0] p= 0.184). Adjusted risk of revision for instability versus no IOPFF over ten years was not statistically significant for calcar cracks (HR 1.3 [CI 0.8 – 2.1], p=0.37), shaft fractures (HR 3.0 [CI 0.0 – infinite], p=0.99) or trochanteric fractures (HR 1.7 [CI 0.9 – 3.2], p=0.11) (Figure 3-6).

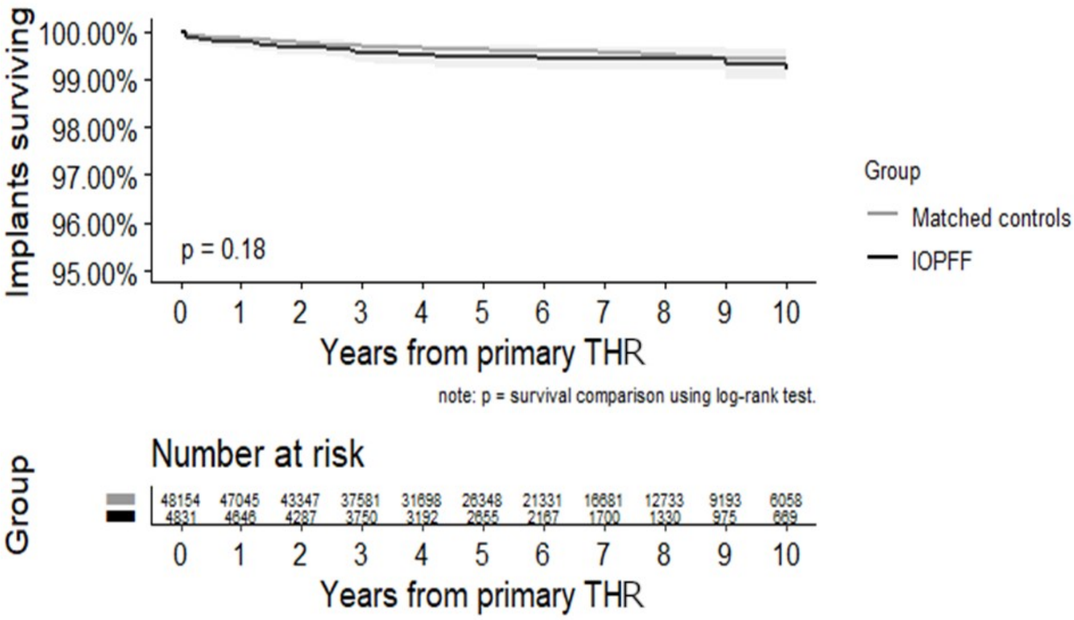
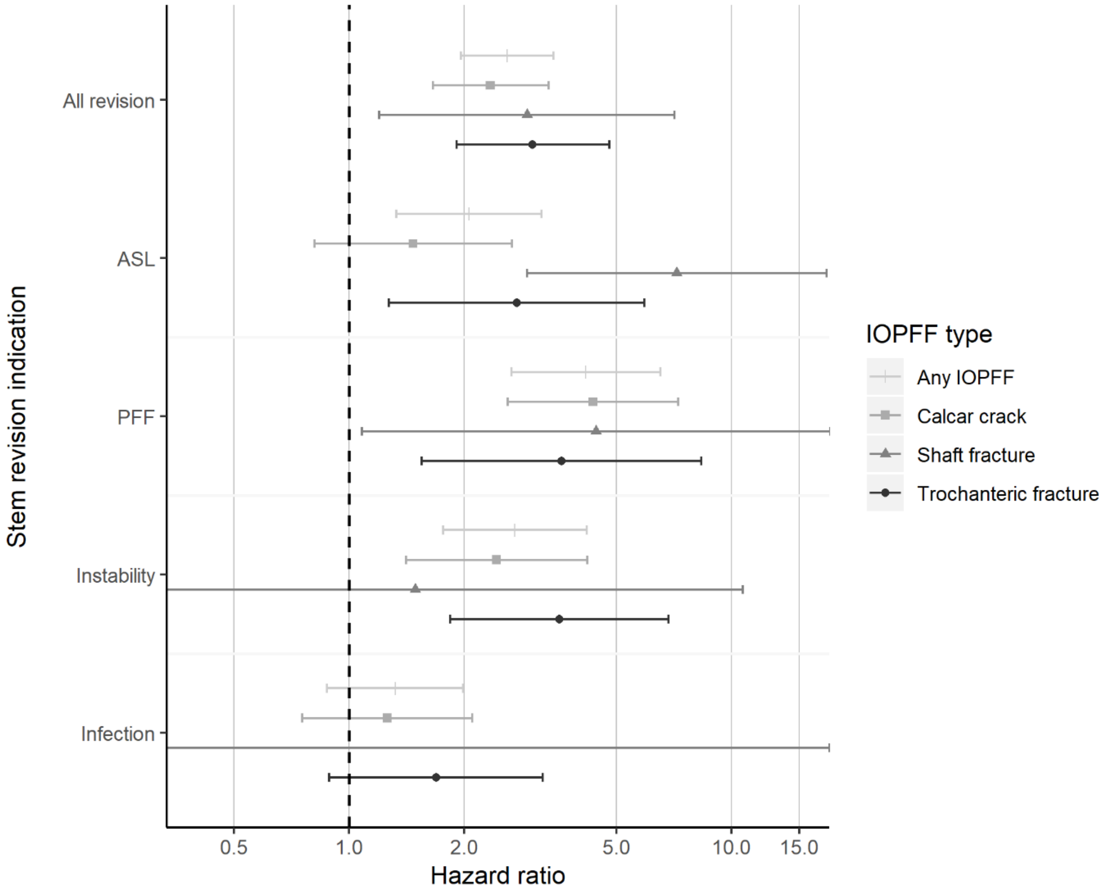


Figure 3-5 Femoral implant survival to revision for infection following THR with IOPFF versus matched controls over 10 years.



Note: Hazard ratio vs control group displayed with 95% confidence intervals on a logarithmic scale. PFF = Periprosthetic fracture of the femur. ASL = Aseptic loosening of the femoral stem.Hazard ratio is IOPFF vs no IOPFF in the first six months apart from ASL, where hazard ratio represents increased risk over the first five years and infection, where hazard is estimated over the course of ten years

Figure 3-6 Hazard ratios for different indications of stem revision for each IOPFF type versus matched controls.

3.1.3.2 Influence of IOPFF on patient survival

Unadjusted six-month patient mortality was 1.7% for patients with IOPFF and 0.9% for patients without IOPFF. Unadjusted ten-year patient mortality was also significantly worse in the IOPFF group compared to controls (29.9% [CI 27.0 – 30.8] versus 25.7% [CI 25.1 – 26.3], p<0.001). The survival difference between IOPFF and controls became apparent within the first six months and very slowly increased up to ten years (Figure 3-7).

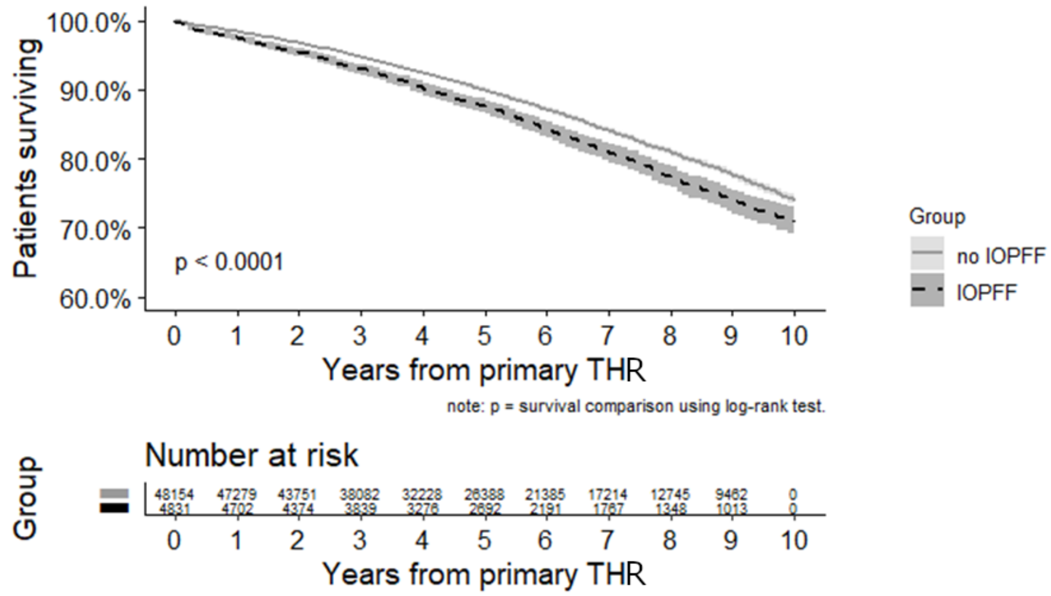


Figure 3-7 Patient survival to death following THR with IOPFF versus matched controls over 10 years.

Estimated hazard of mortality during first six months post-operatively associated with IOPFF versus no IOPFF was 1.8 (CI 1.4 – 2.2, p<0.001). The adjusted HR of death within 90 days for patients with IOPFF who did not go onto revision versus patients with no IOPFF or revision surgery was 1.7 (CI 1.3 – 2.2, p<0.001). The adjusted risk of death within 90 days for patients with IOPFF who went onto revision within 90 days versus patients with no IOPFF and no revision surgery was 4.0 (CI 1.5 – 10.5, p <0.001).

3.1.4 Discussion

Patients with IOPFF incur a higher risk of revision compared to those without IOPFF and the risk of revision is related to the specific IOPFF subtype. Patients with IOPFF have almost double the risk of death at six months, compared to those without IOPFF. Patients who require early revision following IOPFF have a four-fold risk of dying within 90 days.

3.1.4.1 IOPFF and stem survival

Stem survival was worse for all possible revision end points except for revision for infection following IOPFF compared to matched controls. The risk of all revision was 2.6 times the risk of controls for all cause stem revision, which is similar to other studies (Thillemann et al., 2008). IOPFF increased the risk of early revision for all causes and specifically for POPFF, aseptic loosening and instability.

IOPFF have previously been linked to increased risk of revision for periprosthetic fracture (Abdel et al., 2016b; Thillemann et al., 2008). In this study, IOPFF led to significantly worse ten-year implant survival and a greater than 3.5-fold increase in the risk of POPFF revision within the first six months. The greatest risk was following shaft fracture and calcar crack, which both increased the risk of POPFF revision within six months by over four-fold in comparison to matched controls. This demonstrates a clear and strong association between the occurrence of IOPFF and subsequent POPFF revision. Early POPFF revision following known IOPFF may be the result of fixation failure with fracture propagation due to either physiological loading or a new injury. It has previously been suggested that a calcar crack is an innocuous injury when treated appropriately (Berend, M.E. et al., 2006; Schwartz et al., 1989). The true extent of calcar cracks can be difficult to fully identify during primary surgery, which may lead to inappropriate internal fixation. This may be due to reluctance to expose the proximal femur fully and difficulty identifying fractures on intraoperative radiographs. Intraoperative radiographs can be misleading because there is no fracture separation when the implant is removed, and the fracture is difficult to assess when a rasp or implant remains implanted. Use of radiolucent stem replicas intraoperatively may make the full extent of calcar fractures more obvious on intraoperative radiographs. Whilst it is not possible to determine whether IOPFF were appropriately treated with this dataset, it is clear that despite the treatment given to patients included in the NJR, the risk of subsequent POPFF is significantly raised and efforts to prevent POPFF should go hand in hand with efforts to reduce the risk of IOPFF.

Thillemann found that the risk of unspecified IOPFF which underwent intraoperative fixation had a seven-fold relative risk of revision for instability during the initial six-month period (Thillemann et al., 2008). These results demonstrate that the relative risk of revision for instability was four-fold higher with IOPFF. The risk was highest following trochanteric and calcar fractures. Trochanteric fractures can lead to reduced function of the hip muscles, stem subsidence and loss of stem version (Reddy et al., 2017). Calcar fractures may compromise the primary stability during surgery leading to stem subsidence over time which may slacken periarticular structures and lead to instability (Rudiger et al., 2013; Lerch et al., 2007).

IOPFF was associated with a significantly worse 10-year ASL revision rate. Unsurprisingly, shaft fracture increased the risk of ASL revision seven-fold, probably because of the reduced ability of the surgeon to generate adequate fracture stability to withstand large hoop stresses generated by cementless and cemented implants, loss of stability may lead to failure of osseointegration in cementless implants and loss of mantle integrity around cemented implants. Current guidance advocates the use of a distally fixed stem when adequate proximal fixation is not achieved (Tsiridis et al., 2009). It was not possible from this study to ascertain whether such guidance had been implemented. Interestingly calcar cracks did not lead to a significantly increased risk of five-year ASL revision. This suggests that calcar cracks which are not revised for other causes do not lead to implant loosening. It may be that cases with calcar cracks are more likely to be revised for POPFF revision within the first few months rather than ASL later. Trochanteric IOPFF were associated with an almost three-fold increase in risk of five-year ASL revision. Hip muscle dysfunction may increase the resultant peak contact forces and joint reaction force measured in implanted femoral stems

(Bergmann et al., 2001), increasing the stress on the implant-bone interface and the likelihood of failure. Trochanteric fractures may also reduce proximal stability if the trochanteric fracture fragment includes a part of the distal metaphysis which may normally stabilise the upper stem body.

This study did not show any difference in rates of revision for infection between patients sustaining an IOPFF and matched controls. This is surprising given the expected increase in operating time that might be expected following an IOPFF, which has previously been linked to an increased risk of infection (Wang et al., 2019). A failure to demonstrate any difference in rates of infections between groups may be due to a lack of adequate controls in this observational study which prevent matching on other important factors which influenced the risk of infection such as antibiotic prophylaxis.

3.1.4.2 Patient survival following IOPFF

Patient survival in the IOPFF group was significantly worse up to 10-years after primary surgery. The difference in survival was evident within the first six months post-operatively, where the risk of dying increased almost two-fold for any IOPFF when adjusting for all other available factors (Hunt et al., 2013). When modelling the interaction of IOPFF and subsequent revision surgery within six months, patients with IOPFF and no stem revision surgery had double the risk of dying versus those without IOPFF or revision surgery. This demonstrates that part of the excess mortality may come from the IOPFF as a result of increased blood loss, prolonged surgery, reduced mobility and longer hospital stay. Part of the excess mortality in the IOPFF group may be due to increased revision burden since patients who had IOPFF and subsequent stem revision had a four-fold increased risk of dying versus no IOPFF or revision in the first six months.

3.1.4.3 Limitations

Whilst registry data is crucial to the investigation of outcomes following uncommon complications the results show association between recorded variables and observed outcomes and do not necessarily represent causation. Confirmation of causation should be sought using the breadth of good clinical research findings. THR is very successful and further advances are likely to take the form of small incremental changes. Despite this, large numbers included in this study increased statistical power and may have led to results which are statistically significant but do not reach a level of clinical significance and as such should be viewed within the overall clinical context by experienced clinicians. The NJR records self-reported intraoperative fractures and the results are subject to reporting bias, such that fractures not evident to the surgeon or not reported by the surgeon may be missed. The latter may have the effect of increasing the severity of fractures in the IOPFF group if there was a tendency to only report the worst fractures and increasing the likelihood that a small number of fractures were included in the control group. It was not possible to determine the cause of death, and as a result it is not possible to ascribe the increased risk of death to the IOPFF or subsequent revision, even though the link between revision surgery and excess mortality has previously been established (Jones, M.D. et al., 2018). It was not possible to review radiographs to establish fracture patterns, and treatment modalities. It was assumed that the treatments given to hips in this study represented normal practice, but the analysis could not control for the effect of surgeon treatment choice on outcomes following IOPFF. These data do however represent ‘average’ results for the ‘average’ surgeon. Propensity score matching achieved excellent balance between groups but may not have controlled for unobserved characteristics which were important for both stem and patient survival. This analysis was unable to adjust for all the relevant factors which determine post-operative mortality and implant failure since our data did not include radiographic or detailed co-morbidity information and as a result the analysis was likely to be subject to errors due to confounding factors. This study did not evaluate the risk of mortality associated with specific anatomical subtypes of IOPFF and this should be evaluated in future studies. In addition, a small proportion of patients will experience implant failure without undergoing revision surgery (for example, conservative treatment or fixation of periprosthetic fracture) and as such will not be recorded in the NJR. This approach might be improved with data linkage to hospital and primary care records. It is likely that linkage to patient reported outcome measures would further illuminate the true effect of IOPFF on patient outcomes.

3.1.4.4 Conclusions

This study has demonstrated that IOPFF is associated with an increased risk of stem revision in general, stem revision for POPFF, ASL, and instability, and patient mortality following primary THR. The risk of revision was dependent on IOPFF subtype, and the effect of IOPFF subtype was unique to each mode of failure. The risk of subsequent POPFF was greatest when the IOPFF occurred in the shaft followed by calcar then trochanter. The increased risk of POPFF was over four-fold following any type of IOPFF demonstrating that IOPFF is a significant risk factor for subsequent POPFF.

This study has also shown that patients with IOPFF have a higher risk of mortality than those without IOPFF, and this effect appears to be comprised of both an independent risk of IOPFF to the patient and the subsequent risk of revision surgery. Whilst the absolute risk of death is still low, surgeons should make every effort to reduce the risk of IOPFF during primary THR through careful selection of implants and methods. Vigilant identification and treatment of IOPFF is recommended to prevent implant failure and reduce associated excess patient mortality. When IOPFF does occur patients should be counselled regarding the increased risk of implant failure, revision operations and mortality.

This study clearly confirms that IOPFF is strongly associated with risk of early POPFF. It is reasonable to assume that prevention of IOPFF is a useful approach to reduce the risk of a proportion of POPFF following primary THR. This approach may also have the added benefit of reducing associated risks of revision for ASL and instability and the associated increased risk of mortality.

3.2 Risk factors for intraoperative periprosthetic femoral fractures during primary total hip replacement.

3.2.1 Introduction

IOPFF can occur in the trochanteric region, calcar or femoral diaphysis (Masri et al., 2004). In section 3.1 of this chapter a strong relationship between the risk of IOPFF and the subsequent risk of early POPFF revision has been demonstrated. The overall associated increased risk is over four-fold. The risk of POPFF was greatest following shaft fractures, then calcar cracks, followed by trochanteric fractures. It is reasonable therefore to suggest that any strategy to prevent POPFF should include elements to prevent the risk of IOPFF. This may have the direct benefit of reduction of subsequent POPFF risk but also the indirect benefit of reduction in other associated revision risks and risk of mortality.

Prevention of IOPFF by adjusting methods to suit the risk profile of the patient is an obvious means to reduce risk of future POPFF, patient harm and further improve stem survival. Non-modifiable risk factors include female sex, increasing age, poor bone quality and abnormal proximal femur morphology (Abdel et al., 2016b; Nowak et al., 2012; Ricioli et al., 2015; Miettinen et al., 2016; Davidson et al., 2008). Established modifiable risk factors include cementless stem fixation and surgical approach (direct anterior and Hardinge) (Berend, M.E. et al., 2006; Hendel et al., 2002; Hartford et al., 2018). IOPFF is relatively uncommon and previous studies have lacked the size and power to accurately identify other relevant predictors for IOPFF as a whole and for all anatomical subtypes. A deeper understanding of how risk factors relate to the specific anatomical subtype will help to develop an understanding of the mechanism by which the increased risk occurs and thus how it can be reduced by future development of approaches, surgical techniques and implants. An understanding of specific risk factors for shaft and calcar fractures may allow for focused adaption of techniques which may be most beneficial in the reduction of POPFF incidence.

The aim of this study was to identify the risk factors for all IOPFF, and for each anatomical subtype in the NJR.

3.2.2 Methods

3.2.2.1 Database

The NJR dataset was identical to that used in described in section 3.1.2.

3.2.2.2 Participants

793 977 THRs were eligible for analysis. Exclusions were; cases from the Isle of Man (low numbers, n= 153). The resulting subset of data included 793 823 primary THR. Institutional ethical approval was granted, and the manuscript was approved by the NJR.

3.2.2.3 Variables

All variables relating to patient age (years), gender, ASA group (1-2 versus 3-5), year of surgery, side of operation, surgical approach, CGS, minimally invasive surgery, surgeon grade (consultant versus non-consultant), hospital type, indication (osteoarthritis [OA], trauma including fractured neck of femur [NOF], avascular necrosis [AVN], inflammatory arthritis, previous trauma, paediatric hip disease [congenital dysplasia of the hip, Perthes, skeletal dysplasia, slipped upper femoral epiphysis], malignancy, previous arthrodesis, previous infection and other) and stem fixation type (cemented versus cementless) were included. Year of implantation was used to estimate change in incidence of IOPFF with each subsequent year in the registry dataset (cohort effect).

3.2.2.4 Outcome

The study outcome was the occurrence of any IOPFF. Reported untoward intraoperative events in the NJR include: ‘calcar crack’, ‘shaft fracture’, ‘shaft penetration’, ‘trochanteric fracture’ and ‘other’. IOPFF was included as either ‘calcar crack’, ‘shaft fracture’, ‘shaft penetration’, ‘trochanteric fracture’ and text describing IOPFF in the free text `other`. Cases were grouped as calcar, trochanter or shaft fractures (shaft fracture and penetration). Shaft penetration was subsequently dropped because none were recorded.

3.2.2.5 Statistical analysis

Analysis was conducted in two parts: firstly, incidence and risk factors for any IOPFF and secondly incidence and risk factors for each IOPFF subtype. Univariate comparisons of continuous variables were performed with unpaired t-tests, and comparisons of categorical variables were performed with chi-square tests. Multiple comparison of continuous variables was performed with one-way ANOVA. Since the dataset was large and multiple comparisons were made, a significance level of $p < 0.01$ was chosen. A binary multivariable logistic regression model (using log-link) estimated the relative risk (RR) of IOPFF and 95% CI for each variable compared to normal practice where applicable. The model includes all variables and estimates the individual effect of each variable whilst adjusting for the effects of others and CI’s are given to reflect uncertainty of these estimates. In the second part of the analysis, modelling was repeated for fractures of the calcar, shaft and trochanter separately. All analyses were performed using R (v3.5.1, R, Vienna, Austria (R Core Team, 2018)). Models were assessed using the concordance statistic (C-statistic). The concordance statistic was used because it best describes the accuracy of predicted observations. Age was determined to be non-linear through fitting of higher order terms, for clarity age was categorised into five groups (<50, 50<60, 60<70, 70<80, 80+ years). Since the dataset was large, further analysis of interaction terms was performed to gain a deeper understanding of the effect of multiple covariates on the incidence of IOPFF. Interactions were selected *a priori* (Appendix A) and tested by the addition of a single interaction term to the original multivariable models for all IOPFF and each anatomical subtype in turn. The addition of interaction terms was performed in a single step and repeated for each term. Age was included as a continuous variable to increase accuracy of modelling. The interaction term results were assessed visually if the interaction term reached statistical significance.

To estimate the overall relative effect of changing all significant modifiable risk factors, comparisons were modelled to calculate the RR (95% CI) of best versus worst practice. The average risk ratio of IOPFF was calculated comparing typical OA hip patients (female, between 60 and 70 years, ASA one or 2) undergoing THR with the worst and best selection of modifiable risk factors.

3.2.3 Results

3.2.3.1 Part one: All IOPFF

Mean age (SD) of patients in the IOPFF group was statistically different to those without IOPFF (68.3 (12.7) years versus 69.2 (11.0) years) ($p<0.001$) although not clinically significant. IOPFF occurred more commonly in younger (<50) and older (>80) patients. There were a greater proportion of female patients with IOPFF than those without (73.7% versus 61.2%) ($p<0.001$). A greater proportion of patients with IOPFF had a non-OA diagnosis ($p<0.001$) (Table 3-2).

Table 3-2 Summary of cases with and without IOPFF

Variable	*Level*	**No IOPFF** n =788886	**IOPFF** n =4938	p
Side	*Left*	355795 (45.10%)	2318 (46.94%)	0.01
	Right	433091 (54.90%)	2620 (53.06%)	
Age group	*11 < 50*	39044 (4.95%)	401 (8.12%)	<0.001
	50 <60	97113 (12.31%)	693 (14.03%)	
	60 <70	235370 (29.84%)	1346 (27.26%)	
	70 <80	283522 (35.94%)	1567 (31.73%)	
	80 <117	133836 (16.97%)	931 (18.85%)	
Patient gender	*Male*	306259 (38.82%)	1294 (26.20%)	<0.001
	Female	482627 (61.18%)	3644 (73.80%)	
ASA group	*1 & 2*	663280 (84.08%)	3857 (78.11%)	<0.001
	3 - 5	125606 (15.92%)	1081 (21.89%)	
Indication	*Acute trauma including NOF*	22003 (2.79%)	148 (3.00%)	<0.001
	AVN	10476 (1.33%)	123 (2.49%)	
	Previous trauma	7116 (0.90%)	174 (3.52%)	
	Inflammatory arthritis	8559 (1.08%)	102 (2.07%)	
	Malignancy	324 (0.04%)	3 (0.06%)	
	Osteoarthritis	728590 (92.36%)	4194 (84.93%)	
	Other	5841 (0.74%)	68 (1.38%)	
	Paediatric disease	5301 (0.67%)	111 (2.25%)	
	Previous arthrodesis	242 (0.03%)	2 (0.04%)	
	Previous infection	434 (0.06%)	13 (0.26%)	
Stem fixation	*Cemented*	444465 (56.34%)	1901 (38.50%)	<0.001
	Cementless	344421 (43.66%)	3037 (61.50%)	
Lead surgeon grade	*Consultant*	651975 (82.65%)	4077 (82.56%)	0.895
	Non consultant	136911 (17.35%)	861 (17.44%)	
Organisation type	*NHS*	538646 (68.28%)	3813 (77.22%)	<0.001
	Independent Hospital	217267 (27.54%)	999 (20.23%)	
	Treatment centre	32973 (4.18%)	126 (2.55%)	
Approach	*Posterior*	454410 (57.60%)	2721 (55.10%)	0.002
	Anterolateral	297414 (37.70%)	1967 (39.83%)	
	Trochanteric Osteotomy	3017 (0.38%)	14 (0.28%)	
	Other	34045 (4.32%)	236 (4.78%)	
Minimally invasive surgery	*No*	734072 (93.05%)	4595 (93.05%)	1.000
	Yes	54814 (6.95%)	343 (6.95%)	
Computer guided surgery	*No*	767300 (97.26%)	4857 (98.36%)	<0.001
	Yes	21586 (2.74%)	81 (1.64%)	

Note: Results are numbers (% of column group). ASA American Society of Anaesthesiologists grade, NHS National Health Service (England and Wales), NOF Neck of femur fracture, AVN Avascular necrosis. ins denotes insufficient numbers for analysis.

3.2.3.2 Risk factors for IOPFF

Adjusted relative risk of IOPFF almost doubled in females (RR 1.91 [CI 1.79-2.03]) (

Table 3-3). Risk of IOPFF increased significantly in the younger (age <50, RR 1.21 [CI 1.08-1.37]) and older patients (>80, RR 1.23 [CI 1.14-1.34]) versus patients between 70 and 80 years (p<0.01, Figure 3-8). Risk of IOPFF was 1.08 in left sided THR (CI 1.02-1.14) (p<0.01). Risk of IOPFF increased with worse ASA group (3-5) (RR 1.45 [CI 1.35-1.55]). All non-OA indications significantly increased the risk of IOPFF apart from acute trauma and malignancy. Surgical predictors increasing the risk of IOPFF included cementless femoral implants (RR 2.40 [CI 2.26-2.55]) and anterolateral approach (RR 1.09 [CI 1.03-1.16]). Risk of IOPFF was significantly reduced when THR was performed in a non-NHS hospital or when CGS was used (RR 0.51 [CI 0.41-0.65]) (p<0.01).

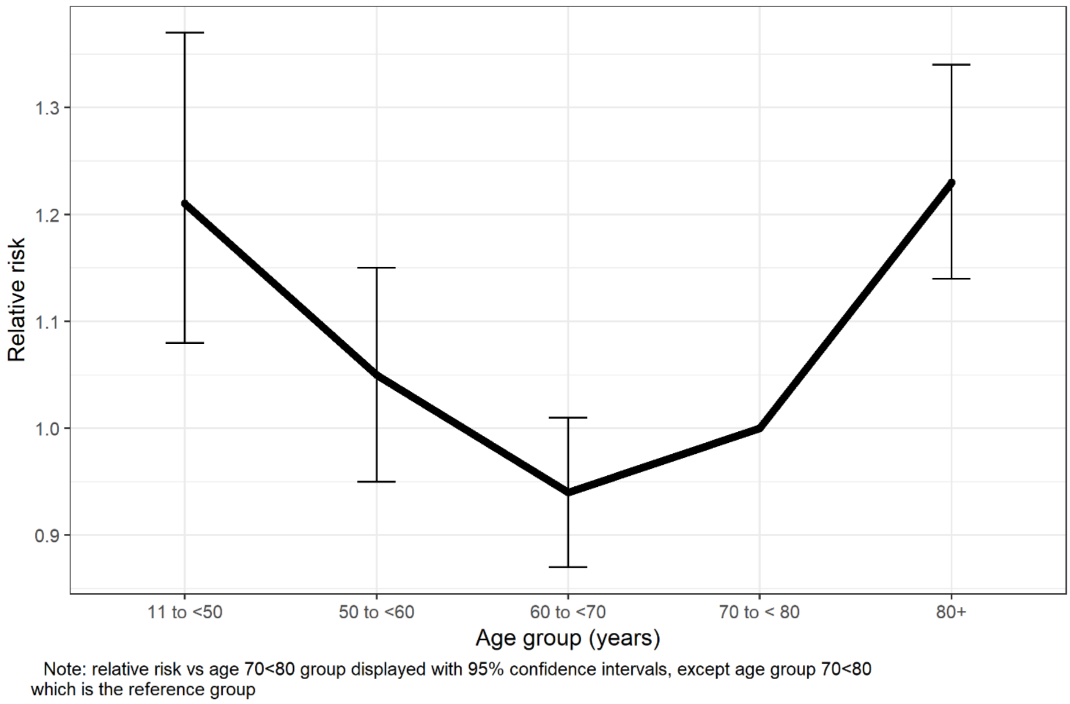


Figure 3-8 Adjusted relative risk of IOPFF in different age groups. Relative risk was adjusted for all model covariates.

Table 3-3 Predictors of any IOPFF during primary total hip arthroplasty

Variable	***Level***	**Relative risk** (95% CI)
Side	*Right*	reference
	Left	1.08 (1.02 - 1.14)*
Gender	*Male*	reference
	Female	1.91 (1.79 - 2.03)*
Age	*11 < 50*	1.21 (1.08 - 1.37)*
	50 < 60	1.05 (0.95 - 1.15)
	60 < 70	0.94 (0.87 - 1.01)
	70 < 80	reference
	80 < 117	1.23 (1.14 - 1.34)*
ASA grade	*ASA 1-2*	reference
	ASA 3-5	1.45 (1.35 - 1.55)*
Indication for surgery	*Osteoarthritis*	reference
	Acute trauma including NOF	1.13 (0.96 - 1.34)
	AVN	1.81 (1.51 - 2.17)*
	Previous trauma	3.80 (3.27 - 4.42)*
	Inflammatory arthritis	1.75 (1.44 - 2.13)*
	Malignancy	2.01 (0.65 - 6.22)
	Other	1.85 (1.45 - 2.35)*
	Paediatric disease	2.78 (2.28 - 3.38)*
	Previous arthrodesis	1.25 (0.31 - 4.96)
	Previous infection	4.92 (2.88 - 8.40)*
Stem fixation	*Cemented*	reference
	Cementless	2.40 (2.26 - 2.55)*
Grade of surgeon	*Consultant*	reference
	Non consultant	0.96 (0.89 - 1.04)
Organisation type	*NHS*	reference
	Independent hospital	0.68 (0.63 - 0.73)*
	Treatment centre	0.58 (0.49 - 0.70)*
Surgical approach	*Posterior*	reference
	Anterolateral	1.09 (1.03 - 1.16)*
	Trochanteric Osteotomy	0.97 (0.57 - 1.63)
	Other	1.08 (0.94 - 1.23)
Surgical technique	*Minimally invasive surgery*	0.98 (0.87 - 1.10)
	Computer guided surgery	0.51 (0.41 - 0.65)*
Cohort affect	*Subsequent year of primary surgery*	0.97 (0.96 - 0.97)*
Observations		793,823
C statistic		0.68

Note: Results are relative risks (95% CI). *ASA* American Society of Anesthesiologists *grade, NHS* National Health Service (England and Wales), *NOF* Neck of femur fracture, *AVN* Avascular necrosis.*p<0.01

3.2.3.3 Part two: IOPFF subtypes

Fractures affecting the calcar were most common (n = 3080) (Table 3-4). Calcar cracks occurred more frequently in patients <60 when compared to other fracture types. A smaller proportion of patients with shaft fractures were female when compared to calcar and trochanteric fractures (69.9% versus 72.7% and 77.0%) (p=0.002). Cementless implants were used more commonly in calcar fractures than shaft or trochanteric fractures (73.0% versus 53.7% and 39.8% respectively) (p<0.001).

Table 3-4 Summary of patients with IOPFF fractures by subtype

Variable	*Level*	**Calcar crack** n=3080	**Shaft fracture** n=352	**Trochanteric fracture** n=1506	p overall
Side	*Right*	1636 (53.12%)	185 (52.56%)	799 (53.05%)	0.980
Age group	*11 <50*	330 (10.71%)	28 (7.95%)	43 (2.86%)	<0.001
	50 <60	511 (16.59%)	30 (8.52%)	152 (10.09%)	
	60 <70	899 (29.19%)	82 (23.30%)	365 (24.24%)	
	70 <80	906 (29.42%)	106 (30.11%)	555 (36.85%)	
	80 <117	434 (14.09%)	106 (30.11%)	391 (25.96%)	
Patient gender	*Female*	2238 (72.66%)	246 (69.89%)	1160 (77.03%)	0.002
ASA group	*1 & 2*	2534 (82.27%)	251 (71.31%)	1072 (71.18%)	<0.001
	3 - 5	546 (17.73%)	101 (28.69%)	434 (28.82%)	
Indication	*Osteoarthritis*	2630 (85.39%)	280 (79.55%)	1284 (85.26%)	0.001
	Acute trauma including NOF	86 (2.79%)	11 (3.12%)	51 (3.39%)	
	AVN	84 (2.73%)	6 (1.70%)	33 (2.19%)	
	Previous trauma	92 (2.99%)	30 (8.52%)	52 (3.45%)	
	Inflammatory arthritis	54 (1.75%)	8 (2.27%)	40 (2.66%)	
	Malignancy	1 (0.03%)	0 (0.00%)	2 (0.13%)	
	Other	43 (1.40%)	7 (1.99%)	18 (1.20%)	
	Paediatric disease	80 (2.60%)	8 (2.27%)	23 (1.53%)	
	Previous arthrodesis	1 (0.03%)	0 (0.00%)	1 (0.07%)	
	Previous infection	9 (0.29%)	2 (0.57%)	2 (0.13%)	
Stem fixation	*Cemented*	831 (26.98%)	163 (46.31%)	907 (60.23%)	<0.001
	Cementless	2249 (73.02%)	189 (53.69%)	599 (39.77%)	
Lead surgeon grade	*Consultant*	2601 (84.45%)	294 (83.52%)	1182 (78.49%)	<0.001
	Non consultant	479 (15.55%)	58 (16.48%)	324 (21.51%)	
Organisation type	*NHS*	2278 (73.96%)	262 (74.43%)	1273 (84.53%)	<0.001
	Independent hospital	713 (23.15%)	80 (22.73%)	206 (13.68%)	
	Treatment centre	89 (2.89%)	10 (2.84%)	27 (1.79%)	
Approach	*Posterior*	1839 (59.71%)	160 (45.45%)	722 (47.94%)	<0.001
	Anterolateral	1109 (36.01%)	164 (46.59%)	694 (46.08%)	
	Trochanteric Osteotomy	8 (0.26%)	2 (0.57%)	4 (0.27%)	
	Other	124 (4.03%)	26 (7.39%)	86 (5.71%)	
Minimally invasive surgery		244 (7.92%)	20 (5.68%)	79 (5.25%)	0.002
Computer guided surgery		54 (1.75%)	5 (1.42%)	22 (1.46%)	0.723

Note: Results are numbers (% of column group). ASA is American Society of Anaesthesiologists grade, NHS is National Health Service (England and Wales), NOF is Neck of femur fracture, and AVN is Avascular necrosis.

3.2.3.4 Risk factors for IOPFF by fracture subtype

Patient factors increasing the risk of IOPFF in all fracture subtypes were female gender and ASA grade three to five (Table 3-5). Relationship between age and risk of IOPFF varied by fracture subtype (Figure 3-9). Risk of calcar crack significantly increased in the youngest age groups (50<60 [RR 1.18 (1.05-1.31)], <50 [RR 1.52 (CI 1.33-1.75)] $p<0.01$). Risk of shaft fracture increased significantly in patients over 80 (RR 1.93 [CI 1.47-2.54] $p<0.01$). Risk of trochanteric fracture increased steadily with age. Indications for THR which increase IOPFF risk for all fracture locations included previous trauma and paediatric disease. Risk of calcar crack also increased for surgical indications including AVN, inflammatory disease, previous infection and ‘other’. Risk of shaft fracture increased for surgical indications including previous infection and ‘other’. Risk of trochanteric fracture increased for surgical indication of AVN and inflammatory hip disease.

Table 3-5 Predictors of IOPFF subtypes during primary total hip replacement

Variable	*Level*	Calcar cracks	Shaft fractures	Trochanteric fractures
			Relative risk (95% CI)	
Side	*Right*	Reference		
	Left	1.07 (1.00 - 1.15)	1.09 (0.88 - 1.34)	1.10 (0.99 - 1.22)
Gender	*Male*	Reference		
	Female	1.91 (1.76 - 2.06)*	1.46 (1.16 - 1.84)*	2.06 (1.82 - 2.32)*
Age	*11 < 50*	1.52 (1.33 - 1.75)*	1.30 (0.82 - 2.05)	0.46 (0.33 - 0.64)*
	50 < 60	1.18 (1.05 - 1.31)*	0.71 (0.47 - 1.07)	0.83 (0.69 - 0.99)
	60 < 70	1.00 (0.91 - 1.09)	0.88 (0.66 - 1.18)	0.84 (0.73 - 0.96)
	70 < 80	Reference		
	80 < 117	1.09 (0.97 - 1.22)	1.93 (1.47 - 2.54)*	1.29 (1.13 - 1.47)*
ASA grade	*1 & 2*	Reference		
	3 to 5	1.27 (1.16 - 1.40)*	1.79 (1.40 - 2.29)*	1.69 (1.50 - 1.90)*
Indication	*Osteoarthritis*	Reference		
	Acute trauma including NOF	1.25 (1.00 - 1.55)	1.26 (0.68 - 2.32)	0.95 (0.72 - 1.26)
	AVN	1.85 (1.48 - 2.31)*	1.35 (0.60 - 3.08)	1.89 (1.33 - 2.68)*
	Previous trauma	3.63 (2.95 - 4.46)*	9.01 (6.14 - 13.24)*	3.09 (2.34 - 4.08)*
	Inflammatory arthritis	1.47 (1.13 - 1.93)*	2.21 (1.09 - 4.50)	2.30 (1.68 - 3.16)*
	Malignancy	1.42 (0.20 - 10.05)	*ins*	2.97 (0.74 - 11.90)
	Other	1.87 (1.38 - 2.53)*	2.82 (1.32 - 6.00)*	1.61 (1.01 - 2.56)
	Paediatric disease	2.58 (2.04 - 3.25)*	3.75 (1.76 - 7.95)*	3.58 (2.32 - 5.53)*
	Previous arthrodesis	0.94 (0.13 - 6.62)	*ins*	2.24 (0.32 - 15.84)
	Previous infection	5.27 (2.76 - 10.05)*	12.00 (2.97 - 48.58)*	2.87 (0.72 - 11.48)
Stem fixation	*Cemented*	Reference		
	Cementless	3.76 (3.46 - 4.09)*	2.05 (1.64 - 2.56)*	1.13 (1.02 - 1.26)
Grade of surgeon	*Consultant*	Reference		
	Non consultant	0.96 (0.86 - 1.06)	0.89 (0.67 - 1.20)	0.98 (0.86 - 1.11)
Organisation type	*NHS*	Reference		
	Independent hospital	0.77 (0.70 - 0.84)*	0.91 (0.70 - 1.19)	0.46 (0.40 - 0.54)*
	Treatment centre	0.63 (0.51 - 0.79)*	0.82 (0.43 - 1.55)	0.41 (0.28 - 0.60)*
Approach	*Posterior*	Reference		
	Anterolateral	0.94 (0.87 - 1.02)	1.54 (1.23 - 1.93)*	1.36 (1.22 - 1.51)*
	Trochanteric Osteotomy	1.03 (0.51 - 2.05)	2.03 (0.51 - 8.16)	0.77 (0.29 - 2.05)
	Other	0.83 (0.69 - 1.00)	2.06 (1.36 - 3.12)*	1.51 (1.21 - 1.89)*
Surgical technique	*Minimally invasive surgery*	1.01 (0.88 - 1.16)	0.82 (0.50 - 1.32)	0.92 (0.72 - 1.18)
	Computer guided surgery	0.53 (0.40 - 0.71)*	0.49 (0.19 - 1.25)	0.48 (0.31 - 0.76)*
Cohort affect	*Subsequent year of surgery*	0.96 (0.95 - 0.97)*	0.96 (0.93 - 0.99)	0.98 (0.97 - 1.00)
Observations		791965	788671	790391
C statistic		0.71	0.69	0.68

Note: Results are relative risks (95% CI). *ASA is* American Society of Anesthesiologists *grade, NHS is* National Health Service, *NOF is* Neck of femur fracture, *and AVN is* Avascular necrosis. *ins* denotes insufficient numbers for meaningful analysis and * is p<0.01

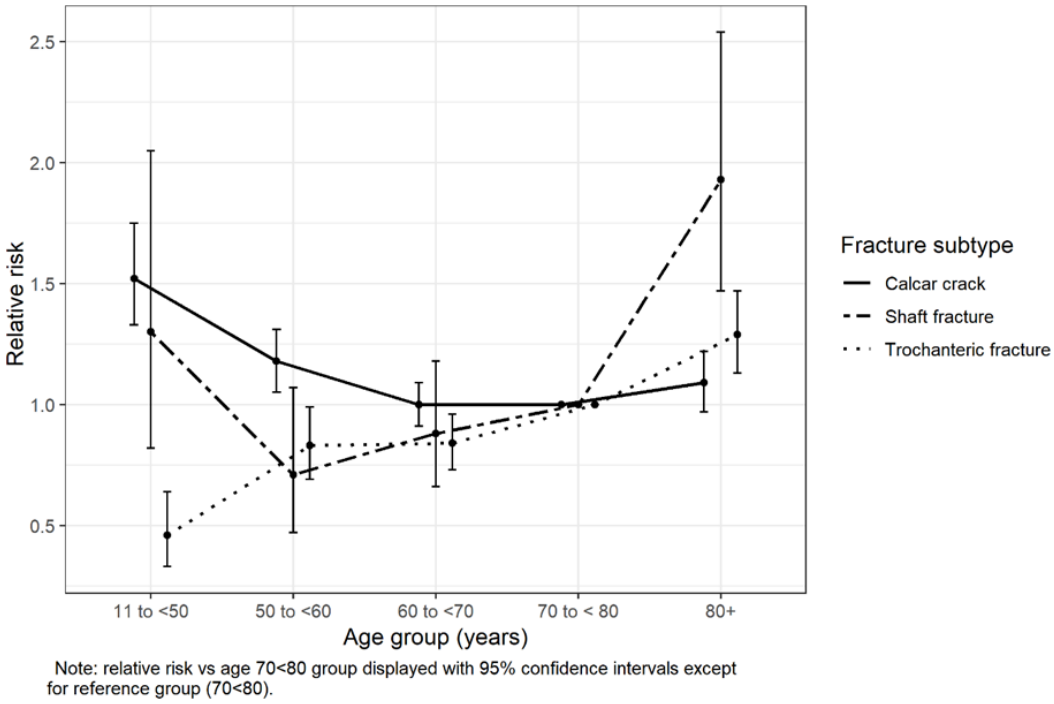


Figure 3-9 Adjusted relative risk of IOPFF for each age group stratified by anatomical subtype.

Cementless implants more than doubled the risk of calcar (RR 3.76 [CI 3.46 – 4.09], $p<0.01$) and shaft fracture subtypes (RR 2.05 [CI 1.64-2.56], $p<0.01$). Posterior approach and CGS significantly decreased the risk of shaft fractures and trochanteric fractures.

3.2.3.5 Interactions between risk factors

The predicted prevalence of any IOPFF increased with worsening ASA group but the effect of ASA was greatest when cementless stems were used in comparison to cemented stems (Figure 3-10). The predicted prevalence of IOPFF in patients with cementless stems was not age dependent and was greater than the prevalence predicted when using a cemented stem, although the risk of IOPFF with a cemented stem increased with age (Figure 3-10). Predicted prevalence of any IOPFF increased with age in patients with OA, whereas patients with a diagnosis of ‘acute trauma including NOF’ and ‘other’ were predicted to experience an inverse relationship, with higher prevalence of any IOPFF in younger age groups (Figure 3-10). The relationship between age and diagnosis remained consistent to the overall effect when patients underwent surgery for OA (Figure 3-10). Patients with a diagnosis of 'other' were predicted higher prevalence of any IOPFF when using cemented and cementless stems in younger age groups and the prevalence of any IOPFF decreased in older patients (Figure 3-10). The predicted prevalence of calcar crack increased in females versus males and in cementless versus cemented stem but the effect of cementless stems on risk of calcar crack was much larger for females than males (Figure 3-11). The predicted prevalence of calcar cracks increased in younger patients in those undergoing THR with cementless stems, whereas the predicted prevalence of calcar cracks with cemented stems was consistently low across the age range of patients in the study (Figure 3-11). The predicted prevalence of shaft fracture was much increased in older females, whereas the predicted prevalence of shaft fracture remained consistently low across all ages with cemented implants (Figure 3-11). The predicted prevalence of trochanteric fracture was higher in younger patients when THR was performed for acute trauma including NOF in comparison to THR performed for osteoarthritis (Figure 3-11). Predicted prevalence of trochanteric fracture was highest in consultants performing 'other' approaches compared to non-consultants using the same approach, whereas predicted prevalence of trochanteric fracture was roughly equivalent between lead surgeon grades using other approaches (Figure 3-11). The fixed effects of statistically significant interactions are given in Table 3-6.

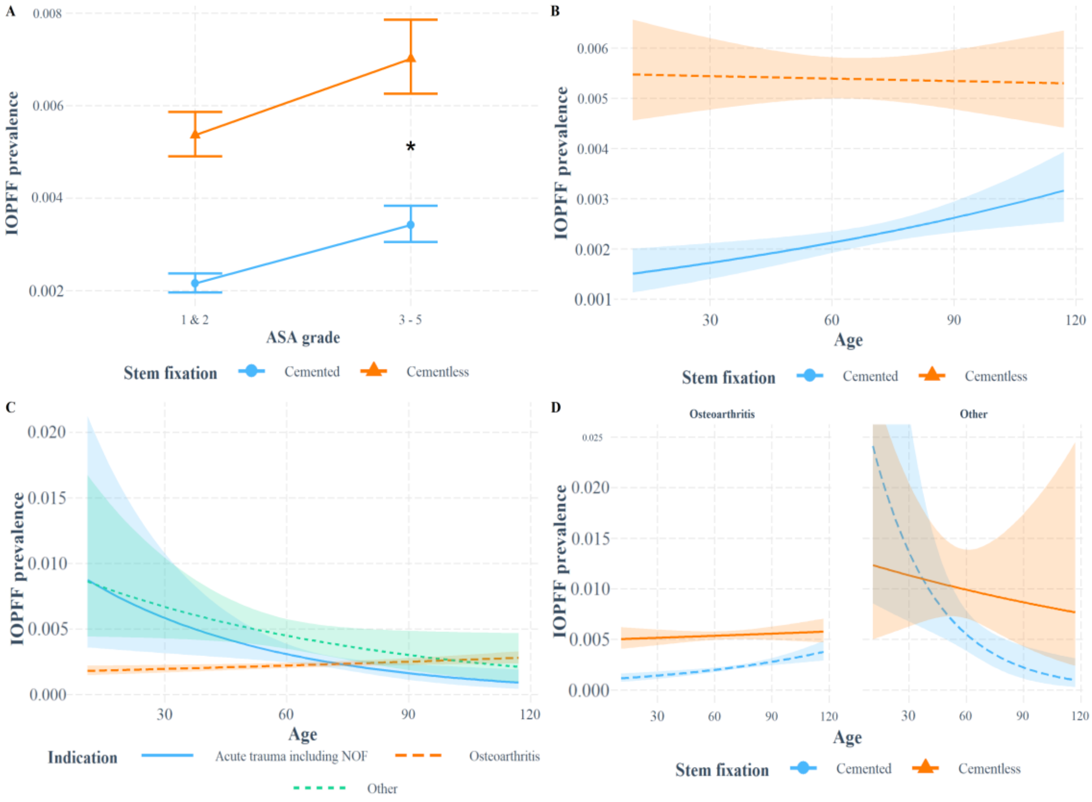


Figure 3-10 Statistically significant interaction terms which predict a change in predicted prevalence of IOPFF using a multivariate model. Note: `A` demonstrates the interaction of ASA grade and stem fixation on risk of IOPFF risk. `B` demonstrates the interaction of patient age and stem fixation on predicted prevalence of any IOPFF. `C` demonstrates the interaction of patient age and indication for primary surgery on predicted prevalence of any IOPFF. Only diagnoses which reached statistical significance and osteoarthritis (reference) are displayed. `D` demonstrates the interaction of patient age, indication for primary surgery and stem fixation on predicted prevalence of any IOPFF. Only diagnoses which reached statistical significance and osteoarthritis (reference) are displayed. * denotes the level of categorical variable at which the interaction reaches significance.

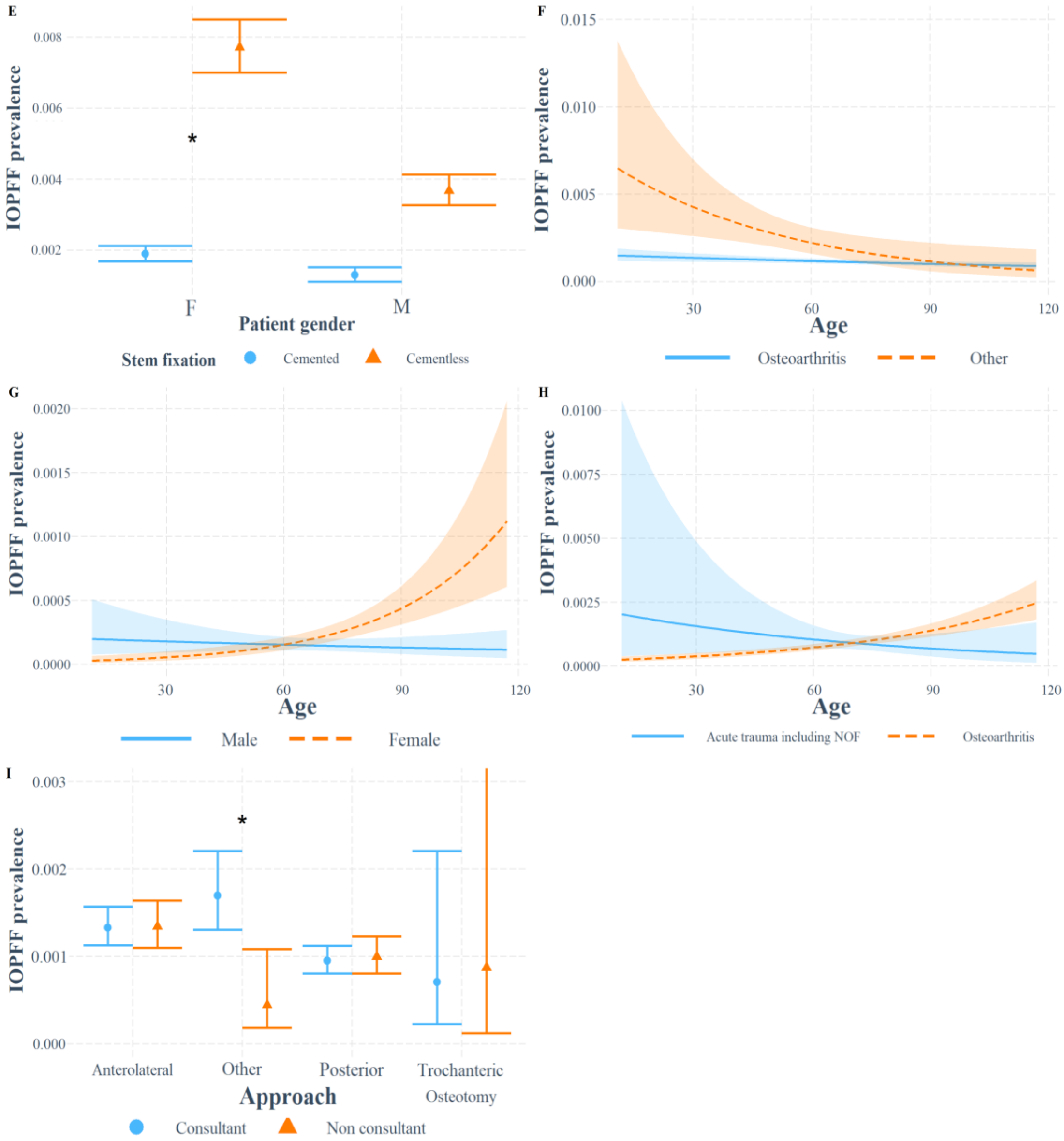


Figure 3-11 Statistically significant interaction terms which predict a change in predicted prevalence of IOPFF using a multivariate model. Note: `E` demonstrates the interaction of patient gender and stem fixation on predicted prevalence of calcar crack. `F` demonstrates the interaction of patient age and indication for surgery on predicted prevalence of calcar crack. Only diagnoses which reached statistical significance and osteoarthritis (reference) are displayed. `G` demonstrates the interaction of patient age and gender on predicted prevalence of shaft fracture. `H` demonstrates the interaction of patient age and indication for surgery on predicted prevalence of trochanteric fracture. `I` demonstrates the interaction of lead surgeon grade and surgical approach on predicted prevalence of trochanteric fracture. * denotes the level of categorical variable at which the interaction reaches significance.

Table 3-6 Fixed Effects of Statistically Significant Interaction Terms in Multivariate Model.

Outcome	Interaction	Interaction level	RR	p
Any IOPFF	ASA : Fixation	ASA grade 3 to 5 : Cementless stem	0.83	<0.01
Any IOPFF	Age : Fixation	Age increase of one year : Cementless stem	0.99	<0.01
Any IOPFF	Age : Indication	Age increase of one year : Acute trauma including NOF	0.96	<0.01
Any IOPFF	Age : Indication	Age increase of one year : Other	0.96	<0.01
Any IOPFF	Age : Indication : Fixation	Age increase of one year : Other: Cementless stem	0.08	<0.01
Calcar crack	Gender : Fixation	Female gender : Cementless stem	1.44	<0.01
Calcar crack	Age : Indication	Age increase of one year : Other	0.96	<0.01
Shaft fracture	Age : Gender	Age increase of one year : Female gender	1.04	<0.01
Trochanteric fracture	Age : Indication	Age increase of one year : Acute trauma including NOF	0.95	<0.01
Trochanteric fracture	lead surgeon : approach	Non-Consultant : Other	0.25	<0.01

Note: IOPFF indicates intraoperative periprosthetic femoral fracture, RR indicates relative risk associated with interaction term, p indicates the significance of the interaction term in the multivariable model indicated in IOPFF type, THR indicates total hip replacement, CGS indicates computer guided surgery, ASA indicated American society of anaesthesiologists and NOF indicates neck of femur fracture

3.2.3.6 Effects of combined predictors

Combined relative risk of calcar IOPPF was 7.72 (95% CI 5.65 to 10.50) when using the worst (cementless stem via 'other' or Anterolateral approach without CGS) versus the best (cemented stem via posterior approach with CGS) selection of modifiable risk factors when operating on a typical OA hip patient (Table 3-7) (p<0.01).

Table 3-7 Odds ratio of IOPFF in a typical OA patient undergoing THR using a selection of worst vs best modifiable risk factors.

Fracture type	OR	(95% CI)	p
All fractures	4.29	(3.34 - 5.51)	<0.001*
Calcar crack	7.72	(5.65 - 10.50)	<0.001*
Shaft fracture	2.93	(1.17 - 7.32)	0.02
Trochanteric	1.64	(1.02 - 2.64)	0.042

Note: Best scenario (Cemented stem, posterior approach and computer guided surgery), worst scenario (Cementless stem, Anterolateral or other approach without computer guided surgery. OR odds ratio, CI confidence interval, * p<0.01

3.2.4 Discussion

This paper outlines new risk factors for IOPFF which can be used to identify and protect patients undergoing THR. Risk of IOPFF is highest at extremes of age and not just the older patient population. In particular, the risk of calcar and shaft fractures increases in younger patients. Higher preoperative ASA grade is associated with increased risk of IOPFF. IOPFF risk did not rise in hip fracture but did increase in all other non-OA diagnoses. Cementless stem use is associated with increased risk of calcar and shaft fractures. Cementless stems appear to be an age *independent* risk factor for any IOPFF. Anterolateral and ‘other’ approaches can increase the risk of trochanteric and shaft fractures versus posterior approach. Computer guided surgery reduced risk of any IOPFF, and its effect appeared to affect all patients consistently. With judicious adjustment of modifiable risk factors, a potential seven-fold reduction in relative risk of IOPFF may be achieved.

3.2.4.1 Patient related risk factors for IOPFF

The risk of IOPFF approximately doubles in females (Abdel et al., 2016b; Miettinen et al., 2016; Ricioli et al., 2015; Ponzio et al., 2015). These results have shown an increasing predicted incidence of shaft fracture with increasing age in females, but no other interaction effect of age on gender in other anatomical subtypes. Female patients had a four-fold increased risk of fracture when cementless stems were used in comparison to cemented stems, whereas males experienced a doubling of fracture risk with cementless stems versus cemented stems. Gender differences and gender-age interactions may exist because females are affected by post-menopausal osteoporosis which reduces bone strength (Osterhoff et al., 2016). A similar risk of POPFF has been associated with females (Singh, J.A. et al., 2013; Meek et al., 2011; Gromov et al., 2017; Berend, M.E. et al., 2006; Lindberg-Larsen et al., 2017) and particularly with cementless stems (Thien et al., 2014). In addition to this it has been demonstrated that the proximal femur of female patients undergoing THR are smaller and disproportionately narrower in the anteroposterior direction at the level of the calcar than male femurs (Bonnin et al., 2015). This may cause femur-implant size mismatch and contribute to the increased risk of fracture in female patients.

The greatest age associated risk was seen in both patients below 50 years and above 80 years old. Prevalence of any IOPFF increased in younger patients with acute fracture and 'other' indications relative to patients with OA. Increasing age has been previously associated with higher IOPFF fracture risk (Abdel et al., 2016b; Ricioli et al., 2015). Young patients may be at greater risk of calcar and shaft fractures because the proximal femoral canal is typically tighter and requires more prolonged and forceful rasping. Many young patients requiring hip replacement have dysplastic proximal femora which may be particularly narrow or osteoporotic. The risk of trochanteric fracture increased with age in patients with OA, but analysis of interactions demonstrated that the predicted prevalence of trochanteric fracture decreased with age to below that of OA in older patients with a diagnosis of acute fracture including NOF. Given that the metaphyseal bone of the trochanter is particularly vulnerable to osteoporosis, it is not clear why patients with NOF might have a lower risk of trochanteric fracture than patients with OA. Perhaps increased surgeon awareness of osteoporosis in patients with NOF may reduce the risk of trochanteric injury.

Patients undergoing left sided THA have an 8% increased risk of IOPFF ($p<0.001$) (table 2). Interestingly this risk was of a similar magnitude to that inferred by an anterolateral approach (versus posterior). This could be due to surgeon handedness, which has been shown to affect surgical performance during THA(Pennington et al., 2014). It may be possible that when surgeons operate on a left hip they are more likely to injure the femur. With the patient supine or in lateral position most surgeons would be holding the rasp or implant with their left hand. It is possible that on average, right handed hammer blows are applied with more force or guidance of rasp or implant with the left lacks as much control as when performed with the right hand. Such hypotheses should be tested with further study.

Inflammatory arthritis, previous trauma and NOF are commonly associated with periarticular osteoporosis and increased risk of IOPFF. This study did not find increased risk of IOPFF with THR for NOF, which is a surprising finding. Patients with NOF are typically older and perhaps more likely to have a wider proximal femoral canal, which reduces femoral stem mismatch. This study confirmed that AVN, previous trauma and previous infection were associated with a significant increase in IOPFF risk (Ricioli et al., 2015). Exposure to steroids, associated osteopenia and / or post-operative bone loss or fibrosis may make exposure and femoral canal preparation precarious. Worse ASA grade is strongly associated with increased IOPFF risk. ASA is likely to be a surrogate marker for health conditions which can affect the integrity of the proximal femoral bone stock. ASA grade may be a useful discriminator for surgeons deciding which implants and techniques to adopt.

3.2.4.2 Surgery / surgeon related risk factors for IOPFF

Increased relative risk of IOPFF associated with cementless implant usage is reflected universally in the literature (Zhao et al., 2017; Abdel et al., 2016a; Abdel et al., 2016b; Berry, 1999; Miettinen et al., 2016; Berend, M.E. et al., 2006; Davidson et al., 2008). We have demonstrated that the effect of cementless stem use resulted in a constant elevated predicted prevalence of any IOPFF across all age ranges. Associated risk of calcar and shaft fractures also independently increased with cementless stem use. Calcar or shaft fractures tend to occur during canal preparation and stem insertion (Abdel et al., 2016b) where most cementless femoral implants use a press fit which increases femoral cortical strains (Jasty et al., 1994). The increased risk of calcar crack associated with cementless stems was most noticeable in female patients and there was no significant age-gender interaction when predicting calcar cracks. It is possible that there are gender differences between the morphology of female and male proximal femurs which may predispose female to calcar cracks during cementless stem implantation but there is little evidence to support this observation.

Cementless stem survival has previously been shown to be better in a younger population of patients perhaps because of better bone stock which reduces the risk of perioperative complications like IOPFF and POPFF (Wangen et al., 2017). In younger patients where it has been shown that cementless femoral stems may survive longer the increased risk of IOPFF and associated sequelae must be weighed up against the potential benefit in stem survival, particularly in patients with proximal femoral features appear weak or which may require prolonged or forceful preparation. The decision to use cementless or a cemented stem is complex and given that risk of IOPFF increased in the youngest patients in this study perhaps surgeons and policy makers should use other standardised variables to identify groups in which survival with cementless stems is better.

Surgical approach to the hip is a contentious topic with rising popularity of the direct anterior approach because of potentially reduced dislocation rates and faster recovery. Hardinge approach has previously been identified as a risk factor for IOPFF (Zhao et al., 2017; Miettinen et al., 2016; Berend, M.E. et al., 2006; Hendel et al., 2002). The Hardinge and direct anterior approach can place significant forces on trochanteric muscle attachments and the femur, which are under tension during canal preparation and implantation (Hendel et al., 2002; Hartford et al., 2018). Increased rotational loading of the trochanter and shaft during anterolateral and other approaches may explain the specific increased risk of IOPFF. These results predicted that consultant surgeons experienced a higher prevalence of trochanteric fractures during ‘other’ approaches compared to non-consultant grade surgeons. This is likely to be the result of selection bias, with consultant surgeons electing to perform ‘other’ approaches on more challenging cases. The absolute predicted risk of consultant lead surgeons performing ‘other’ approaches was higher than any other group and highlights the particular risk associated with these approaches. Further work to adapt these approaches to reduce femoral strains may help to reduce associated risk of IOPFF.

This is the first study to demonstrate an association between CGS and a reduced risk of any IOPFF, calcar and trochanteric subtypes. CGS typically requires pre-operative 3D imaging, which may allow more accurate planning of implant size and can give feedback on direction of femoral preparation and implantation. This may reduce the risk of implant femur size mismatch and the subsequent risk of fracture. There were no clinically plausible interactions between CGS and other variables in this study. This may suggest that CGS is an independent protective factor against any IOPFF. However, confounding may exist since CGS may also be a surrogate marker for careful higher volume surgeons and surgeons may select easier or more difficult cases for CGS assistance. We identified higher incidence of IOPFF in patients undergoing surgery in public hospitals. In the UK surgery undertaken in independent hospital are more likely to be performed by consultant surgeons and patients tend to be fitter and cases less complex which may introduce confounding. Although the overall risk of IOPFF seems low, the surgeon can reduce the risk significantly further by modifying all possible risk factors which they have control over.

3.2.4.3 Limitations

This observational study benefits from the power of large numbers which can give insight into relatively rare complications but are constrained by the innate availability of data. There are important risk factors which cannot be included such as proximal femoral morphology, proximal femoral bone mineral density, specific implant/rasp design and shape, force of impaction and control over surgical techniques. Given this constraint, the performance of models used in this study are adequate, but results should be appraised alongside other data. NJR IOPFF data are self-reported immediately after surgery and may miss shaft fractures which are only seen on post-operative radiographs. This may explain why there are no reported shaft penetrations in this study. Abdel et al reported 5.6% of all IOPFF were shaft fractures and 24% of these were discovered on post-operative radiographs (Abdel et al., 2016b). In this study shaft IOPFF accounted for 7.1 % of all IOPFF, but this may be an underestimate given these limitations. Cementless femoral implants may be used preferentially in cases of IOPFF if the surgeon prefers to use a cementless distally fixing modular implant, which may bias results. Cementless modular implants, however, were used in only 3.2% of all the IOPFF in our analysis, which could introduce only a small error into our estimates of the effect of fixation. The analysis of stem properties associated with intraoperative fracture is not feasible as the NJR only records the final implant used and not the precise preparation equipment (rasps and or reamers) used. It is likely that the numbers reported here are an underestimate of IOPPF as the fractures are only reported if the surgeon is aware of their occurrence during surgery.

3.2.4.4 Conclusions

The risk of all IOPFF increases in females, less fit patients and in those with a non-OA indication for surgery. A large cumulative reduction in IOPFF risk appears to be associated with use of cemented implants, posterior approach and CGS. It is likely that with modification of these factors the risk of subsequent direct POPFF surgery and indirect risk of POPFF may also be reduced.

Understanding the effect of combined factors is paramount when choosing the safest technique and implant choice, to minimise IOPFF and future revision risk. Future work should elucidate the effect of CGS as well as direct anterior approach on the risk of IOPFF given that there are significant effects of CGS and that the use of the direct anterior approach is increasing.

Chapter 4 Analysis of cementless stem design factors associated with post-operative periprosthetic femoral fractures after total hip replacement.

This chapter will describe a study which estimates the relationship between patients, surgical and implant related risk factors and subsequent POPFF. This study forms the basis of the publication:

Lamb JN, Baetz J, Messer-Hannemann P, Adekanmbi I, van Duren BH, Redmond A, West RM, Morlock MM, Pandit HG. *A calcar collar is protective against early periprosthetic femoral fracture around cementless femoral components in primary total hip arthroplasty: a registry study with biomechanical validation.* **Bone and Joint Journal** 101-B (7):779-786 Jul 2019.

4.1 Introduction

As previously described in the literature review, POPFF occurs in up to 5% of primary THR. Management of these cases is complex and costly with reported one-year mortality between 11 and 13% (Gitajn, I.L. et al., 2017; Bhattacharyya et al., 2007). A significant proportion require revision surgery which is expensive and has unpredictable outcomes (Phillips, J.R. et al., 2011). The incidence of POPFF is predicted to increase by 4.6% per decade, over the next 30 years (Pivec et al., 2015). Patient based risk factors have received much attention but many of these factors are in general, not easily modifiable. Modifiable risk factors for POPFF need to be better understood to minimise the incidence of this significant complication.

Implant choice remains one of the few surgically modifiable risk factors and the risk of POPFF is highest around cementless stems (Thien et al., 2014; Abdel et al., 2016b; Wangen et al., 2017; Berry, 1999; Carli et al., 2017; Lindberg-Larsen et al., 2017). Despite the overwhelming popularity of the cementless stem worldwide, the exact features of cementless stems which lead to an increased risk of POPFF are not well understood. Given the popularity of cementless stems globally and the increased associated risk of POPFF, further study of the specific risks associated with cementless femoral stems is warranted. The risk of POPFF is greatest in the early post-operative period and is four-fold around cementless versus cemented stems in the first 90 days (Lindberg-Larsen et al., 2017). Risk of POPFF differs between implant brands (Carli et al., 2017; Thien et al., 2014). Cementless stems are a heterogeneous group, with many variations in surface treatments, body shapes, lengths and various combinations of collars and wings, even within a single stem model. Comparison using stem models categorised by design groups has previously been performed (Khanuja et al., 2011) but the contribution of a specific design feature to the risk of POPFF is difficult to ascertain. Analysis of POPFF revision rates attributable to specific design features may better inform future implant design. The overall incidence of POPFF is relatively low and consequently the large sample sizes available in arthroplasty registries are needed to establish association between design features and risk of POPFF.

Implant design features which potentially alter the risk of early POPFF include a medial calcar collar, which reduces subsidence, increases rotational stability and the force to fracture in a quasi-static loading model (Demey et al., 2011; Whiteside et al., 1988). Increasing sagittal taper has been associated with increased POPFF risk (Carli et al., 2017; Watts et al., 2015). Anatomical stem designs have been associated with lower risk of POPFF versus tapered designs in cementless stems (Carli et al., 2017). Additionally, modern surface finishes are reported to impart greater primary stability, which may reduce the risk of early POPFF (Miles et al., 2015).

The aim of the analysis reported in this chapter was to establish cementless stem design features which were associated with increased risk of early POPFF revision surgery in the NJR.

4.2 Methods

4.2.1 Participants

The NJR records patient and surgical data for all THRs performed at hospitals in England and Wales since 2003 (Lenguerrand et al., 2018). This study used all primary THRs with a stemmed cementless femoral implant in the NJR from 2003 to 2016. Femoral implant catalogue codes were used to gather manufacturer-provided implant design data.

4.2.2 Registry data

349 161 THRs were eligible for analysis. Exclusions were: implantation prior to formal reporting of Intraoperative periprosthetic femoral fracture (IOPFF) in 01/04/2004 (n = 3270), missing follow up data (n = 4), missing design data (n= 590), non-standard length stems (tip intended to finish at the mid-diaphysis, n= 7038) and 612 cases were excluded from regression due to insufficient numbers for meaningful analysis (indications: previous arthrodesis, previous infection, malignancy [n = 247] , fully porous coated stems [n = 143], and approach: trochanteric osteotomy [n = 222]). 337 647 cases were included in subsequent analyses. Institutional ethical approval was granted for this study.

4.2.3 Patient and surgical variables

Variables included were patient age (years), gender, American Society of Anaesthesiologists group (1-2 vs 3-5), side of operation, surgical approach (anterolateral [Hardinge, anterolateral and lateral], posterior, other), computer guided surgery, minimally invasive surgery, surgeon grade (consultant/non-consultant), hospital type (NHS, Independent hospital, Independent treatment centre), indication for surgery (osteoarthritis, trauma including hip fracture, avascular necrosis, inflammatory arthritis, previous trauma, paediatric hip disease and other) and IOPFF (yes/no).

4.2.4 Implant variables

All registry variables relating to stem design: calcar collar (yes/no), surface finish, surface features and stem shape were included in subsequent analysis. Surface finishes were coded (MIN = mineralised with hydroxyapatite or calcium phosphate, POR = non-mineralised porous finish, GRIT = grit blasted or roughened, NONE = no surface finish). Stems were then coded according to surface finishes in proximal and distal regions (proximal: distal, e.g. MIN: NONE stands for a stem coated proximally with hydroxyapatite and no distal surface finish). Surface shape (Flat, Horizontal ridges, Vertical ridges), Stem shape in cross section (rectangular, oval or round), body taper in the coronal, sagittal or axial plane (Single, double or triple taper respectively) and sagittal stem shape (curved vs straight) were included.

4.2.5 Outcomes

The primary outcome of registry analysis was implant survival until POPFF revision within 90 days.

4.2.6 Statistical analysis

Non-normally distributed continuous variables were expressed as median values with interquartile range (IQR). Since the dataset was large and multiple comparisons were made, a significance level of $p < 0.01$ was chosen. Survival was estimated using a Cox multivariable model. POPFF revision at 90 days only counted if not preceded by IOPFF to reduce confounding. Implants in patients who died or were not revised for POPFF at 90 days were censored. HR estimates were adjusted for all other patient, surgical and design variables (Table 4-1 and Table 4-2). Multivariable regression estimated the adjusted hazard ratio of revision with 95% confidence intervals (HR [CI

95%]) for each implant design factor. All analyses were performed using R (v3.5.1, R, Vienna, Austria). Regression models were stratified by gender to satisfy the assumptions of proportionality and then assessed using the concordance statistic.

4.3 **Results**

The two year incidence of POPFF revision was 0.21% (707/337647) and the overall incidence of POPFF revision was 0.34% (1180/337647), 44.0% occurred (520/1180) within 90 days and 48.9% (578/1180) occurred within six months of surgery (Figure 4-1).

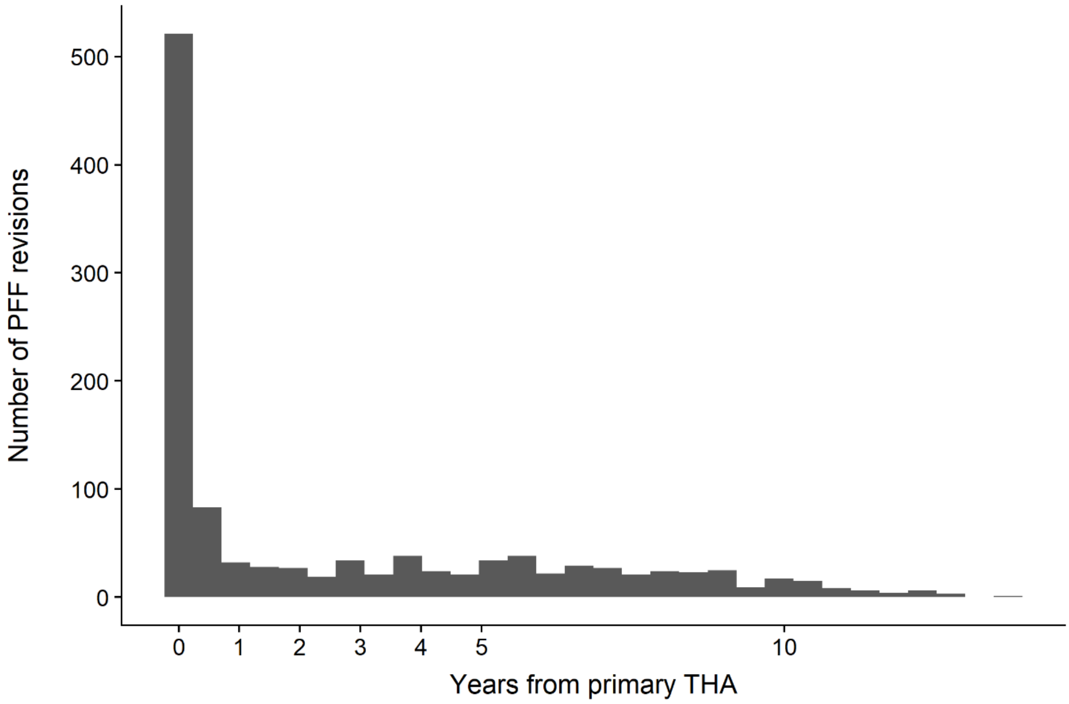


Figure 4-1 Histogram demonstrating the frequency of cases occurring after primary total hip replacement using a cementless femoral stem in six monthly intervals.

Median (IQR) follow-up time was 5.5 years (3.13 – 8.10). Baseline demographics are displayed in Table 4-1.

Table 4-1 Baseline characteristics of cases included in survival and regression analysis.

Variable	*Level*	**Total** n = 337647
Patient gender (%)	*Male*	148093 (43.9)
	Female	189554 (56.1)
Side (%)	*Left*	153432 (45.4)
	Right	184215 (54.6)
Age group (%)	*11 to 49*	25787 (7.6)
	50 to 59	62063 (18.4)
	60 to 69	121046 (35.8)
	70 to 79	97603 (28.9)
	80 to 117	31148 (9.2)
ASA grade (%)	*1*	62846 (18.6)
	2	233422 (69.1)
	3	40091 (11.9)
	4	1248 (0.4)
	5	40 (0.0)
Organisation type (%)	*NHS*	216733 (64.2)
	Independent Hospital	104548 (31.0)
	Treatment centre	16366 (4.8)
Indication (%)	*Osteoarthritis*	317054 (93.9)
	Acute trauma including hip fracture	5467 (1.6)
	Avascular necrosis of the hip	4960 (1.5)
	Previous trauma	1982 (0.6)
	Inflammatory arthritis	3239 (1.0)
	Other	2074 (0.6)
	Paediatric disease	2871 (0.9)
Approach (%)	*Posterior*	203688 (60.3)
	Anterolateral	117953 (34.9)
	Other	16006 (4.7)
Surgeon grade (%)	*Consultant*	293799 (87.0)
	Non consultant	43848 (13.0)
Computer guided surgery (%)		9100 (2.7)
Minimally invasive surgery (%)		33711 (10.0)

Note: ASA indicated American Society of Anaesthesiologists

Most cementless stems were collarless double tapered with a fully mineralised coating (Table 4.2).

Table 4-2 Stem design characteristics of cases included in survival and regression analysis.

Variable	*Level*	**Total** n = 337647
Collar (%)	*Collared*	117222 (34.7)
	Collarless	220425 (65.3)
Surface finish location (%)	GRIT:GRIT	13056 (3.9)
	MIN:GRIT	9804 (2.9)
	MIN:MIN	223229 (66.1)
	MIN:NONE	73576 (21.8)
	POR:GRIT	1595 (0.5)
	POR:NONE	16387 (4.9)
Taper (%)	*Double taper*	275481 (81.6)
	Single taper	54203 (16.1)
	Triple taper	7963 (2.4)
Metaphyseal surface shape (%)	*Flat*	140459 (41.6)
	Horizontal ridges	184872 (54.8)
	Vertical ridges	12316 (3.6)
Diaphyseal surface shape (%)	*Flat*	73024 (21.6)
	Vertical ridges	264623 (78.4)
Metaphyseal cross section (%)	*Rectangular*	303364 (89.8)
	Oval	34173 (10.1)
	Round	110 (0.0)
Sagittal body shape (%)	*Straight*	331201 (98.1)
	Curved	6446 (1.9)

Note: Surface finish location indicated the surface finish of proximal: distal surface areas. GRIT Grist blasted or roughened surface, MIN mineralised surface, POR non mineralised porous surface, NONE no surface finish.

4.3.1 Influence of patient factors on 90-day POPFF revision risk

The regression model correctly predicted early POPFF in 72% of the cases (concordance statistic 0.72). Regression models were stratified by patient gender to satisfy the assumptions of proportionality, which prevented estimation of HR of POPFF revision between males and females. After adjustment for all patient, surgeon and surgical variables, patient predictors which increased the hazard of 90-day POPFF revision in the final multivariate survival model were age (versus 11 to <50 years) 70 <80 years (HR 3.2 [CI 2.0 – 5.3], p<0.001) and age >80 (HR 5.8 [CI 3.5 – 9.6], p=0.001) , ASA grades three to five versus one and two (HR 1.5 [CI 1.2 – 1.9], p=0.001) and acute trauma including NOF as indication for surgery versus OA (HR 1.9 [CI 1.2 – 3.2], p<0.001). Use of CGS reduced the hazard of POPFF revision within 90 days and was borderline statistically significant (HR 0.4 [CI 0.2 – 0.8], p =0.01).

4.3.2 Influence of design factors on 90-day POPFF revision risk

Design variables which significantly increased the risk of POPFF revision within 90 days, were collarless design (HR 4.7 [CI 3.5 – 6.3], p<0.001), surface finish (reference GRIT:GRIT coating: MIN:MIN coating, HR 4.6 [CI 2.3-9.3], p<0.001; MIN:NONE coating, HR 4.8 [2.3 – 9.95], p<0.001; POR:GRIT coating, HR 7.9 [CI 2.8 – 21.7], p <0.001; and POR:NONE coating, HR 4.8 [CI 2.8 – 21.7], p<0.001). Triple taper design also increased early POPFF revision risk (HR 1.8 [CI 1.4 – 4.1], p<0.01, Figure 4-2).

Design variables		HR	p
Design variables			
Collar	Collared	1.0	
	Collarless	4.7	<0.001*
Surface finish and location	GRIT:GRIT	1.0	
	MIN:GRIT	3.4	0.01
	MIN:MIN	4.6	<0.001*
	MIN:NONE	4.8	<0.001*
	POR:POR	ins	
	POR:GRIT	7.9	<0.001*
	POR:NONE	4.8	<0.001*
Taper	Double taper	1.0	
	Single taper	1.7	0.08
	Triple taper	1.8	<0.01*
Metaphyseal surface shape	Flat	1.0	
	Horizontal ridges	1.2	0.35
	Vertical ridges	1.6	0.09
Diaphyseal surface shape	Flat	1.0	
	Vertical ridges	0.7	0.05
Metaphyseal cross section	Rectangular	1.0	
	Oval	1.3	0.21
	Round	4.5	0.15
Saggital body shape	Straight	1.0	
	Curved	1.8	0.06

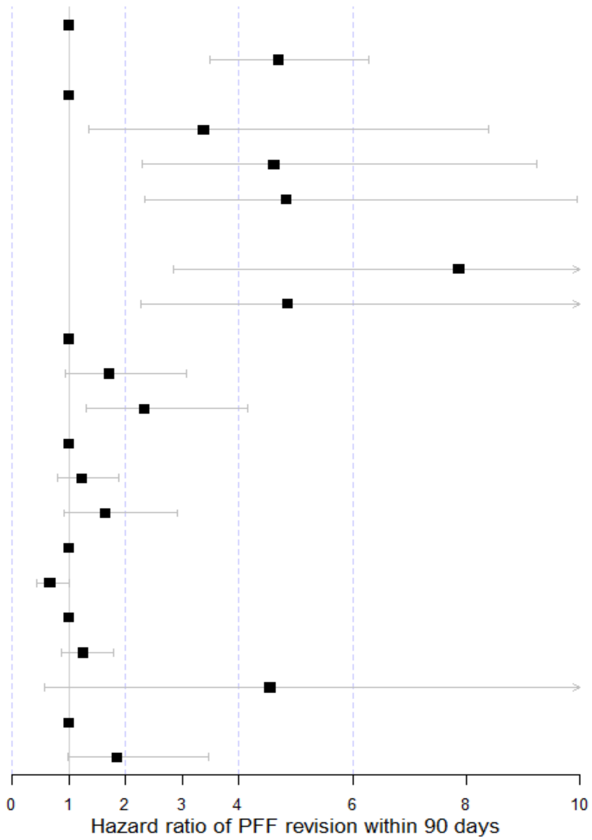


Figure 4-2 Forest plot demonstrating the associated hazard ratio of design variables for POPFF revision with 90 days following primary total hip replacement using a cementless femoral stem. Note: HR denotes hazard ratio versus comparator (HR = 1.0), MIN = mineralised with hydroxyapatite or calcium phosphate, POR = non-mineralised porous finish, GRIT = grit blasted or roughened, NONE = no surface finish. Stems were then coded according to surface finishes in proximal and distal regions (proximal: distal, e.g. MIN:NONE stands for a stem coated proximally with hydroxyapatite and no distal surface finish.

4.4 Discussion

Almost half of all POPFF revisions around cementless stems occurred within six months of implantation. Increasing age, worse ASA grade, diagnosis of NOF was associated with an increased hazard of POPFF and CGS was associated with a reduced risk of POPFF revision. Collarless implants were associated with a nearly five-fold relative risk of early POPFF versus collared implants. Early POPFF revision risk is significantly increased in all mineralised and non-mineralised porous coated cementless stems and in stems which are tapered from lateral to medial in the axial plane.

The findings in this analysis regarding the increased risk associated with increasing age are in line with previous work (Thien et al., 2014; Meek et al., 2011; Watts et al., 2015; Cook et al., 2008; Berend, K.R. et al., 2016; Palan et al., 2016; Broden et al., 2015; Chatziagorou et al., 2019b). In addition, these results demonstrate a clear relationship between worsening ASA grade and increased risk of POPFF within 90 days of THR using a cementless stem, which is in agreement with previous findings (Singh, J.A. et al., 2013). The risk of POPFF revision increases in patients who undergo THR for NOF which has been previously demonstrated (Watts et al., 2015; Thien et al., 2014). Unfortunately this analysis was not able to quantify the effect of patient sex on the risk of POPFF, however it is likely that the risk of POPFF is greatest in females as described in Chapter Two and demonstrated in the literature (Thien et al., 2014). Given this constraint and the weight of evidence, it is likely that female sex increases the risk of POPFF and should be considered by surgeons planning a THR. It is reasonable to assume that the former risk factors are non-modifiable and represent a cohort of patients in which the selection of modifiable risk factors, namely implant selection, may be most useful. Similarly, to findings reported for IOPFF, CGS was associated with a large reduction in POPFF risk, with borderline statistical significance. As with IOPFF it is possible that CGS may reduce the risk of POPFF by allowing for more accurate pre-operative planning, implant selection and implant insertion (where CGS systems offer this functionality).

Calcar collars may improve implant stability through imparting compressive loads on the calcar and were commonly used on cementless implants to reduce stem subsidence (Whiteside et al., 1988). Problems with imperfect calcar collar contact after insertion and a randomised controlled trial showing no benefit have discouraged the use of this type of design (Meding et al., 1997). Revision due to POPFF within 90 days is uncommon (0.3%) and an appropriately powered randomised controlled trial to show the benefit of a collar with the endpoint of POPFF would require unrealistically large patient numbers. This study shows that a collar is associated with an almost five-fold reduction in early POPFF revision risk, probably due to earlier cortical load transfer during injury. Cortical bone is anisotropic and strongest when loaded in compression (Mirzaali et al., 2016; Osterhoff et al., 2016). During injury the collar can load the calcar in compression increasing the force required for a fracture. This mechanism may increase the force required to cause a POPFF around a collared implant versus collarless implants. The calcar possibly acts as a check-rein which prevents excessive peri-prosthetic trabecular deformation and may improve the resistance to trabecular deformation after high energy injuries which do not cause cortical fracture.

Proximal porous coating has been shown to increase load transfer to the proximal femur (Miles et al., 2015; Keaveny, T. M. and Bartel, 1993) and increase force required to fracture using an axial loading POPFF model (Miles et al., 2015). This work has demonstrated an increased risk of early POPFF with mineralised and non-mineralised porous coated stems. Where there is no direct calcar loading, it may be preferable to load the femoral shaft during rotational insult, which is innately more flexible than the stiffer proximal metaphyseal bone (Otani et al., 1993). These results have shown an almost doubled risk of early POPFF associated with cementless stems which are tapered medial to lateral in the axial plane versus conventional double tapered stems. Medial to lateral taper is thought to increase proximal loading of the femur (Wroblewski et al., 2001) and has been successfully incorporated into cementless designs (Hayashi et al., 2012). When compared to double tapered stems, a triple taper (medial to lateral) may increase the loading of trabeculae adjacent to the narrower medial implant surface during an injury, leading to greater trabecular deformation and greater risk of eventual cortical fracture.

4.4.1 Limitations

This registry analysis estimated the risk of POPFF revision and whilst this includes most cases of POPFF in UK practice (Khan, T. et al., 2017) it was likely to be an underestimate of real POPFF incidence, which also includes cases where POPFF undergo internal fixation or conservative management (Chatziagorou et al., 2018). The two year prevalence of POPFF revision was lower than the 0.47% prevalence of POPFF revision reported by Thien *et al.* (Thien et al., 2014), which may partly be due to different surgical practices and implant usage. Patients with IOPFF were excluded from the analysis of early POPFF to reduce confounding, it may be that a proportion of early POPFF are due to unrecognised or unreported IOPFF which propagate during the early post-operative stage. When hypothesising mechanisms of action, the likely fracture pattern around cementless femoral stems based on the best available evidence but the mechanism and pattern of injury in our registry data is not verifiable because the patient notes and radiographs were not available. The choice of implant characteristics investigated was based on review of the current literature, but this may change as a deeper understanding of how design influences early POPFF risk develops. The implant design itself or the combination of certain implant features might have biased our findings. This should be investigated in more detail in the future. Given that this is a new approach to the analysis of registry data, it may be appropriate that the influence of further variables on early POPFF risk or other research questions will be investigated in a similar way. This analysis does not consider the potential for a medial calcar collar to alter the risk of other failure modes such as aseptic loosening. Further work is required to evaluate the effect of a calcar collar on the overall survival of the THR construct such that the benefits in reduction of POPFF risk are not negated by an increase in the risk of other important failure modes.

4.4.2 Conclusions

These results demonstrate a significant increased risk of early POPFF revision associated with collarless implants, mineralised and porous non-mineralised coated implants and triple tapered cementless stem designs. Given the predicted rise in POPFF rates, the use of a medial calcar collar may help to improve future cementless stem survival by reducing the risk of early POPFF. The greatest effect of implant selection on risk of POPFF may be possible in the most high-risk groups including: Older patients, with worse ASA grade and a diagnosis of NOF. Appropriate biomechanical experimentation is required to establish likely causative mechanisms by which the risk factors identified in this analysis might be validated

Chapter 5 Development of a manual segmentation technique for the analysis of post-operative periprosthetic fracture patterns

Results from Chapter Four generated new hypotheses of how design features may influence the future risk of POPFF. A reasonable approach would then be to test such hypotheses experimentally using simulated POPFF in vitro methods. In order to further understand the aetiology of POPFF and to ensure that subsequent biomechanical testing represents real-life POPFF fracture mechanics it is essential that an objective evaluation of fracture pattern occurs. It is also reasonable to hypothesise that design features may also affect the mechanism and thus the fracture patterns which occur during POPFF.

As described in Chapter Two, there is no available method which can be used to describe a single or group of POPFF fracture patterns. It is essential that researchers in this field have an objective way to compare fracture patterns between implant designs and patient groups such that more robust hypotheses can be generated and then tested. The application of such methods in the field of POPFF research is a useful and necessary step to understand common mechanisms leading to POPFF and how implant design affects the mechanisms of fracture. This chapter will outline the development of a method to quantify and analyse POPFF fracture patterns.

The development of a fracture segmentation method is described in sequence from a simplistic task (Section 5.1) to a more complex task (Section 5.2). In this process an estimate of the likely error associated with each component of the final task can be obtained. The final method is then used in Chapter 6 to evaluate fracture patterns in a group of POPFF which occurred following cementless hip replacement in order to understand the likely mechanisms leading to POPFF in general and in which factors may influence POPFF fracture patterns. This study will be used to advance the understanding of likely fracture mechanisms occurring in POPFF and the possible effect of patient and implant factors. The estimated mechanism of early POPFF will then be used to inform the selection of experimental simulation method in Chapter Seven.

5.1 Development of a method to quantify POPFF patterns

5.1.1 Introduction

Recent analyses have shown large differences in the risk of POPFF associated with the different designs of the femoral stem (Carli et al., 2017; Palan et al., 2016), which has been developed further by the work reported in Chapter Four. The mechanism by which a femoral stem design feature may infer increased risk of POPFF is not clearly understood. Fracture patterns can be viewed as a force footprint, which summarises the trajectory of a fracture forces through a bone. Detailed analysis of fracture patterns may provide an insight into common fracture mechanisms for any particular stem or patient group and further develop our understanding of how femoral stems break the femur during a POPFF. As discussed in Chapter Two, the POPFF features which may depend on the mechanics of the injury are fracture location along the length of the femur and the fracture type. The development of a method in this chapter will focus on methods to reproducibly measure these specific fracture features.

Since the digitisation of medical imaging in the last two decades it is possible to perform analysis of fracture patterns in a much more objective way. A digital image is a matrix of pixels (‘picture elements’) which is a standard area of the image programmed to display a certain colour by the display device. It is possible to identify regions of pixels representing certain features using a process of segmentation, which can be performed manually, semi-automatically or automatically (Withey and Koles, 2008). Segmentation may rely on various methods of pixel analysis, which are beyond the scope of this analysis but can be used to detect fracture lines from radiographic images (Deng, H. et al., 2016; Donnelley and Knowles, 2005). Withey and Koles admit that semi-automated and automated segmentation is a difficult task (Withey and Koles, 2008). Such an approach may be more difficult when interpreting POPFF where the fracture line may be partly obscured by the femoral implant and image obtained in the emergency setting may include non-standard views and additional features (clothing, splints etc.), which may reduce the accuracy of automated methods.

Image analysis in the field of orthopaedics is a growing area following the renewed popularity of convolutional neural networks in the field of image analysis. Convolutional neural networks describe a process by which many electronic images are read by an automated computer program and a statistical relationship between pixels in the images and a known outcome or *label* (for example, fracture or no fracture), is defined. The relationship can be refined by a process of feedback and training. Such techniques have been used successfully in simple fracture detection with excellent results (Gale et al., 2017; Thian et al., 2019; Urakawa et al., 2019). A recent review and meta-analysis of deep-learning methods of disease detection in medical imaging identified an equivalent sensitivity and specificity between machine and human image analysis (Liu et al., 2019). These methods are currently limited by the large number of images required (>10 000) for training the computer program and a lack of transparency in some models as to how and why a decision is reached (Topol, 2019). These restrictions make the use of such techniques in the field of POPFF challenging since the number of images available for analysis is relatively small, but it is likely that such techniques will continue to develop.

Given these constraints the most realistic solution is likely to be a manual fracture segmentation method. This is likely to be the slower than an automated process and relies on expert knowledge to correctly identify fracture patterns (Withey and Koles, 2008). Manual segmentation is subject to within and between observer variability (Withey and Koles, 2008). Variability is likely to originate from the variability in the skill of manual segmentation (i.e. the use of computer equipment and software) and the subjective assessment of where a real-world fracture line occurs. Quantifying the variability attributable to each source is key to understanding the limitations of a manual segmentation technique and should be defined explicitly prior to full-scale implementation of such a technique.

The aim of this study is to develop a repeatable method of fracture line analysis using expert-lead manual segmentation. Firstly, a simple line manual segmentation task will estimate the absolute error and the within and between observer error when drawing over a line. Secondly, a simple fracture edge manual segmentation task will assess the absolute error and the within and between observer error when drawing a fracture edge on a cropped radiograph depicting a single fracture in a femoral cortex.

5.1.2 Methods

5.1.2.1 Data source

This study used non-identifiable data from patients which was collected during their treatment for periprosthetic fracture in four large UK teaching hospitals. This project was approved by the Leeds School of Medicine research and Ethics Committee prior to collection of data. All patients admitted with a diagnoses of POPFF were identified from a mixture of clinical coding records, theatre records and referral records. Diagnosis was confirmed on review of radiographic records.

5.1.2.2 Data quality

Radiographs were obtained in '.jpg' format with a maximum compression of 90% of original resolution quality. Image resolution was estimated for 35 images which contained a calibration ball of known dimensions (Table 5-1). Mean (SD) pixel size was estimated at 0.12 mm (0.001) or equivalent to approximately eight pixels per millimetre.

Table 5-1 Radiograph resolution estimates using calibration ball.

Variable	Value
number of images	35
Image description	
Pelvis anteroposterior view	31
Femur anteroposterior view	4
Pixel diameter of calibration ball (mean (SD))	204.7 (12.5)
mm per pixel (mean (SD))	0.12 (0.01)

Note: mm per pixel indicates mm (millimetres) per pixel based on a 25mm calibration ball used in the plain radiograph

5.1.2.3 Participants

All fracture manual segmentation tasks were performed by two specialist trainees in Trauma and Orthopaedics (JL and Bernard van Duren). Participants underwent twenty minutes of training and familiarisation with the software and computer equipment set up prior to initiating the task.

5.1.2.4 Fracture segmentation

Initial image segmentation testing required to develop the protocol were divided into two tasks: manually segmenting a line and manually segmenting a fracture edge.

5.1.2.4.1 Manual segmentation of a line task

A cropped image of a single fracture femoral cortical edge (Figure 5-1) was obtained from the dataset and a solid black line was drawn on an image overlying the edge of the fracture using a standard optical computer mouse using image manipulation software (GIMP, GNU Image Manipulation Program, The GIMP Development Team, v 2.10.18, 2019). The line was drawn in a single attempt and the assessor could redraw the line if an error occurred. The radiograph layer was removed from the image leaving a single line in place. The line was then used as a target for the first manual segmentation task.

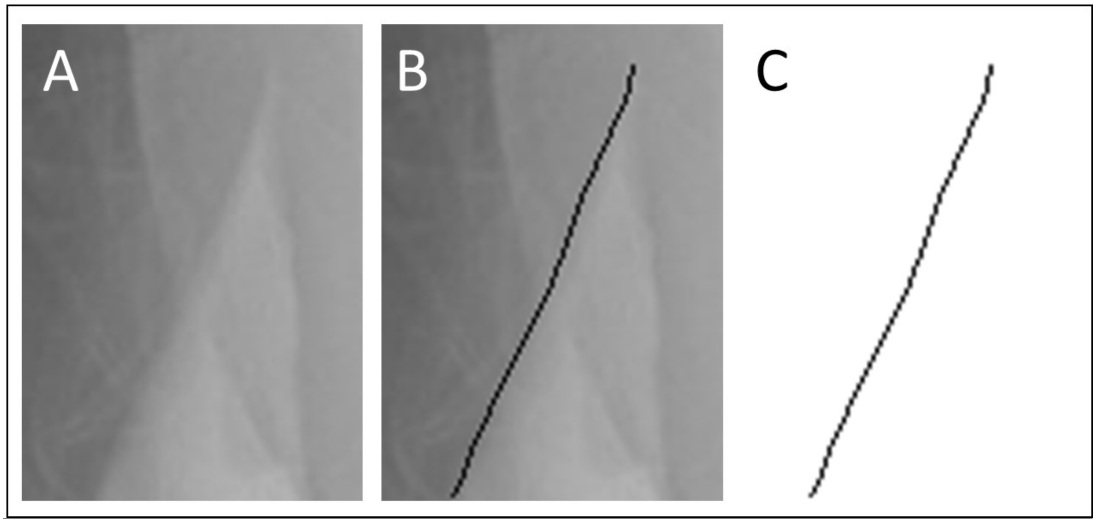


Figure 5-1 Creation of target line on a fractured femoral cortical edge for manual segmentation tasks. \`A\` indicates the untraced fracture edge, \`B\` indicates the fracture edge with the back line traced over the top and \`C\` indicates the target line with radiograph layer removed.

Multiple attempts of line manual segmentation were then performed using a single pixel line drawing tool. The attempt was drawn on a separate overlying image layer. Attempts were performed in a single attempt and the assessor could redraw the line if an error occurred. The entire task was repeated by a second assessor (BvD) to allow for estimation of between assessor variations. Each attempt was exported a single uncompressed image file ('.tif') for analysis. The entire task was repeated without reference to the previous attempt by the two assessors and each trial was saved as a separate image. The time between repetitions was thirty minutes.

5.1.2.4.2 Manual segmentation of a fracture edge task

To assess the reproducibility of the manual segmentation technique when interpreting 'real-world' fractures the assessors traced the fracture line edge (Figure 5-1A) in a single pixel width solid line on an overlying image layer using GIMP, and an identical technique as outlined above. The entire task was repeated without reference to the previous attempt by the two assessors and each trial was saved as a separate image. The time between repetitions was thirty minutes.

5.1.2.5 Image analysis and statistical methods

A sample size of seven for each assessor was chosen to create a minimum practically useful dataset for the pilot. Each trial image was loaded as a data frame object consisting of pixel coordinates and pixel value (relating to colour value of the pixel) for each pixel in the image using R (v3.6.2, R Core Team, Vienna, Austria). The co-ordinate values for each pixel with a value equal to the pen tool used to mark the fracture during the task was used in further analysis.

5.1.2.5.1 Estimation of absolute error of manual segmentation

The error of manual segmentation tasks was estimated by residuals which compared the coordinates of the target line with the segmented line pixel value for attempts made by both assessors. The residual in each axes were calculated by subtracting the maximum corresponding coordinate value of the target line for each attempt by each assessor (Figure 5-2). To assess error, mean (SD [standard deviation]) of residual values were calculated in both x and y axes between the target line and the segmented line. When assessing variability within assessors and between assessors, where no target line exists, the corresponding coordinate values for x and y axes respectively, were centred (value – mean for each x value) to account for increasing values in the corresponding opposite axis as the diagonal line progressed from left to right. Variability within and between assessors was estimated by the mean residual (SD) of the centred values in the x and y axes for all attempts by that assessor respectively. All pixel values were converted to millimetres (mm) using the estimated real-world image resolution.

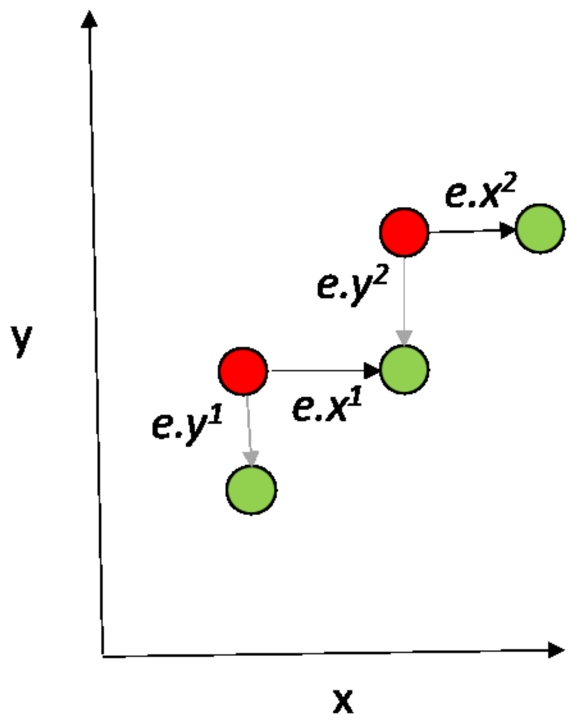


Figure 5-2 Schematic demonstration of calculation of residual values (e) for pixels in the target line (red) and the segmented line (green). Note: *e.y* denotes residual in the y axis and *e.x* denotes the residual in the x axis. Superscript notation defines each residual measurement. The mean residual between the pixels making either line can be calculated from residual values in each axis to assess error of the segmentation line.

5.1.2.5.2 Error in estimation of fracture position

Fracture location was assessed by comparing the absolute y coordinates of the fracture line (Figure 5-3). All pixel values were converted to millimetres (mm) using the estimated real-world image resolution.

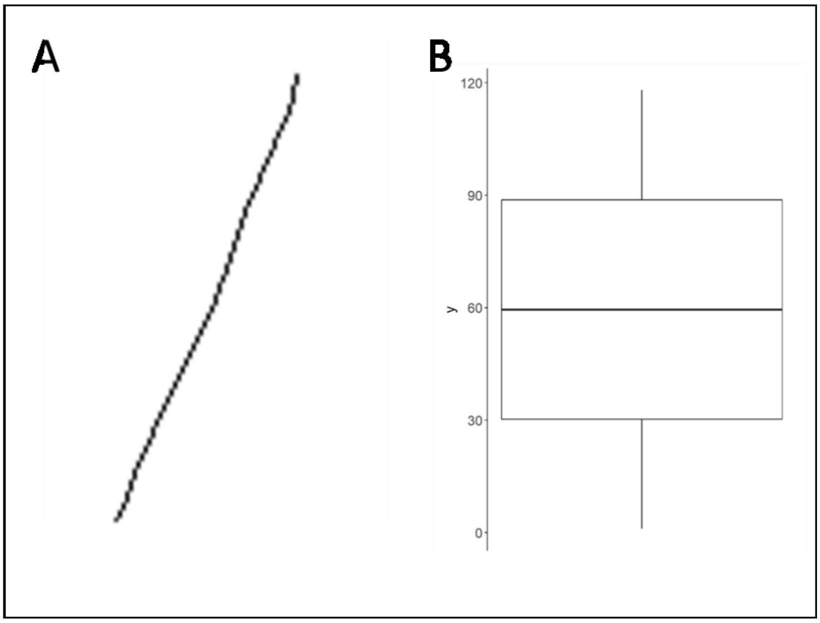


Figure 5-3 Fracture position measurement. A depicts the fracture line and B depicts a boxplot of y coordinate values for the fracture line. Median y value depicted with box hinges at the interquartile range (IQR) and whiskers to a maximum of 1.5 times the IQR)

Normally distributed continuous data were summarised using mean values (SD) and non-normally distributed continuous variables were summarised using medians (IQR). Overall comparisons between outcome measures were performed with ANOVA and pairwise comparisons were made using Mann-Whitney U tests where data was not normally distributed or t-tests where the data were normally distributed.

5.1.3 Results

5.1.3.1 Error in manual segmentation task

Mean (SD) for residuals in both x and y axes was less than a mean (SD) of 0.04 (0.21) mm during segmentation of a line task and -0.28 (0.38) mm during segmentation of a fracture task (Table 5-2). Mean residual values were greater in the y axis than x axis for both tasks for each assessor. Error increased marginally in segmentation of a fracture task but were less than a maximum mean residual of -0.28 (0.38) mm ($p<0.001$).

Table 5-2 Residual values in x and y axes for line and fracture segmentation tasks.

	Segmentation of line	Segmentation of fracture	p
Assessor 1			
Pixels	3863	3588	
Residual values (mm)			
y axis (mean (SD))	-0.03 (0.21)	-0.23 (0.34)	<0.001
x axis (mean (SD))	0.01 (0.08)	0.12 (0.16)	<0.001
Assessor 2			
Pixels	3864	3708	
Residual values (mm)			
y axis (mean (SD))	-0.05 (0.21)	-0.32 (0.40)	<0.001
x axis (mean (SD))	0.02 (0.08)	0.13 (0.16)	<0.001
Overall			
Pixels	7727	7296	
Residual values (mm)			
y axis (mean (SD))	-0.04 (0.21)	-0.28 (0.38)	<0.001
x axis (mean (SD))	0.02 (0.08)	0.12 (0.16)	<0.001

Note: Values in mm derived from image scaling estimates (1 pixel = 0.12mm). SD indicates standard deviation; p value is result of t-test comparison by row.

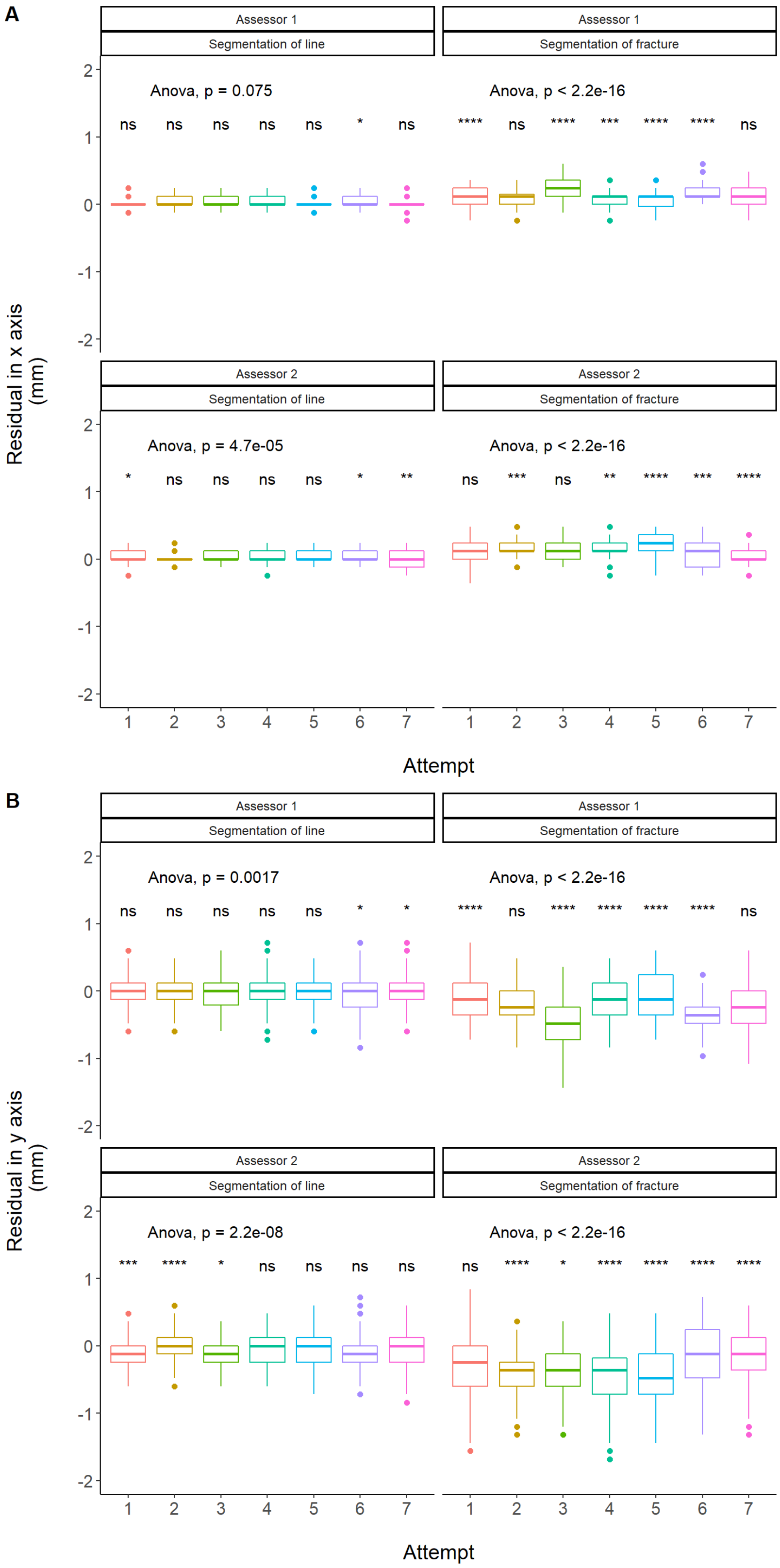


Figure 5-4 Variation in residual values in x and y axis (A and B respectively) for each task and each assessor during repeated segmentation attempts. Overall comparisons between attempts and base mean for each respective plot were performed using ANOVA and pairwise comparisons between target and each attempt to assess intra-assessor variation were performed with t tests. *: p <= 0.05, **: p <= 0.01, ***: p <= 0.001, ****: p <= 0.0001, 'ns' indicates p is >0.05.

Overall variation in error of segmentation was low and residual values were within +/-1mm for line segmentation and +/-2mm for fracture segmentation tasks (Figure 5-4). Variation within each assessor was low but reached statistical significance in all but one task, for one assessor. Variation within assessors was greater for segmentation of a fracture task versus segmentation of a line task.

5.1.3.2 Error in fracture position

Comparison of absolute pixel coordinate values in x and y axes demonstrate no significant differences between the target and all attempts (ANOVA $p>0.05$) for each assessor in either axis for the segmentation of a line task (Figure 5-5). Comparison between target line and repeated attempts demonstrated no significant within assessor variation (ANOVA, p range 0.98 to 1.0).

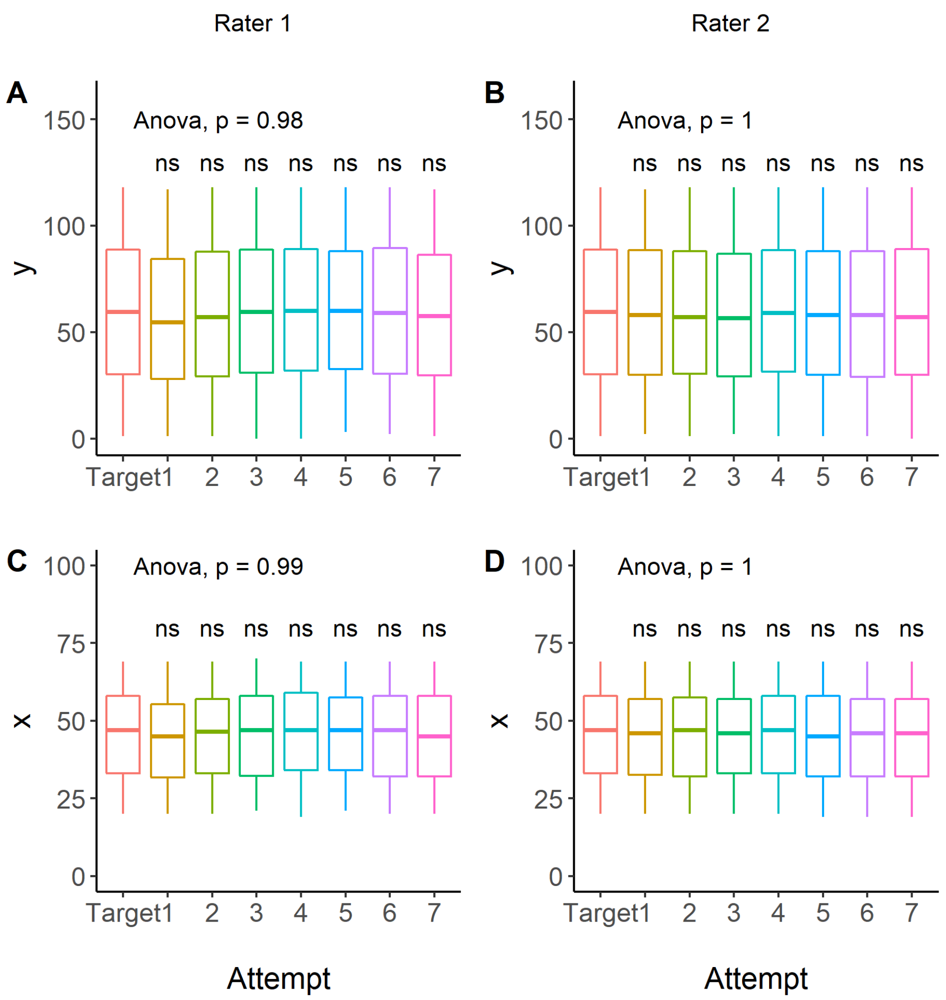


Figure 5-5 Absolute fracture location measures in manual line segmentation task. Facets showing y (A and B) and x (C and D) coordinate values between target and manual line segmentation attempts for assessors one (A and C) and two (B and D). Overall comparisons between target line and attempts for each assessor were performed using ANOVA and pairwise comparisons between target and each attempt to assess intra-assessor variation were performed with Mann Whitney U tests. 'ns' indicates p is >0.05.

Comparison of absolute pixel coordinate values in x and y axes demonstrate no overall significant differences between the target and all attempts (ANOVA p>0.05) for each assessor in either axis for the segmentation of a fracture task (Figure 5-6). Comparison between target line and repeated attempts demonstrated no significant within assessor variation (p>0.05).

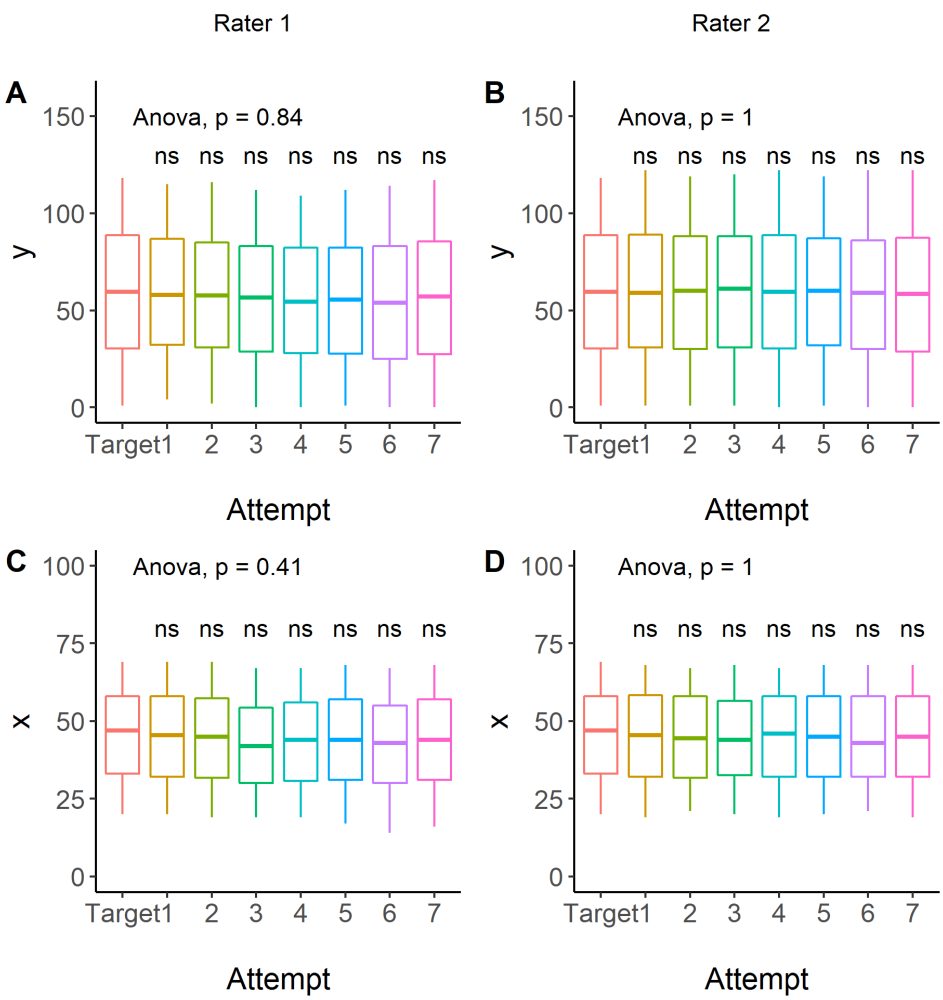


Figure 5-6 Absolute fracture position measures in manual fracture segmentation task. Faceted plots demonstrating y (A and B) and x (C and D) coordinate values between target and manual fracture segmentation attempts for assessors one (A and C) and two (B and D). Overall comparisons between target line and attempts for each assessor were performed using ANOVA and pairwise comparisons between target and each attempt to assess intra-assessor variation were performed with Mann Whitney U tests. 'ns' indicates p is >0.05.

Estimates of fracture position of segmented lines between assessors was only significantly different between assessors in one case (y values when segmenting a fracture, p= 0.04). The absolute difference in median fracture pixel location was three pixels in the worst case (0.36mm, Table 5-3).

Table 5-3 Fracture coordinate values in x and y axes for line and fracture segmentation tasks stratified by assessor.

	Assessor 1	Assessor 2	p
Segmentation of line			
Coordinates	n = 1115	n = 1134	
x (median [IQR])	47.00 [32.50, 58.00]	46.00 [32.00, 57.00]	0.75
y (median [IQR])	58.00 [30.00, 88.00]	58.00 [30.00, 88.00]	0.81
Segmentation of fracture			
Coordinates	n = 1094	n = 1115	
x (median [IQR])	44.00 [31.00, 56.00]	45.00 [32.00, 58.00]	0.06
y (median [IQR])	56.00 [28.25, 84.00]	59.00 [30.00, 88.00]	0.04

Note: IQR indicates interquartile range, p value is result of Mann Whitney U test comparison between assessors.

5.1.4 Discussion

This study has demonstrated excellent accuracy of manual segmentation of a distinct line and a fracture edge. Error of segmentation was within one millimetre when a line was segmented and two millimetre when a real-life fracture was segmented. Error varied significantly within each assessor but remained within acceptable limits. Study outcomes using manual segmentation for a simple task were highly accurate and consistent both within and between assessors. Fracture position estimates from segmentation did not differ significantly from the target fracture position.

A maximum threshold for error is difficult to estimate given that no current gold standard exists for manual segmentation of fractures. Current systems for POPFF fracture classification classify fractures according to position of the fracture relative to the femoral stem (Duncan and Masri, 1995). Required accuracy of a segmentation system can be estimated given that the overarching aim of the segmentation is to define the fracture position along the length of the femur. Estimated fracture position should be accurate enough to allow differentiation between key structures in the femur. For example it may be useful to determine whether the fracture has occurred at the level of the lesser trochanter, which is a structure occupying a space of between 3.2mm and 17.6mm on an AP hip radiograph (Worlicek et al., 2017). In order to do this the final segmentation technique should have an error which is less than half of this. Given that in the worst-case error is likely to be within +/- 0.8mm 95% of the time, the current testing methods show early acceptability for simple tasks.

Error of the manual segmentation method was least when segmenting a clearly defined line and greatest when segmenting a real-life fracture edge. Absolute segmentation residuals reduced by approximately six-fold between either task. This observation demonstrates the added difficulty posed by an indistinct fracture line over a clearly visible line. In real-life POPFF imaging radiographs also have the added complexity of an implant which may obscure a clear view of the fracture. In addition, fracture lines are most apparent on plain radiographs when the x-ray beam can pass directly through the fracture gap (fracture in the coronal plane). When the fracture gap does not allow the x-ray beam to pass through (fracture line in the sagittal plane) the fracture may not be clearly defined. Given that the femur is an approximately cylindrical structure, absence of clearly defined fractures is likely to be an ongoing problem when interpreting plain radiographs. It is likely that the absolute residual values would increase when looking at indistinct fractures on real-world POPFF radiographs.

Assessment of reproducibility within assessors demonstrated significant variation in the segmentation residuals between trials and between assessors. The error was at worst, less than 2mm, which is encouraging and suggests good real-world consistency. The reliability of outcome measure (fracture position) was also acceptable with no significant differences in fracture position between trials for each assessor. Significant differences are likely because of the high precision of segmentation for each trial leading to results which may achieve statistical significance but not real meaningful difference.

Between assessor's variations were small in terms of residual error and fracture position. Standard deviation of residuals of the segmented line and fracture for all attempts by both assessors was 0.4mm in the worst case (y axis, fracture segmentation task), indicating that 95% of attempts by either assessor may fall within a 0.8mm range of accuracy. Variation between assessors in fracture position only reached significance when assessing segmented fracture position in the y plane. In this example median fracture position difference is less than 0.4mm. These results suggest that the variation between assessors is small enough to not affect clinical interpretation.

5.1.4.1 Limitations

The method described in this study involves the use of a standard computer mouse and open source image manipulation software, the latter may not normally be used by specialists in trauma and orthopaedics. Using such tools has obvious drawbacks because the lack of familiarity may increase the inaccuracy of measurements and reduce reliability within and between assessors. However, this pilot study demonstrates a high level of accuracy is possible and a low level of meaningful variability is evident either between or within assessors. Whilst this study demonstrates the efficacy of manual segmentation methods in a very simple example, the application such techniques will need to be explored in a more complex POPFF segmentation scenario. It is likely that fracture identification will become more challenging in these scenarios and the next step in technique development must ensure that segmentation is reliable when normal differences in interpretation exist between assessors. Manual segmentation methods take time to complete and further work should focus on the development of reliable automated segmentation techniques to reduce the time burden on assessors.

5.1.4.2 Conclusions

This short study has demonstrated the development of a repeatable method of fracture line analysis using manual segmentation. This method can accurately segment and characterise simple fractures in a repeatable way. Errors are within acceptable limits and are a useful reference for comparison of errors attributable to more complex segmentation tasks in subsequent studies. Further work is required to apply this technique to a real-life POPFF analysis scenario.

5.2 Development of a POPFF manual segmentation algorithm

5.2.1 Introduction

Current and historical methods of POPFF description rely on the broad classification into groups or classes of fractures (Whittaker et al., 1974; Bethea et al., 1982; Mont, Michael A. and Maar, 1994; Johansson et al., 1981; Parrish and Jones, 1964; Duncan and Masri, 1995; Duncan and Haddad, 2014), which are clinically useful, but necessitate the loss of large amounts of potentially useful information about the nature and exact position of the fracture. Recent analysis has sought to describe fracture patterns but relies on subjective categorical description of fractures (Fenelon et al., 2019). It has been demonstrated that femoral fracture location and fracture shape are closely associated with the nature of the deforming forces (Tyler A. Kress, 1995; Gitajn, I. and Rodriguez, 2011; Rupprecht et al., 2011). Since the change in fracture patterns with varying position along the femur are likely to represent changes in the anatomical structure of the femur along its length, a relative measure of femoral location is likely to be useful in most cases.

Given that each femur will be of different length and most are obtained in an emergency setting with non-standard views and lack of scaling measures, the accuracy of absolute measurements is likely to be poor. Current Orthopaedic practice makes good use of the Vancouver / UCS classification as a relative measure, since the fracture location in categorised relative to the tip of the femoral stem (Duncan and Masri, 1995; Duncan and Haddad, 2014). A similar approach could be used when manually segmenting POPFF images to obtain a measure of fracture location relative to the length of the femur. Estimates of fracture position relative to the femur would involve measurements with reference to standard anatomical landmarks which have a relatively reliable relationship with overall femur length and structure. Such an approach might be achieved by segmenting each femur and then scaling to a standard template, which represents an ‘average’ femur using reliable bony landmarks which are relatively insensitive to changes in alignment and rotation. Automated proprietary methods exist for 2D segmentation of the intact proximal femur (BoneFinder, Centre for Imaging Sciences, The University of Manchester, UK) but these methods are not readily applicable to the whole femur with an implant in situ or when a fracture is present. In the absence of satisfactory automated methods, a manual approach could be used. Each image could be scaled to fit a template representing a standard femur. Such a template could be derived from radiographs of replica femurs, which are based on multiple 3D scanning of real human femoral specimens (SawBones, 2020). Scaling could be performed using the femoral length and or visible anatomical landmarks. Real world radiographic imaging rarely captures the whole femur in a single image. This limitation can be overcome by joining sequential images of the femur using bone and implant landmarks. When this is not possible, femoral landmarks can be used to scale the image. Distance from proximal border of femoral head to top of LT is the strongest proximal predictor of overall femoral length (Khanal et al., 2017; Steele and McKern, 1969; Jacobs, 1992) with a correlation co-efficient of over 0.75 in a European population. In the absence of a native femoral neck, distance from GT to LT may be used as an approximation but is a less precise predictor, $R = 0.55$ to 0.58, (Singh, S. et al., 2013; Parmar et al., 2015).

Given the variability between fracture images in femoral alignment and rotation, it is likely that pre-analysis transformation will be required to allow for comparison between images. To reduce the confounding, restriction of analysis to a single ‘standard’ view may be most useful. A majority of POPFF cases are likely to have AP views of the femur which would allow estimation of fracture position without unnecessary loss of data.

The aims of this study were to:

1- Describe the development of a manual segmentation method to estimate fracture location in a set of real POPFF radiographs.
2- Assess the error and repeatability of fracture segmentation in a random sample of patients with POPFF.

5.2.2 Segmentation method development

A template for a standard AP femur was derived from a plain radiograph of an anatomically accurate composite femur (SawBones, WA USA). The plain radiograph outline was identified using an edge detection filter (The GIMP Development Team, v 2.10.18, 2019) and a template was extracted from the resultant image (Figure 5-7). The template was flipped to represent a right femur in AP view and colour was changed to yellow to aid identification over greyscale radiographs and the GT and LT landmarks were indicated for ease of radiograph scaling.

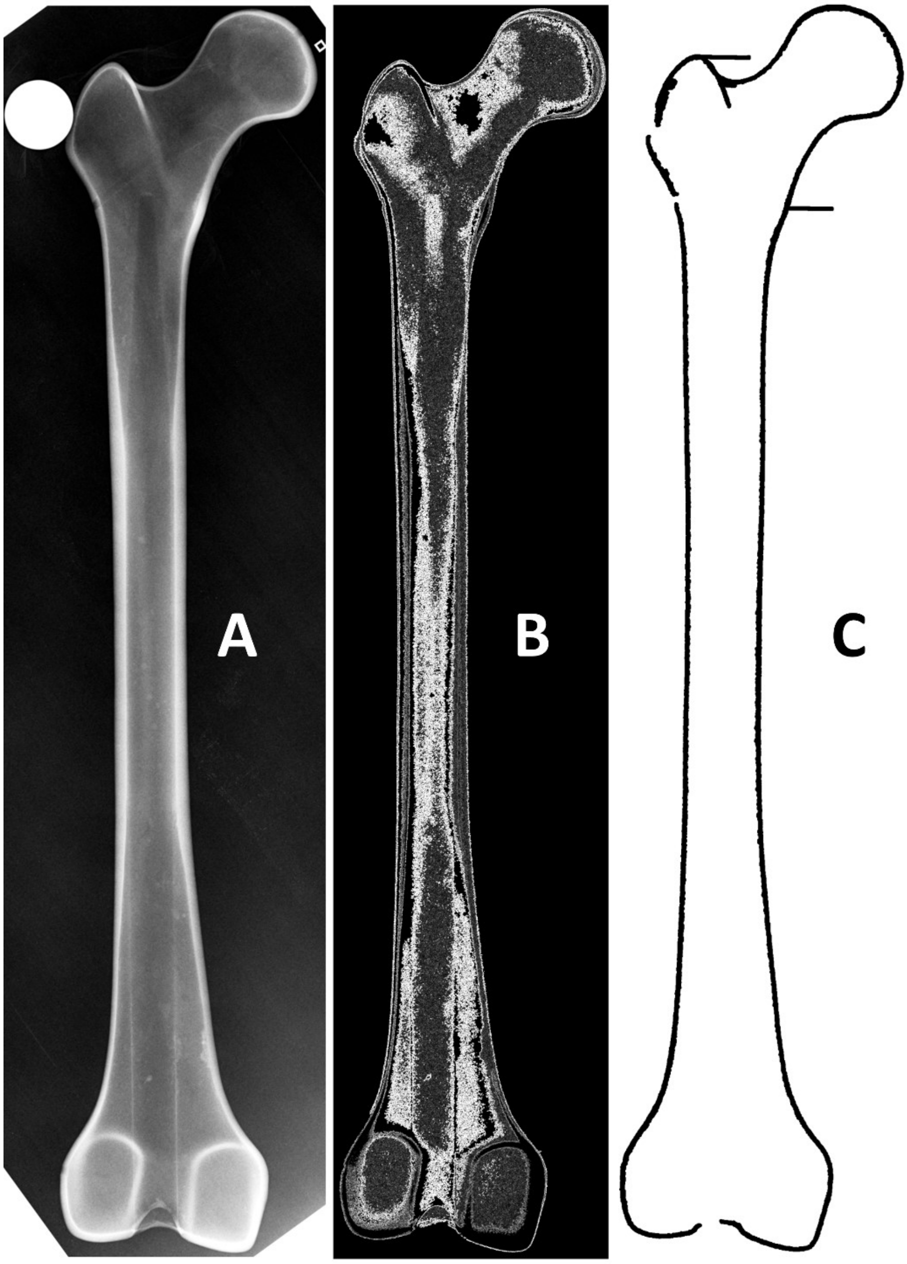


Figure 5-7 Development of a femoral template. A is plan AP femoral radiograph of composite femur, B is radiograph (A) following edge detection and C is the final template with horizontal lines indicating proximal greater tuberosity and midpoint of lesser tuberosity.

Sequential images from the same study were joined using visible implant and bone landmarks (Figure 5-8). Images were flipped so that they represented a right femur on AP view.

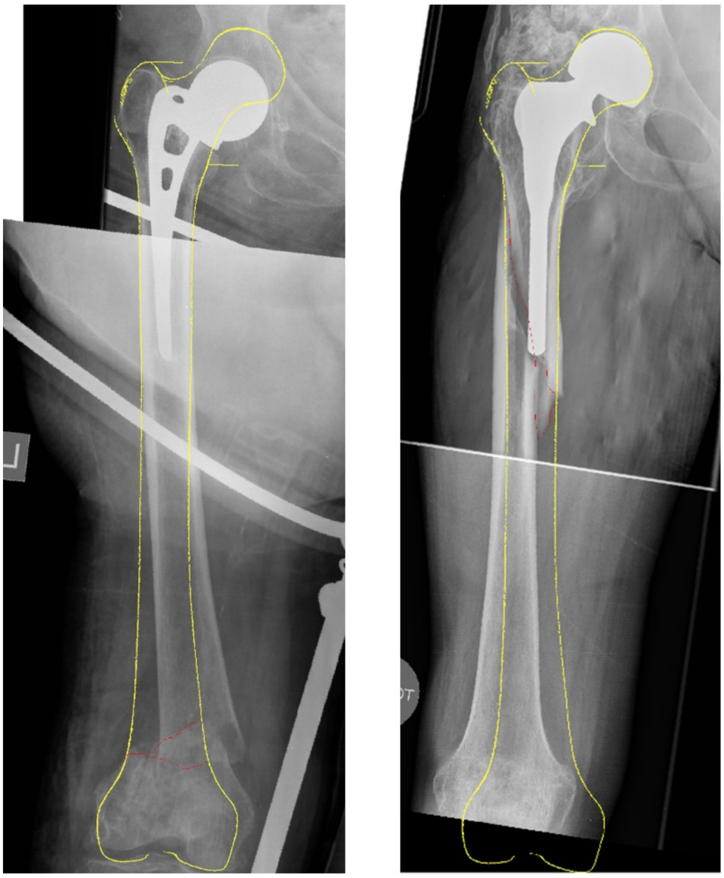


Figure 5-8 Images joined using bone and implant landmarks to obtain a full femur view. Template overlying landmarks of proximal femur demonstrating acceptable approximation to total femoral length. Template is then aligned to landmarks on a fracture fragment (left shows alignment with distal condyles and right shows alignment with proximal tuberosities). Note: Template is yellow, and fracture is red.

Femoral fractures with displacement were analysed by using available bone landmarks on each fracture fragment. The radiograph was translated until the fragments fit in the template and the additional fracture line was recorded (Figure 5-9).

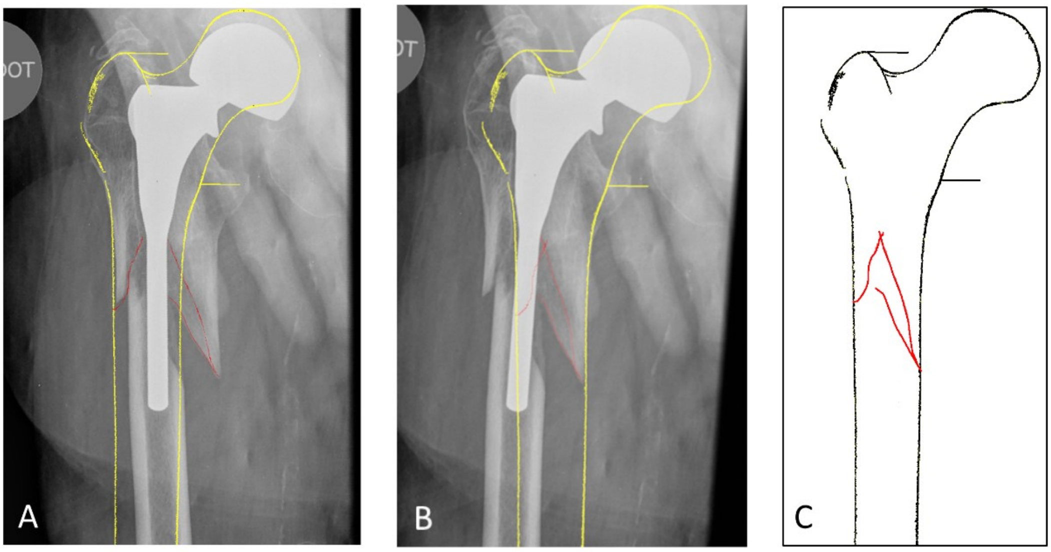


Figure 5-9 Manual segmentation of a POPFF using proximal femoral radiograph. A indicates alignment of template over greater tuberosity fragment, B indicates alignment of the template over the lesser trochanter fragment and C indicates the final fracture segmentation on the template (shown in black in panel C for clarity). Note: Template in yellow and fracture in red unless otherwise stated.

To allow estimation of fracture location relative to femoral implant, the shoulder and tip of the femoral implant were marked on the template (Figure 5-10).

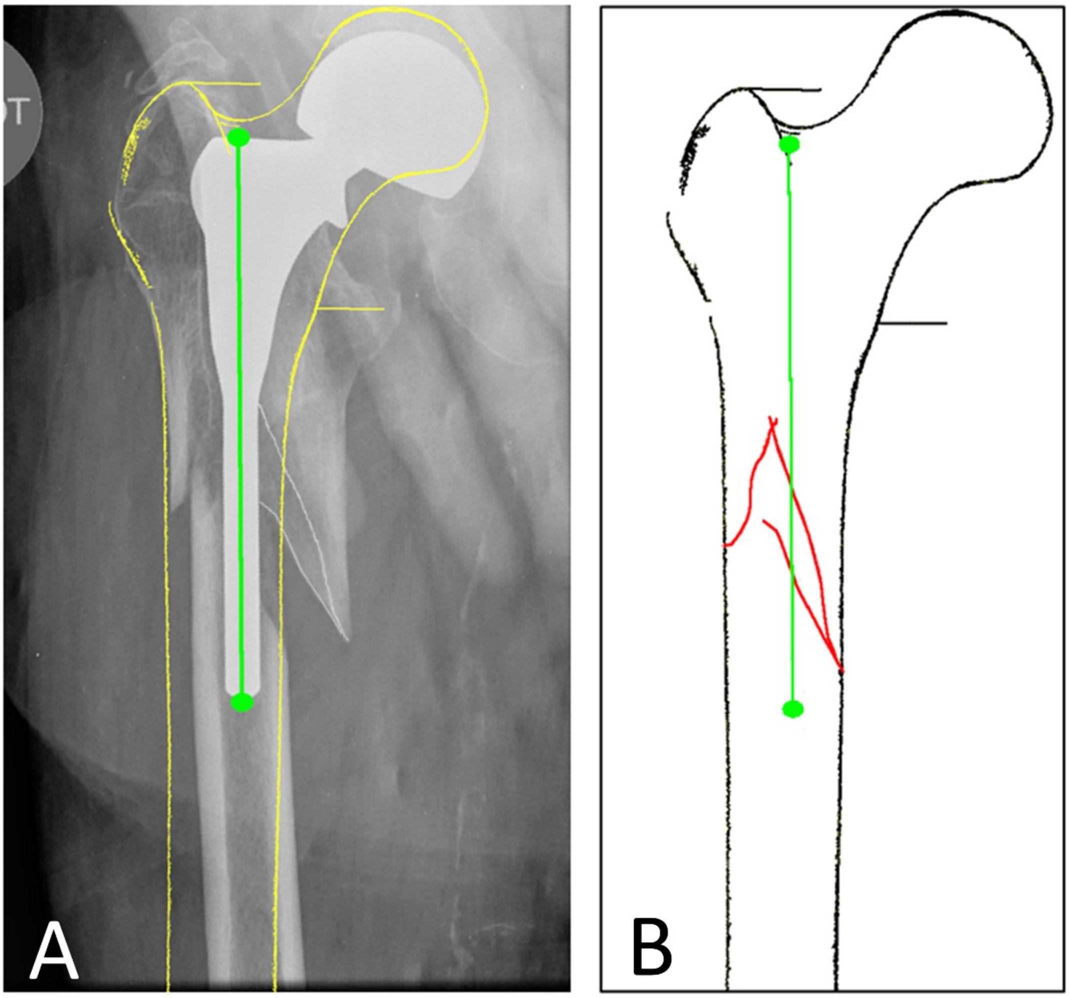


Figure 5-10 Stem marking from POPFF radiograph onto the standard template. A line approximating the long axis of the femoral stem was drawn (green line) and the proximal and distal points of the stem were marked (green circles). Note: Template is yellow (A) and black (B) for clarity.

5.2.2.1 Fracture classification methods

As previously discussed in the literature review (Chapter Two), POPFF fracture type may be classified into oblique, transverse, wedge fractures, spiral fractures and metaphyseal split fractures.

5.2.3 Methods

5.2.3.1 Data source

The data used in this study is as described in section 5.1.2 of this thesis. Only AP views of the femur were included.

5.2.3.2 Inclusion criteria

All patients with a plain anteroposterior radiograph demonstrating a POPFF following primary hip replacement with a cementless femoral stem were included in this analysis.

5.2.3.3 General methods

A random sample of 12 POPFF cases were selected from the complete dataset and manual segmentation was performed once and repeated after an interval of two months. The sample of twelve randomly selected cases were manually segmented by a second assessor who has undergone training over a period of two days. The aggregated and absolute results were compared between repeated segmentation by one assessor to assess within assessor reliability and between the original segmentation attempt and the second assessor to assess between assessor reliability.

5.2.3.4 Image preparation

Antero-posterior view of the femur were extracted for each case and flipped where necessary so that each case represented a right femur on AP view. Where adjacent femoral images were available, images were scaled, transformed and joined using implant and bony landmarks to ensure accuracy.

5.2.3.5 Segmentation method

Manual image segmentation was performed by drawing the visible fracture edges onto a standard size femoral template depicting an intact adult right femur (758 by 3121 pixels at 100% scaling). The femoral template consisted of an outline of an intact femur, and was derived from the outline of a plain radiograph of a composite femur modelled on a medium sized composite osteoporotic femur (10 pounds per cubic foot (PCF) Solid Foam with 16 mm Canal, Medium, Sawbones, WA, USA). The total length of the femur on plain radiograph was 447mm, giving a resolution of 0.14mm per pixel. The outline was obtained using proprietary edge detection using GIMP (The GIMP Development Team, v 2.10.18, 2019) and checked for accuracy. Anatomical locations relating to the greater and lesser trochanter were marked on the template and the template colour was set to yellow to allow for easy differentiation from underlying grey-scale radiographs.

The femur template was added as an image layer overlying the radiograph (single or joined image) and the radiograph was scaled and transformed (whilst maintaining aspect ratio) so that the bony landmarks on the radiograph matched the anatomical landmarks of the template overlying it (Figure 5-8).

Fracture edges were drawn in red (red = 100%, green = 0% and blue = 0%) with a single pixel width using image manipulation software (GIMP, The GIMP Development Team, v 2.10.18, 2019) as described above. The stem tip and shoulder were marked in green (red = 0%, green = 100% and blue = 0%) as described above. The template image layer was then exported so that each case was represented by a single template with fracture lines and stem length marked on it.

5.2.3.6 Variables

Fracture type (AO group), Fracture location relative to normalised femur (metaphyseal proximal pole = 0, distal metaphyseal pole = 1) and fracture location relative to stem (stem shoulder = 0, stem tip = 1).

5.2.3.7 Statistical methods

Data were tested for normality and non-normally distributed continuous variables were described as medians with interquartile ranges (IQR). To assess error the fracture position along the axis of a normalised femur (minimum fracture pixel position, median fracture pixel position and maximum fracture pixel position) was compared between repeated blinded segmentation attempts by the author after two months (Within assessor error) and between different assessors (between assessor error, by the author and SJ). To assess the proximity between fracture pixels in repeated segmentation tasks, the median (IQR) minimum Euclidian distance (straight-line distance) between the coordinates of each pixel and all other pixels in the repeated data set was calculated (Figure 5-11).

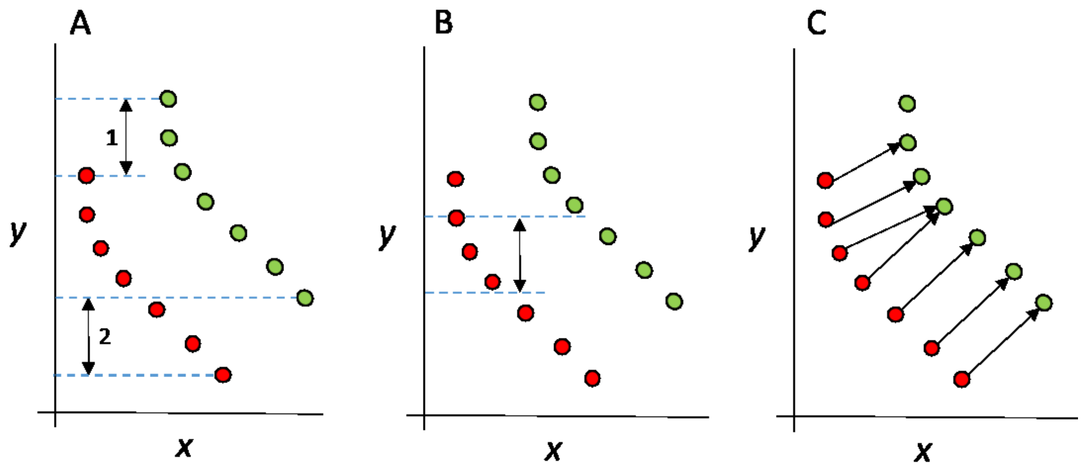


Figure 5-11 Distance measures between original (red) and repeated (green) fracture pixels. Note: comparison of minimum y values (A - 1), maximum y values (A - 2), median y values (B) and minimum Euclidian distance (C).

Visual comparisons of fracture plots for all repeated trials were performed using two-dimensional kernel density plots (`heat map`) which express the density of fracture pixels in a two-dimensional space. Fracture pixel coordinates were scaled to a normalised femur, the femoral stem and shown with reference to the fracture type. One-dimensional density of fracture position on the long axis of the femur were also displayed for each fracture subtype using violin plots.

5.2.4 Results

5.2.4.1 Numerical comparison

Median error for fracture position between repeated segmentation attempts by the same assessor was two percent or less on a normalised femur and less than 8mm in real terms (Table 5-4). Median error for fracture position (minimum, median, maximum and Euclidian) between segmentation attempts by two separate assessors was one percent or less on a normalised femur and less than 10mm in real terms.

Table 5-4 Error in fracture pixel segmentation between repeated trials within the same assessor and between different assessors.

	Error on normalised femur	Error in real terms
Within assessor comparison		
Fracture minimum (median [IQR])	0.00 [-0.01 to 0.00]	-1.4mm [-4.3 to 1.4]
Fracture centre (median [IQR])	0.00 [-0.01 to 0.01]	0.8mm [-5.1 to 6.7]
Fracture maximum (median [IQR])	-0.01 [-0.02 to 0.00]	-4.4mm [-8.38 to -0.36]
Minimum Euclidean distance (median [IQR])	0.01 [0.01 to 0.02]	9.7mm [6.0 to 13.3]
Between assessor comparison		
Fracture minimum (median [IQR])	-0.02 [-0.04 to 0.00]	-7.5mm [2.2 to 17.1]
Fracture centre (median [IQR])	-0.01 [-0.01 to 0.00]	-3.6mm [-0.6 to -6.6]
Fracture maximum (median [IQR])	-0.01 [-0.02 to 0.01]	-3.4mm [4.3 to -11.1]
Minimum Euclidean distance (median [IQR])	0.01 [0.01 to 0.02]	5.6mm [3.6 to 7.7]

Note: IQR indicates interquartile range.

5.2.4.2 Graphical comparison

Fracture pattern densities were similar between repeated measures on a normalised femur and relative to the femoral stem (Figure 5-12).

There was some variation between assessors noticeable on two-dimensional kernel density plots with the second assessor recording a greater density of fractures in the lateral inferior border of the greater trochanter whereas the original assessment recorded highest densities in the subtrochanteric region.

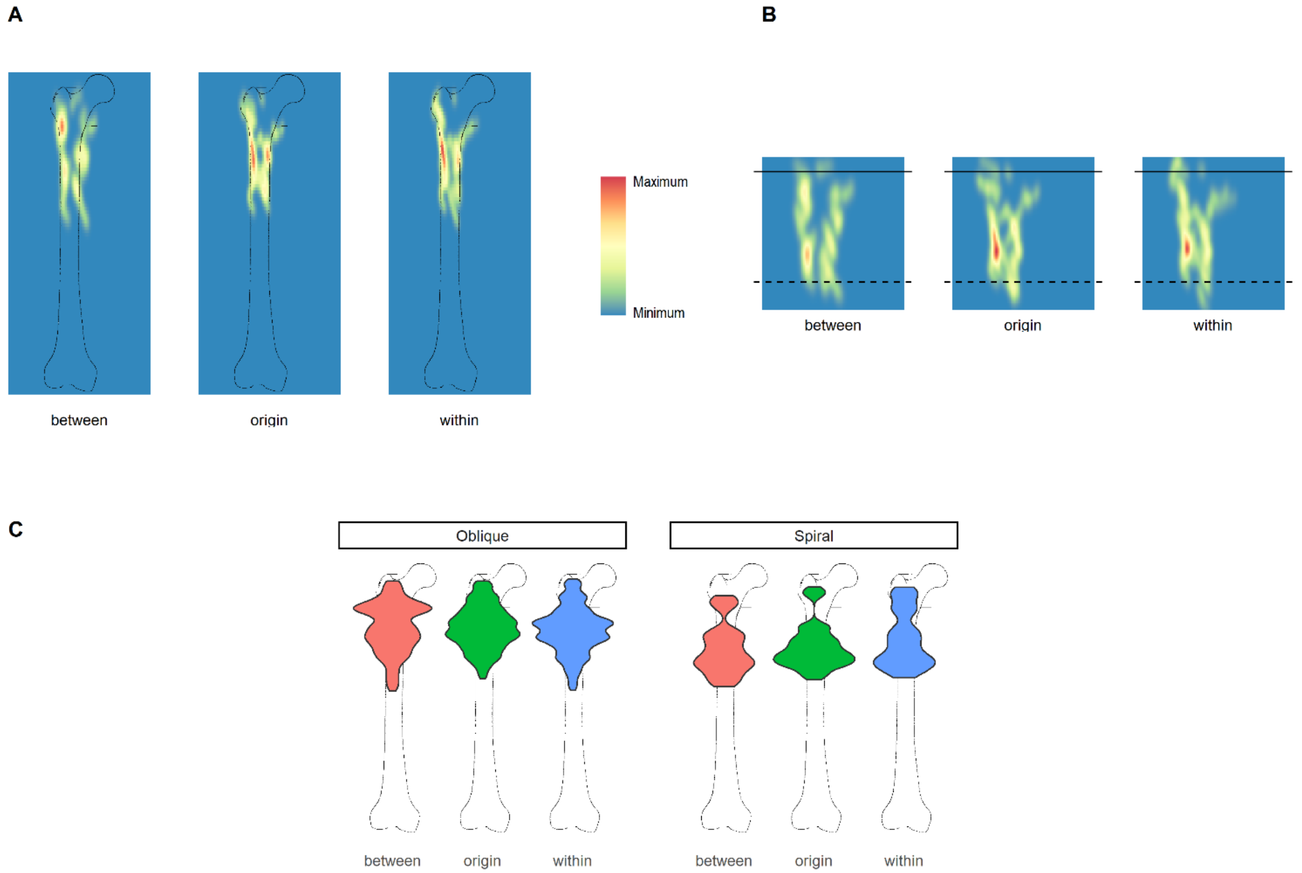


Figure 5-12 Fracture pattern density of a normalised femoral template (A) and relative to the femoral stem position (B) and between fracture subtypes. Origin indicates the original segmentation attempt, between is the trial conducted by a second assessor and within is the second trial by the same assessor.

5.2.5 Discussion

This study has demonstrated that the novel manual segmentation method is a reasonable method by which POPFF can be recorded and summarised with an overall error of two percent or less of the normalised femur length or less than 10mm in real terms. In addition, the use of graphical summaries may provide a useful tool for the description of groups of fracture patterns.

The results described are difficult to compare to the current literature given the novelty of the approach used. Current methods in studies describing POPFF involve multiple images of fractures (Jones, C. et al., 2015) or summaries using Vancouver classification systems (Abdel et al., 2016b; Abdel et al., 2016a; Chatziagorou et al., 2019a). Neither approach seems to adequately describe fracture patterns with enough precision to allow useful estimation of potential fracture mechanisms. The unified classification system and Vancouver systems (Duncan and Haddad, 2014; Duncan and Masri, 1995) are able to specify proximity to the stem, which typically occupies between 100mm and 170mm of the proximal femur, or approximately one third. Whilst this approach has obvious clinical relevance in terms of treatment planning, it does not give a useful idea to the reader as to where exactly the femur has fractured and thus how the fracture might have occurred. Given that the results from this validation study suggest an error of just 2% of overall femur length or 10mm in real terms, it would be reasonable to suggest that the methods described are a substantial improvement in the ability to accurately describe fracture location on the femur beyond current methods.

To put the error into context, the smallest anatomical feature of the femur, where a fracture might pass through on plain anteroposterior radiograph of the femur is the lesser trochanter, which ranges from three to 18mm in visible medial to lateral dimension, depending on femoral anteversion (Worlicek et al., 2017). Given this value one might expect a sufficient level of accuracy of segmentation to be less that the total size of the lesser trochanter, which might be 10mm on plain radiograph. The results demonstrate that in general the manual segmentation technique surpassed that requirement on most measures of fracture position error both on repeated assessment by the same and different assessors. The increase in error in segmentation from simple fracture edge segmentation (part one of this chapter) to segmentation of real-life periprosthetic fracture patterns from 2mm to 10mm, is likely to be related to the additional processes including: image joining and scaling, template positioning and the additional complexity of periprosthetic fracture patterns. Future reduction in error is likely to arise from improvements in these processes.

Graphical comparisons were also useful and present the viewer with a straightforward and easily understandable summary of fracture locations. In addition, demonstration of fracture position by fracture type allows the reader to understand which fractures are contributing to the overall fracture densities in the kernel density plot. This will be useful for understanding, not just the mechanism of fracture but where these mechanisms are acting on the femur to initiate fracture.

5.2.5.1 Limitations

There are many limitations with this work. Not all fractures are visible on plain radiographs. Radiograph beams may be blocked by the stem or fractures occurring out of plane of the beam may not be visible. The evaluation of this error is difficult given that lack of a proven gold standard with which to compare the results of this study too. One option is spiral CT scans, which subjectively are far better at detecting fractures in the periprosthetic femur but have no published sensitivity to detect fracture and the limited usage in patients in this dataset does not allow useful comparison. Sources of error in the preparation and segmentation process include lack of whole femur radiographs in the dataset, which means that sequential images must be joined, manual scaling and positioning of the image beneath the femoral template, identification of fracture lines and manual segmentation. All these steps may be automated in future and given the relatively promising performance of the methods in this study; such development may be warranted.

5.2.5.2 Conclusions

This study has demonstrated that periprosthetic femoral fractures may be summarised and analysed using a manual segmentation method. The error associated with this method is likely to be adequate for useful interpretation of fracture mechanisms.

Chapter 6 Analysis of fracture patterns in post-operative periprosthetic fracture of the femur around a cementless femoral stem.

This chapter describes the application of novel radiographic analysis technique developed in the preceding chapter to a data set of periprosthetic femoral fractures.

6.1 Introduction

An understanding of determinants of fracture pattern is important for three reasons. Firstly, understanding the mechanism of fracture helps us to understand common mechanical vulnerabilities of the femur-implant construct during POPFF. For example, if an implant has a higher than expected fracture frequency of rotational fractures, an increase in rotational stability may lead to a reduction in fracture frequency. Secondly, the risk following treatment is heavily dependent on fracture patterns. Fracture patterns around the stem have greater perioperative morbidity (Gitajn, I.L. et al., 2017; Reeves et al., 2019; Boylan et al., 2018) and may have a greater risk of mortality (Bhattacharyya et al., 2007) than fractures of the femoral shaft. Given that the risk of POPFF is never likely to be zero, an understanding of how the resulting fracture type might be manipulated by patient and implant selection at the time of primary surgery may be a useful preventative strategy. Finally, if we are to test design improvements, we must understand how to construct tests which accurately replicate the mechanisms which implant designs must resist.

Currently the literature on POPFF risk related to implant design focuses on two ends of the research spectrum. Clinical studies focus predominantly on the association of implant brand (Thien et al., 2014) and overall design features (Carli et al., 2017) on the risk of POPFF. At the opposite end of the spectrum, biomechanical testing has focussed on contribution of implant design on the force required to cause POPFF, using a range of methodology and approaches (Jakubowitz and Seeger, 2015). In between these two growing bodies of research is clear space where evidence linking the two should lie. Current evidence includes large observational studies using clinical fracture classification tools, which do not fully describe fracture mechanism (Abdel et al., 2016b; Khan, T. et al., 2017) and subjective assessments of fracture patterns, which do not differentiate cases based on time to fracture or precise design features (Fenelon et al., 2019), and make translation into biomechanical methods difficult. A useful addition to this domain should describe the distribution of real-life injury mechanisms occurring during POPFF such that biomechanical testing methods can be validated and then translated back into useful changes in implant design and clinical practice. Such work should also be able to illuminate the hypotheses derived from clinical studies on patient and implant factors which may affect the risk and mechanism of POPFF. Chapter Three outlined patient and design features which are associated with large changes in the risk of revision for POPFF, it is not unreasonable to imagine that such features may enact this effect through a change in fracture location towards the femoral shaft or a change in fracture mechanism, which may make revision surgery more or less difficult.

The aim of this exploratory study was to use a manual segmentation method to:

1- Describe fractures resulting from POPFF around cementless stems

2- Compare fractures occurring around cementless stems according to recorded patient and implant characteristics.

3- Describe the likely fracture patterns occurring within 90 days of implantation.

6.2 Methods

6.2.1 Data source

The data used in this study is as described in Chapter Five of this thesis. Only AP views of the femur were included.

6.2.2 Data quality

For all included images the mean (SD) for pixel dimensions was 2299.34 (575.56) wide by 2642.06 (476.83) high. 78.9% (112 of 142) of images had a pixel density of 96 x 96 pixels per inch (PPI) and 21.2% (30 of 142) of images had pixel density of 72 x 72 PPI.

6.2.3 Inclusion criteria

All patients with a plain AP radiograph demonstrating a UCS grade B or C POPFF following primary hip replacement with a cementless femoral stem were included in this analysis.

6.2.4 Image preparation

Full femur radiographs were used when available. Where this was not available, adjacent femoral images were scaled, transformed and joined using implant and bony landmarks to ensure accuracy. All images were flipped as required so that the images analysed all represented a right femur on standard AP view.

6.2.5 Segmentation method

Manual image segmentation was performed by drawing the visible fracture edges onto a standard size femoral template depicting an intact adult right femur (758 by 3121 pixels, 100% size of radiographic template) as described in the preceding chapter.

6.2.6 Variables

Patient age in years, sex and date of primary THR and date of POPFF were recorded. Date of plain radiographs prior to POPFF were used to establish whether the implant had been in situ for less than 90 days (early POPFF) or 90 days and longer (late POPFF) prior to fracture. This was used to identify stems which were unlikely to be stabilised by osseointegration. To compare the differences according to age, all patients were split into two groups (those younger than 80 years old and those aged 80 years or older) since this has been previously shown to be an age above which the risk of POPFF increases significantly (Zhu et al., 2015).

Variables derived from radiographs included: side of injury, brand of stem, construct type (hemiarthroplasty versus total hip replacement) and ipsilateral knee replacement. Stem design variables derived from the stem brand included: Collar versus no collar, grit blasted finish versus non-grit blasted finish, stem taper and stem metaphyseal cross sectional shape. All patients with hip hemiarthroplasty had a preceding hip fracture.

Fracture variables extracted from plain radiographs were Unified Class (Duncan and Haddad, 2014), fracture type (oblique, transverse, wedge, spiral and metaphyseal split), fracture location relative to femur (metaphyseal proximal pole = 0, distal metaphyseal pole = 1) and fracture location relative to stem (stem shoulder = 0, stem tip = 1). Normalisation of fracture position relative to the femoral shaft was performed by reversing and rescaling the y co-ordinates such that the y values for pixels at the metaphyseal proximal pole were equal to zero and increased to a value of one at the distal most point on the femoral condyles. The x coordinate values were then rescaled by the same value to maintain the aspect ratio of the recorded fractures. Normalisation of fracture position relative to the femoral stem was performed by reversing and rescaling the y co-ordinates such that the y values for pixels at the stem shoulder were equal to zero and increased to a value of one at the distal most point on femoral stem.

The x coordinate values were then rescaled by the same value to maintain the aspect ratio of the recorded fractures.

6.2.7 Statistical methods

To assess relationships between variables and fracture type univariate comparisons were made. Data were tested for normality and normally distributed continuous variables were summarised as mean values with standard deviation and non-normally distributed variables as medians with interquartile range. Numerical univariate comparisons between continuous variables with normal distribution were performed with t-test and non-normally distributed continuous variables with a Mann Whitney U test. Univariate comparison of ordinal and nominal variables were performed with Chi-squared tests for two groups and ANOVA tests for more than two groups. Graphical univariate comparisons were made with kernel density plots ('heat map') which express the density of fracture pixels in each two-dimensional space. One-dimensional density of fracture position on the long axis of the femur were also displayed for each fracture subtype using violin plots.

Given the retrospective nature of the data, univariate comparisons are likely to result in imbalance between the groups which may preclude useful interpretation. To overcome this, multivariate modelling was performed to assess the associated contribution of patient and implant factors on fracture position and type along the length of the femur.

Fracture position along the length of the femoral axis was modelled using a linear regression model to estimate the effect of variables on the fracture centroid position on a normalised femur with 95% CI. Variables were selected using an exhaustive search method. Fracture type (UCS and fracture type) was modelled using multinomial logistic regression to estimate the effect of variables on the OR with 95% CI of having a certain fracture type relative to a reference value. Odds of UCS grade was referenced against likelihood of B1 fracture and odds of fracture type was referenced against likelihood of `oblique` fracture. Wedge and transverse fractures were excluded due to low numbers, which reduced the power of the model. Variables were selected using relevant feature selection algorithm (random forests method) to maximise the accuracy of the model. The level of statistical significance was set at alpha = 0.05.

6.3 Results

125 patients from four centres were included in the study. The median (IQR) age of patients was 79.0 years (69.5 to 84.3) and 59.2% (74 of 125) were female (Table 6-1). The median time from primary surgery to POPFF was 0.6 years (IQR 0.1 to 3.6 years for 40 cases with complete data).

Table 6-1 Baseline demographics of Unified Class 'B' and 'C' periprosthetic femoral fractures around cementless femoral stems.

variable	Level	result
n		125
Age in years (median [IQR])		79.1 [69.5 to 84.3]
Gender (%)	*Female*	74 (59.2)
	Male	51 (40.8)
Time to POPFF in years (median [IQR])		0.6 [0.1, 3.6]
	Missing data (%)	85 (68.0)
POPFF before 90 days (%)	*Yes*	16 (12.8)
	No	56 (44.8)
	Missing data	53 (42.4)
Construct type (%)	*Total hip replacement*	91 (72.8)
	Hemiarthroplasty	34 (27.2)
Stem brand (%)	*ABG*	7 (5.6)
	AML	1 (0.8)
	Austin Moore	13 (10.4)
	Corail	35 (28.0)
	Fitmore	1 (0.8)
	Furlong Evolution	2 (1.6)
	Furlong HAC	40 (32.0)
	Mittelmeier	1 (0.8)
	Omnifit	4 (3.2)
	Oxford	1 (0.8)
	Quadra	1 (0.8)
	Stanmore	1 (0.8)
	Taperloc	7 (5.6)
	Taperloc microplasty	1 (0.8)
	Thompson	1 (0.8)
	Zweimuller	9 (7.2)
Unified classification (%)	*B1*	44 (35.2)
	B2	53 (42.4)
	B3	11 (8.8)
	C	17 (13.6)
Fracture type (%)	*Transverse*	5 (4.0)
	Wedge	2 (1.6)
	Oblique	61 (48.8)
	Spiral	41 (32.8)
	Metaphyseal split	16 (12.8)

Note: Statistics shown are numbers with percentages of variable displayed in parentheses unless otherwise stated. IQR indicates interquartile range, POPFF indicates periprosthetic fracture of the femur, HAC indicates hydroxyapatite coated.

6.3.1 Fracture patterns occurring in POPFF around cementless stems.

The greatest density of fracture lines was in the subtrochanteric area of the femur and located about the distal two thirds of the stem (Figure 6-1).

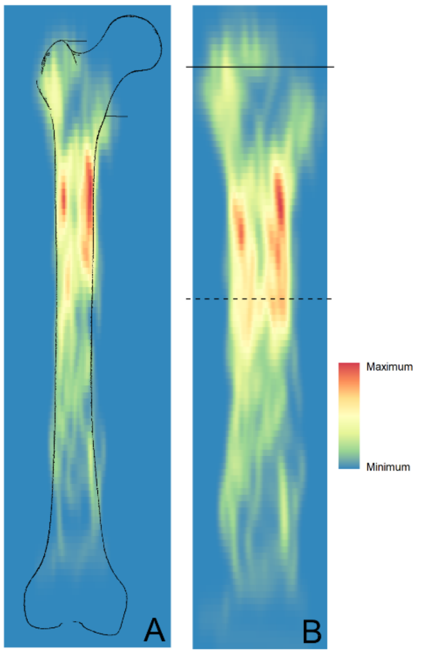


Figure 6-1 Fracture density of all fractures scaled to a standardised anteroposterior femur (A) and normalised to a stem length in situ (B). Solid horizontal line indicates stem shoulder level and dashed line indicates stem tip level.

The most common fracture type was an oblique pattern (n = 61 [48.8 %]) followed by spiral (n = 41 [32.8 %]) and metaphyseal split fractures (n = 16 [12.8 %], Table 6-1).

Oblique fractures were located predominantly in the proximal third of the femur and spiral fractures predominantly in the femoral diaphysis. Transverse and wedge fractures were located in the proximal and distal metaphysis and at the level of the stem tip respectively (Figure 6-2).

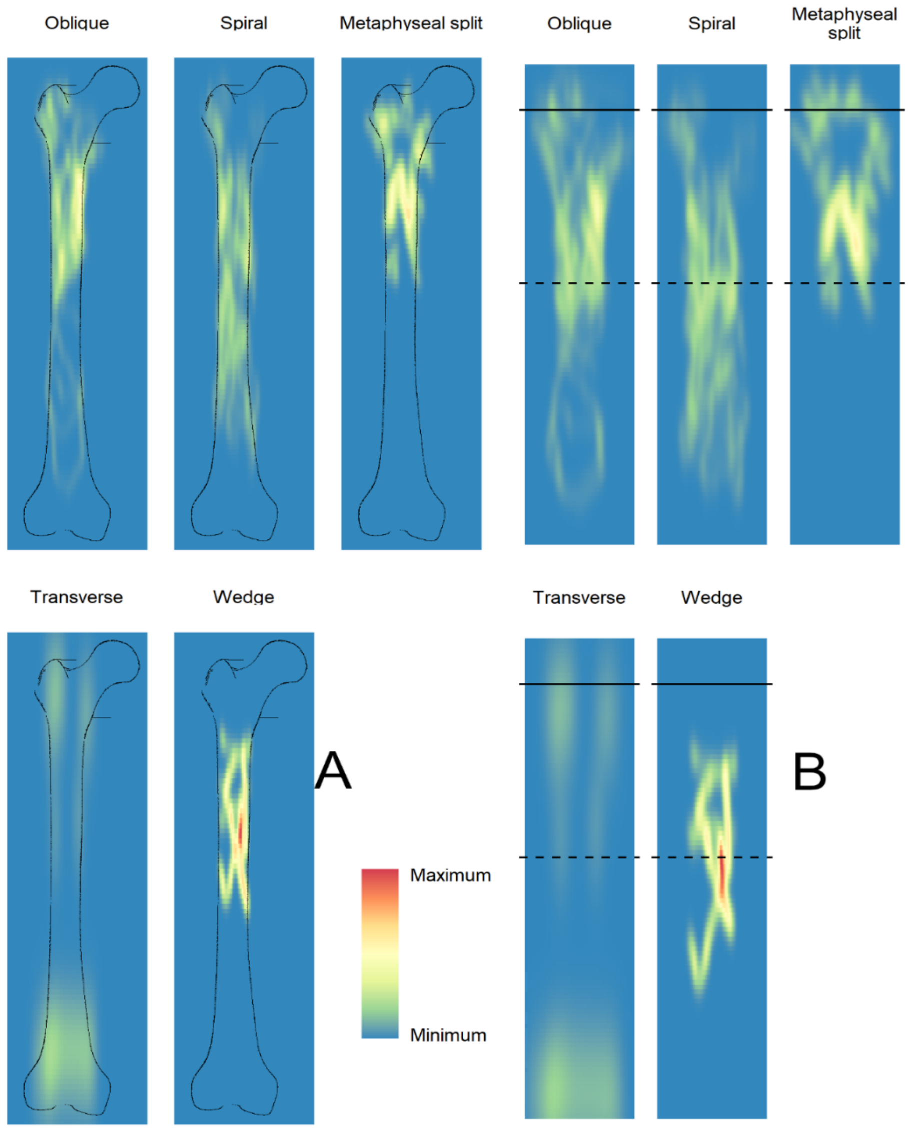


Figure 6-2 Fracture locations for all periprosthetic femoral fractures stratified by fracture type, scaled to a standardised anteroposterior femur (A) and normalised to a stem length in situ (B). Solid horizontal line indicates stem shoulder level and dashed line indicates stem tip level.

6.3.2 Univariate analysis of factors influencing fracture characteristics

The following results will demonstrate the associations between each individual variable and the distribution of fractures using univariate analysis.

6.3.2.1 Univariate comparison by gender

Female patients were older than male patients (81.0 years [IQR 70.6 to 85.9] versus 76.1 years [IQR 67.3 to 81.1], $p = 0.05$), had similar proportions of hemiarthroplasty construct types, a greater number of stems with a collar (68.9% versus 45.1%, $p = 0.01$), grit blasted surface finish (26.0% versus 11.8%, $p = 0.85$) and a double taper (49.3% versus 32.0%, $p = 0.05$, Table 6-2). Females experienced greater than three times the number of UCS grade C fractures than Males (18.9% versus 5.9%, p overall =0.17), although fracture types were similar.

Table 6-2 Univariate numerical comparison of fracture pattern by gender.

Variable	Level	Female	Male	p
n		74	51	
Age (median [IQR])		81.0 [70.6, 85.9]	76.1 [67.3, 81.1]	0.05
Gender (%)	*Female*	74 (100.0)	0 (0.0)	<0.001
	Male	0 (0.0)	51 (100.0)	
Construct type (%)	*Total hip replacement*	52 (70.3)	39 (76.5)	0.575
	Hemiarthroplasty	22 (29.7)	12 (23.5)	
Collar (%)	*Collarless*	23 (31.1)	28 (54.9)	0.013
	Collared	51 (68.9)	23 (45.1)	
Surface coating (%)	*Grit blasted*	19 (26.0)	6 (11.8)	0.085
	Non-grit blasted	54 (74.0)	45 (88.2)	
Taper (%)	*Single*	37 (50.7)	32 (64.0)	0.051
	Double	36 (49.3)	16 (32.0)	
	Triple	0 (0.0)	2 (4.0)	
Metaphyseal cross-sectional shape (%)	*Oval*	12 (16.4)	9 (17.6)	1
	Rectangular	61 (83.6)	42 (82.4)	
UCS (%)	*B1*	26 (35.1)	18 (35.3)	0.166
	B2	29 (39.2)	24 (47.1)	
	B3	5 (6.8)	6 (11.8)	
	C	14 (18.9)	3 (5.9)	
Fracture type (%)	*Oblique*	40 (54.1)	21 (41.2)	0.26
	Spiral	23 (31.1)	18 (35.3)	
	Metaphyseal split	6 (8.1)	10 (19.6)	
	Transverse	4 (5.4)	1 (2.0)	
	Wedge	1 (1.4)	1 (2.0)	

Note: Numbers with percentage of each variable given in parentheses unless otherwise stated. IQR indicates interquartile range, Grit blasted indicates a stem which has a grit blasted surface finish without additional coatings, and UCS indicates Unified Classification System.

The density of fractures in male femurs was concentrated in the subtrochanteric region of the femur versus a more even distribution of fractures along the femoral axis in females. Most fractures were concentrated in the distal half of the stem body, with females experiencing a greater density of fractures distal to the stem tip than males (Figure 6-3). Females experienced a greater density of spiral and oblique fracture in the femoral shaft than males.

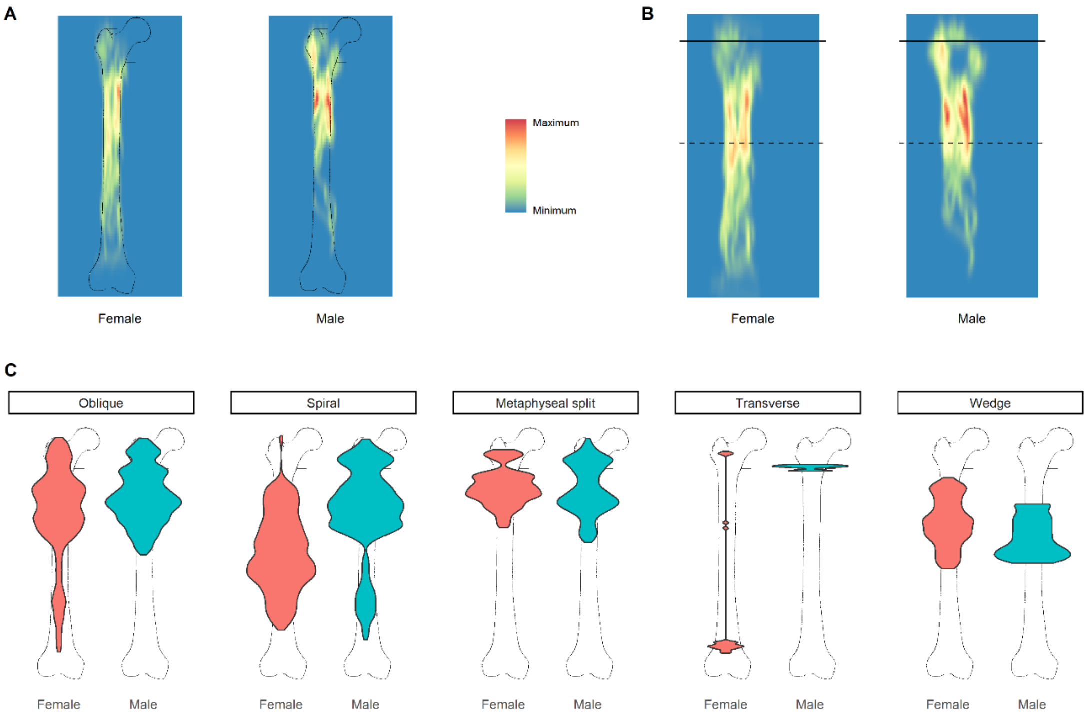


Figure 6-3 Univariate comparison of fracture position by gender. Figures show fracture density on a standardised anteroposterior femoral template (A), normalised to stem length in-situ (B) and on a normalised femoral template for each fracture type (C).

6.3.2.2 Univariate comparison by age group

Older patients had a greater number of hemiarthroplasties than younger patients (42.4% versus 13.6%, p<0.01). Stems used in older patients included a greater proportion of stems with grit blasted surface finishes (32.8% versus 9.1%, p<0.01, Table 6-3). Older patients experienced greater than three times the number of UCS C fractures than younger patients (22.0% versus 6.1%) and fewer B1 fractures (27.1% versus 42.4%, p overall= 0.04). Fracture type overall was similar between older and younger patients.

Table 6-3 Univariate numerical comparison of fracture pattern by age.

Variable	Level	80 Years or older	Younger than 80 years	p
n		59	66	
Age (median [IQR])		85.0 [81.1, 88.6]	70.3 [64.1, 76.0]	<0.001
Gender (%)	*Female*	39 (66.1)	35 (53.0)	0.193
	Male	20 (33.9)	31 (47.0)	
Construct type (%)	*Total hip replacement*	34 (57.6)	57 (86.4)	0.001
	Hemiarthroplasty	25 (42.4)	9 (13.6)	
Collar (%)	*Collarless*	21 (35.6)	30 (45.5)	0.348
	Collared	38 (64.4)	36 (54.5)	
Surface coating (%)	*Grit blasted*	19 (32.8)	6 (9.1)	0.002
	Non-grit blasted	39 (67.2)	60 (90.9)	
Taper (%)	*Single*	24 (42.1)	28 (42.4)	0.994
	Double	32 (56.1)	37 (56.1)	
	Triple	1 (1.8)	1 (1.5)	
Metaphyseal cross-sectional shape (%)	*Oval*	13 (22.4)	8 (12.1)	0.199
	Rectangular	45 (77.6)	58 (87.9)	
UCS (%)	*B1*	16 (27.1)	28 (42.4)	0.037
	B2	26 (44.1)	27 (40.9)	
	B3	4 (6.8)	7 (10.6)	
	C	13 (22.0)	4 (6.1)	
Fracture type (%)	*Oblique*	26 (44.1)	35 (53.0)	0.44
	Spiral	23 (39.0)	18 (27.3)	
	Metaphyseal split	8 (13.6)	8 (12.1)	
	Transverse	2 (3.4)	3 (4.5)	
	Wedge	0 (0.0)	2 (3.0)	

Note: Numbers with percentage of each variable given in parentheses unless otherwise stated. IQR indicates interquartile range, Grit blasted indicates a stem which has a grit blasted surface finish without additional coatings, and UCS indicates Unified Classification System.

Fractures in younger patients were concentrated around the medial subtrochanteric region, whereas fractures in older patients were distributed along the length of the femoral axis (Figure 6-4). Relative to the stem, distribution was like the femoral distribution with fractures in younger patients concentrated around the medial distal half of the femoral stem versus a broader distribution of fractures in older patients. Older patients experienced a greater density of oblique and spiral fractures of the femoral shaft relative to proximal femur.

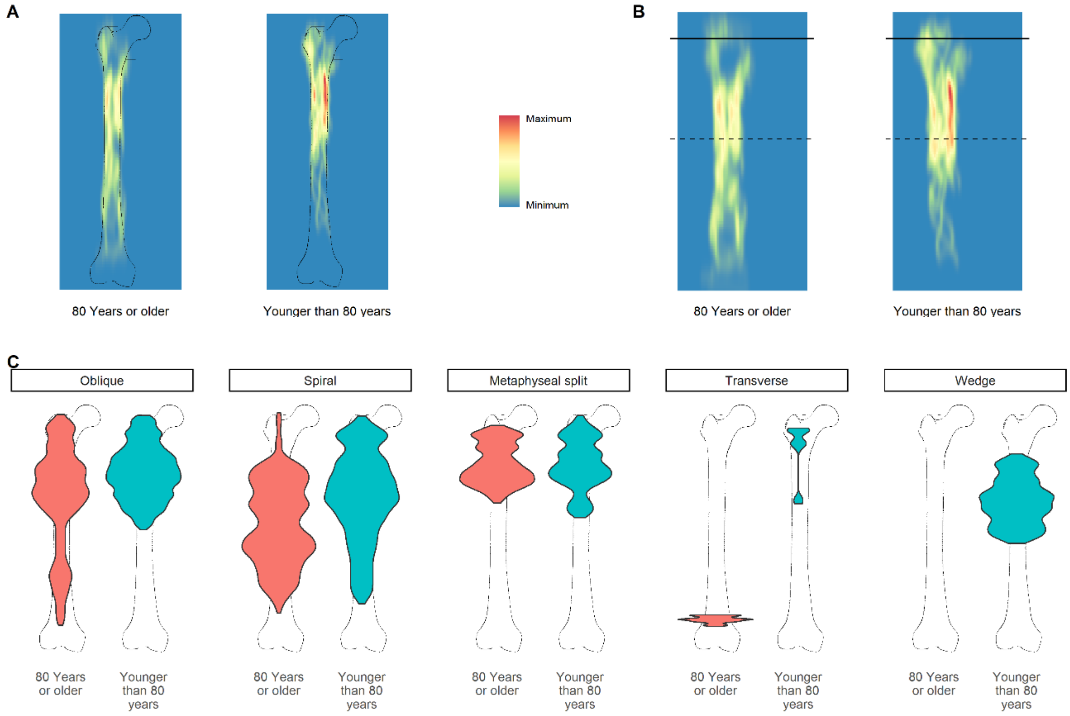


Figure 6-4 Univariate comparison of fracture position by age group. Figures show fracture density on a standardised anteroposterior femoral template (A), normalised to stem length in-situ (B) and on a normalised femoral template for each fracture type (C).

6.3.2.3 Univariate comparison by construct type

Patients with THRs were younger than those with hemiarthroplasty (77.0 years [IQR 68.9 to 81.0] versus 87.0 years [IQR 78.5 to 89.0], p<0.001) but had a similar gender distribution. For patients with THR versus hemiarthroplasty constructs; less stems had a calcar collar (44% versus 100%, p<0.01), less stems had a grit-blasted surface finish (12.2% versus 41.2%, p<0.01), more stems were single tapered (61.8% versus 41.2%) and less stems were double tapered (36.0% versus 58.8%, p overall=0.06).

For patients with THR versus hemiarthroplasty, the proportion of patients with UCS C fractures was almost six times less (6.6% versus 32.4%) and proportion of UCS B2 fractures was greater (47.3% versus 29.4%, p overall<0.01, Table 6-4). Fracture type for those with THR was also different to those with hemiarthroplasty, with approximately double the proportion of oblique fractures (57.1% versus 26.5%) and half the number of spiral fractures (26.4% versus 50.0%, p overall= 0.04).

Table 6-4 Univariate numerical comparison of fracture pattern by replacement construct.

Variable	Level	Total hip replacement	Hemiarthroplasty	p
n		91	34	
Age (median [IQR])		77.0 [68.9, 81.0]	87.0 [78.5, 89.0]	<0.001
Gender (%)	*Female*	52 (57.1)	22 (64.7)	0.575
	Male	39 (42.9)	12 (35.3)	
Construct type (%)	*Total hip replacement*	91 (100.0)	0 (0.0)	<0.001
	Hemiarthroplasty	0 (0.0)	34 (100.0)	
Collar (%)	*Collarless*	51 (56.0)	0 (0.0)	<0.001
	Collared	40 (44.0)	34 (100.0)	
Surface coating (%)	*Grit blasted*	11 (12.2)	14 (41.2)	0.001
	Non-grit blasted	79 (87.8)	20 (58.8)	
Taper (%)	*Single*	32 (36.0)	20 (58.8)	0.059
	Double	55 (61.8)	14 (41.2)	
	Triple	2 (2.2)	0 (0.0)	
Metaphyseal cross-sectional shape (%)	*Oval*	7 (7.8)	14 (41.2)	<0.001
	Rectangular	83 (92.2)	20 (58.8)	
UCS (%)	*B1*	32 (35.2)	12 (35.3)	0.001
	B2	43 (47.3)	10 (29.4)	
	B3	10 (11.0)	1 (2.9)	
	C	6 (6.6)	11 (32.4)	
Fracture type (%)	*Oblique*	52 (57.1)	9 (26.5)	0.04
	Spiral	24 (26.4)	17 (50.0)	
	Metaphyseal split	11 (12.1)	5 (14.7)	
	Transverse	3 (3.3)	2 (5.9)	
	Wedge	1 (1.1)	1 (2.9)	

Note: Numbers with percentage of each variable given in parentheses unless otherwise stated. IQR indicates interquartile range, Grit blasted indicates a stem which has a grit blasted surface finish without additional coatings, and UCS indicates Unified Classification System.

For patients with total hip replacement, overall fracture density was concentrated in the subtrochanteric region of the femur, whereas fractures around hemiarthroplasty constructs were distributed more evenly along the femoral diaphysis (Figure 6-5). Relative to the femoral stem, fractures around total hip replacement were concentrated around the distal half of the femoral stem, whereas fractures around hemiarthroplasties were more evenly distributed around the femoral stem tip.

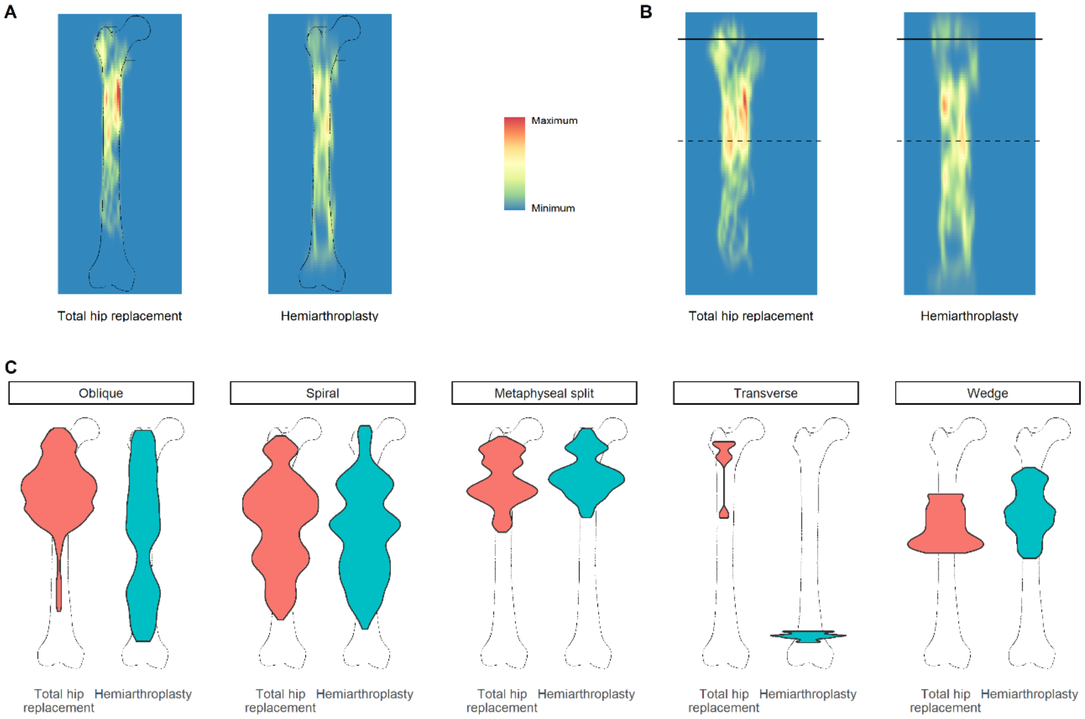


Figure 6-5 Univariate comparison of fracture position by construct type. Figures show fracture density on a standardised anteroposterior femoral template (A), normalised to stem length in-situ (B) and on a normalised femoral template for each fracture type (C).

The difference in fracture distribution appeared to be due to a difference in oblique fracture distribution, with a greater concentration of oblique fractures around total hip replacements occurring in the proximal femur versus a more even distribution along the femoral axis in patients with hemiarthroplasty.

6.3.2.4 Univariate comparison by time to periprosthetic fracture

Patients with early POPFF were of younger, had a similar gender distribution and had a statistically similar proportion of construct type to patients with late POPFF (Table 6-5).

Patients Early POPFF included more B2 fractures and fewer B3 fractures although the overall difference in UCS grading was not significant (p =0.12). Early POPFF fracture types were also different to late POPFF, with more spiral and metaphyseal split types and fewer transverse and wedge types (p overall =0.08).

Table 6-5 Univariate numerical comparison of fracture pattern by time from primary surgery to periprosthetic fracture of the femur.

Variable	Level	Within 90 days	90 days or later	p
n		16	56	
Age (median [IQR])		70.3 [64.7, 81.2]	80.0 [72.7, 86.5]	0.043
Gender (%)	*Female*	10 (62.5)	32 (57.1)	0.924
	Male	6 (37.5)	24 (42.9)	
Construct type (%)	*Total hip replacement*	11 (68.8)	41 (73.2)	0.972
	Hemiarthroplasty	5 (31.2)	15 (26.8)	
Collar (%)	*Collarless*	3 (18.8)	23 (41.1)	0.179
	Collared	13 (81.2)	33 (58.9)	
Surface coating (%)	*Grit blasted*	1 (6.2)	14 (25.5)	0.191
	Non-grit blasted	15 (93.8)	41 (74.5)	
Taper (%)	*Single*	3 (18.8)	35 (64.8)	0.002
	Double	12 (75.0)	19 (35.2)	
	Triple	1 (6.2)	0 (0.0)	
Metaphyseal cross-sectional shape (%)	*Oval*	1 (6.2)	11 (20.0)	0.361
	Rectangular	15 (93.8)	44 (80.0)	
UCS (%)	*B1*	5 (31.2)	20 (35.7)	0.128
	B2	10 (62.5)	19 (33.9)	
	B3	0 (0.0)	7 (12.5)	
	C	1 (6.2)	10 (17.9)	
Fracture type (%)	*Oblique*	11 (68.8)	25 (44.6)	0.076
	Spiral	2 (12.5)	23 (41.1)	
	Metaphyseal split	3 (18.8)	3 (5.4)	
	Transverse	0 (0.0)	4 (7.1)	
	Wedge	0 (0.0)	1 (1.8)	

Note: Cases with unknown date of primary surgery are excluded from the comparison. Numbers with percentage of each variable given in parentheses unless otherwise stated. IQR indicates interquartile range, Grit blasted indicates a stem which has a grit blasted surface finish without additional coatings, and UCS indicates Unified Classification System.

A greater density of fractures occurred in the proximal femur for early POPFF versus late POPFF (Figure 6-6). Relative to the stem, maximum density of late POPFF was located around the stem shoulder, whereas early POPFF fracture density was spread over the distal half of the stem and beyond.

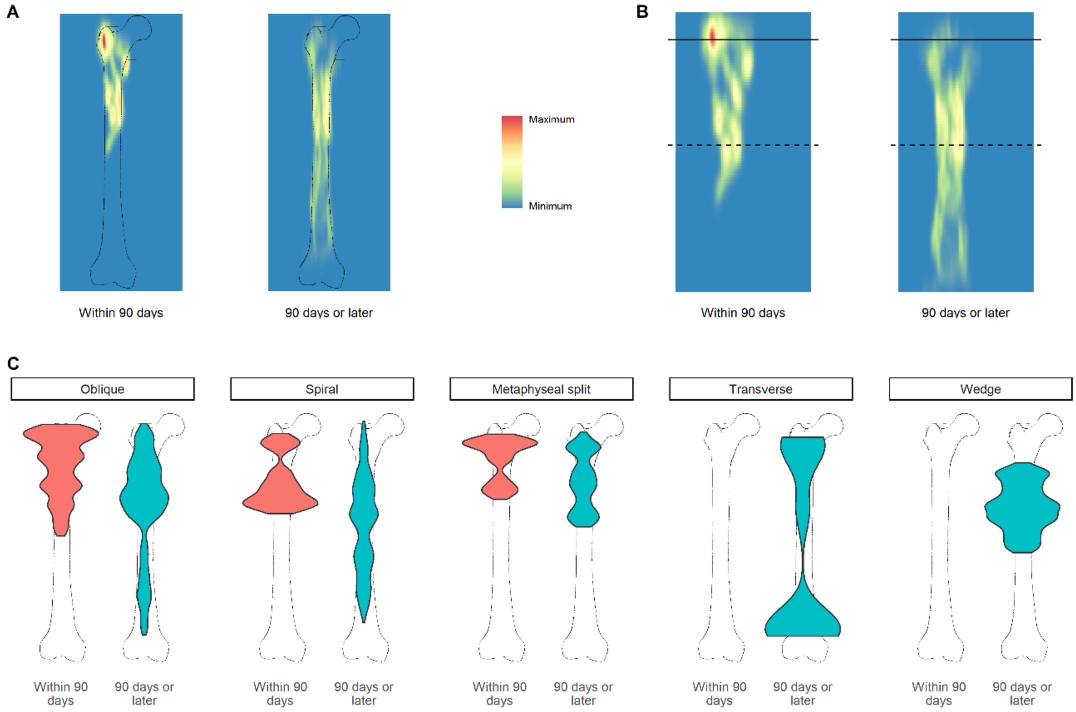


Figure 6-6 Univariate comparison of fracture position by time to periprosthetic fracture. Figures show fracture density on a standardised anteroposterior femoral template (A), normalised to stem length in-situ (B) and on a normalised femoral template for each fracture type (C).

6.3.2.5 Univariate comparison by stem collar

Median age of patients with a collarless stem was less than those with a collared stem (IQR) age (77.8 [69.5, 81.0] years versus 80.1 [69.7, 88.0] years, p= 0.05), included more males (54.9% males in collarless group versus 31.1% in collared group, p= 0.01) and no patients with hemiarthroplasty constructs (0.0% versus 45.9%, p<0.01). Patients with a collarless stem had a significantly different UCS profile versus the collared group (p<0.001), with fewer B1 fractures (21.6% versus 44.6%), a greater proportion of B2 fractures (64.7% versus 27.0%) and fewer type C fractures (2.0% versus 21.6%). Fracture type did not differ significantly between collarless and collared stem groups (p= 0.54, Table 6-6).

Table 6-6 Univariate numerical comparison of fracture pattern by calcar collar.

Variable	Level	Collarless	Collared	p
n		51	74	
Age (median [IQR])		77.8 [69.5, 81.0]	80.1 [69.7, 88.0]	0.051
Gender (%)	*Female*	23 (45.1)	51 (68.9)	0.013
	Male	28 (54.9)	23 (31.1)	
Construct type (%)	*Total hip replacement*	51 (100.0)	40 (54.1)	<0.001
	Hemiarthroplasty	0 (0.0)	34 (45.9)	
Collar (%)	*Collarless*	51 (100.0)	0 (0.0)	<0.001
	Collared	0 (0.0)	74 (100.0)	
Surface coating (%)	*Grit blasted*	9 (17.6)	16 (21.9)	0.722
	Non-grit blasted	42 (82.4)	57 (78.1)	
Taper (%)	*Single*	41 (80.4)	28 (38.9)	<0.001
	Double	8 (15.7)	44 (61.1)	
	Triple	2 (3.9)	0 (0.0)	
Metaphyseal cross-sectional shape (%)	*Oval*	7 (13.7)	14 (19.2)	0.58
	Rectangular	44 (86.3)	59 (80.8)	
UCS (%)	*B1*	11 (21.6)	33 (44.6)	<0.001
	B2	33 (64.7)	20 (27.0)	
	B3	6 (11.8)	5 (6.8)	
	C	1 (2.0)	16 (21.6)	
Fracture type (%)	*Oblique*	28 (54.9)	33 (44.6)	0.548
	Spiral	16 (31.4)	25 (33.8)	
	Metaphyseal split	6 (11.8)	10 (13.5)	
	Transverse	1 (2.0)	4 (5.4)	
	Wedge	0 (0.0)	2 (2.7)	

Note: Numbers with percentage of each variable given in parentheses unless otherwise stated. IQR indicates interquartile range, Grit blasted indicates a stem which has a grit blasted surface finish without additional coatings, and UCS indicates Unified Classification System.

Fractures in patients with collarless stems were concentrated in the subtrochanteric region versus a greater spread of fracture density along the femoral axis for fractures around collared stems. This difference appeared to be due to a greater density of oblique and spiral fractures in the femoral diaphysis (p <0.01, Figure 6-7).

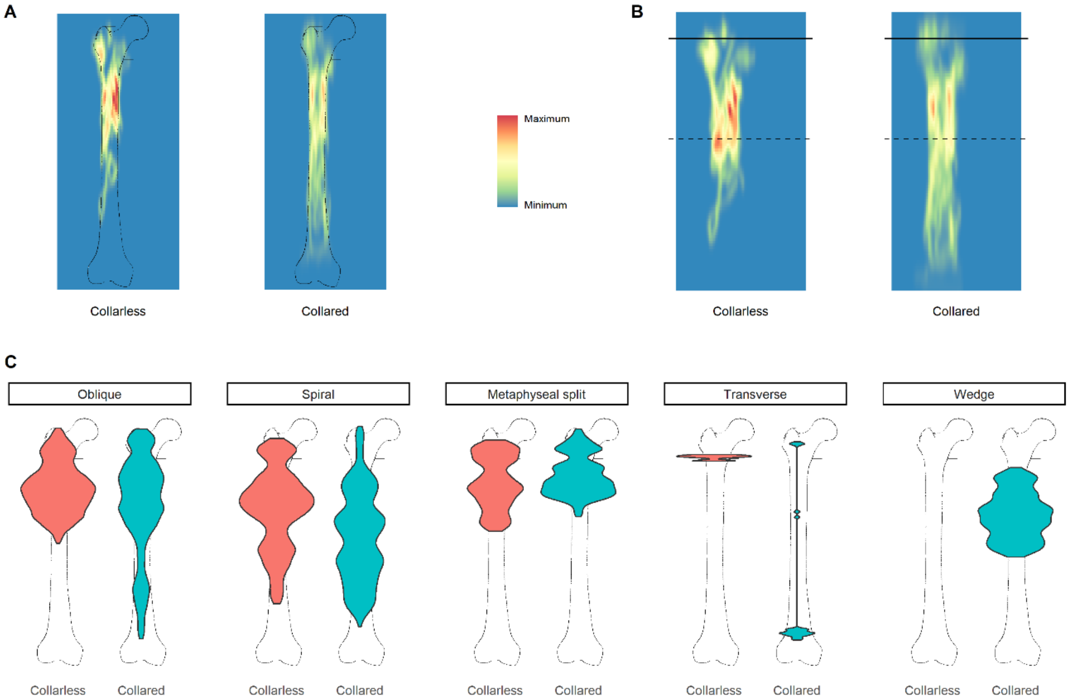


Figure 6-7 Univariate comparison of fracture position by collar. Figures show fracture density on a standardised anteroposterior femoral template (A), normalised to stem length in-situ (B) and on a normalised femoral template for each fracture type (C).

6.3.2.6 Univariate comparison by stem surface finish

In comparison to patients who had stems with non-fully grit blasted surface finishes, patients with fully grit blasted surface finish were (84.3 years [IQR 81.0 to 89.0] versus 76.1 years [68.2 to 81.5], p <0.001), included fewer males (24.0% versus 45.5%, p= 0.09), included fewer total hip replacement construct types (44.0% versus 79.8%, p<0.01) and included more stems with oval metaphyseal cross-sectional shape (56.0% versus 7.1%, p<0.01, Table 6-7).

In comparison to patients who had stems with non-fully grit blasted surface finishes, patients with fully grit blasted surface finished stems fractured with a greater proportion of UCS C fractures and less UCS B2 fractures but the overall difference did not reach statistical significance (p overall=0.26) Distribution of fracture types between the groups was similar (p=0.3).

Table 6-7 Univariate numerical comparison of fracture pattern by surface finish.

Variable	Level	Fully grit blasted	Not fully grit blasted	p
n		25	99	
Age (median [IQR])		84.3 [81.0, 89.0]	76.1 [68.2, 81.5]	<0.001
Gender (%)	*Female*	19 (76.0)	54 (54.5)	0.085
	Male	6 (24.0)	45 (45.5)	
Construct type (%)	*Total hip replacement*	11 (44.0)	79 (79.8)	0.001
	Hemiarthroplasty	14 (56.0)	20 (20.2)	
Collar (%)	*Collarless*	9 (36.0)	42 (42.4)	0.722
	Collared	16 (64.0)	57 (57.6)	
Surface coating (%)	*Grit blasted*	25 (100.0)	0 (0.0)	<0.001
	Non-grit blasted	0 (0.0)	99 (100.0)	
Taper (%)	*Single*	15 (62.5)	54 (54.5)	0.649
	Double	9 (37.5)	43 (43.4)	
	Triple	0 (0.0)	2 (2.0)	
Metaphyseal cross-sectional shape (%)	*Oval*	14 (56.0)	7 (7.1)	<0.001
	Rectangular	11 (44.0)	92 (92.9)	
UCS (%)	*B1*	8 (32.0)	36 (36.4)	0.264
	B2	8 (32.0)	45 (45.5)	
	B3	3 (12.0)	7 (7.1)	
	C	6 (24.0)	11 (11.1)	
Fracture type (%)	*Oblique*	14 (56.0)	46 (46.5)	0.301
	Spiral	7 (28.0)	34 (34.3)	
	Metaphyseal split	1 (4.0)	15 (15.2)	
	Transverse	2 (8.0)	3 (3.0)	
	Wedge	1 (4.0)	1 (1.0)	

Note: numbers with percentage of each variable given in parentheses unless otherwise stated. IQR indicates interquartile range, Grit blasted indicates a stem which has a grit blasted surface finish without additional coatings, and UCS indicates Unified Classification System.

Overall distribution of fractures appeared to be similar relative to the normalised femur and to the femoral stem (Figure 6-8). Distribution of fracture types on a normalised femur where also not greatly different in appearance.

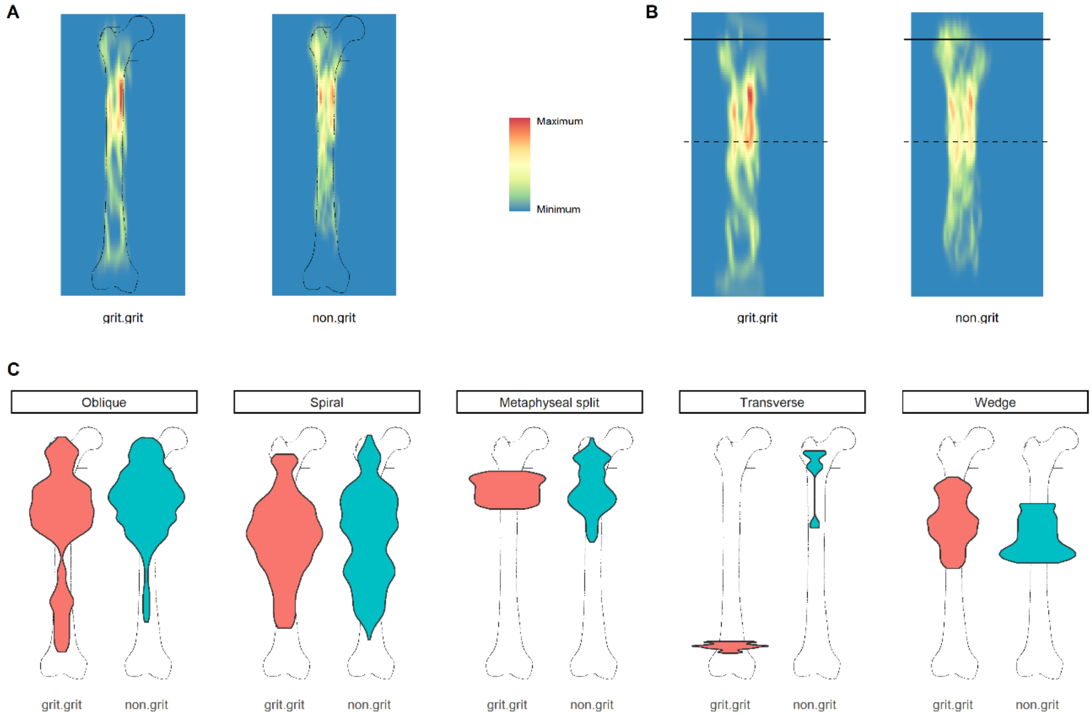


Figure 6-8 Univariate comparison of fracture position by surface finish. Figures show fracture density on a standardised anteroposterior femoral template (A), normalised to stem length in-situ (B) and on a normalised femoral template for each fracture type (C).

6.3.2.7 Univariate comparison by stem taper

Only two patients had a femoral stem which was triple tapered and these were excluded from the figures. The age distribution for patients with single and double tapered stems was broadly similar. Patients with double tapered stems versus single tapered stems included more male patients (46.4% versus 30.8%), a greater proportion of total hip replacements (79.7% versus 61.5%) and a greater proportion of stems with oval metaphyseal cross sectional shape (30.4% versus 0.0%, Table 6-8). UCS and fracture type for patients with single versus double tapered stems were similar overall.

Table 6-8 Univariate numerical comparison of fracture pattern by taper.

Variable	Level	Single	Double	Triple	p
n		52	69	2	
Age (median [IQR])		79.1 [69.4, 84.2]	78.7 [70.2, 84.0]	61.5 [52.3, 70.8]	0.551
Gender (%)	*Female*	36 (69.2)	37 (53.6)	0 (0.0)	0.051
	Male	16 (30.8)	32 (46.4)	2 (100.0)	
Construct type (%)	*Total hip replacement*	32 (61.5)	55 (79.7)	2 (100.0)	0.059
	Hemiarthroplasty	20 (38.5)	14 (20.3)	0 (0.0)	
Collar (%)	*Collarless*	8 (15.4)	41 (59.4)	2 (100.0)	<0.001
	Collared	44 (84.6)	28 (40.6)	0 (0.0)	
Surface coating (%)	*Grit blasted*	9 (17.3)	15 (21.7)	0 (0.0)	0.649
	Non-grit blasted	43 (82.7)	54 (78.3)	2 (100.0)	
Taper (%)	*Single*	52 (100.0)	0 (0.0)	0 (0.0)	<0.001
	Double	0 (0.0)	69 (100.0)	0 (0.0)	
	Triple	0 (0.0)	0 (0.0)	2 (100.0)	
Metaphyseal cross-sectional shape (%)	*Oval*	0 (0.0)	21 (30.4)	0 (0.0)	<0.001
	Rectangular	52 (100.0)	48 (69.6)	2 (100.0)	
UCS (%)	*B1*	21 (40.4)	22 (31.9)	0 (0.0)	0.661
	B2	19 (36.5)	32 (46.4)	2 (100.0)	
	B3	4 (7.7)	6 (8.7)	0 (0.0)	
	C	8 (15.4)	9 (13.0)	0 (0.0)	
Fracture type (%)	*Oblique*	25 (48.1)	34 (49.3)	0 (0.0)	0.79
	Spiral	18 (34.6)	22 (31.9)	1 (50.0)	
	Metaphyseal split	7 (13.5)	8 (11.6)	1 (50.0)	
	Transverse	1 (1.9)	4 (5.8)	0 (0.0)	
	Wedge	1 (1.9)	1 (1.4)	0 (0.0)	

Note: Numbers with percentage of each variable given in parentheses unless otherwise stated. IQR indicates interquartile range, Grit blasted indicates a stem which has a grit blasted surface finish without additional coatings and UCS indicates Unified Classification System.

Overall distribution of fractures appeared to be similar relative to the normalised femur and to the femoral stem (Figure 6-9). Distribution of fracture types on a normalised femur demonstrated a greater density of diaphyseal oblique fractures and proximal spiral fractures for double versus single tapered stems. Single tapered stems had a greater distribution of oblique fractures in the proximal femur and a greater distribution of spiral fractures in the femoral diaphysis.

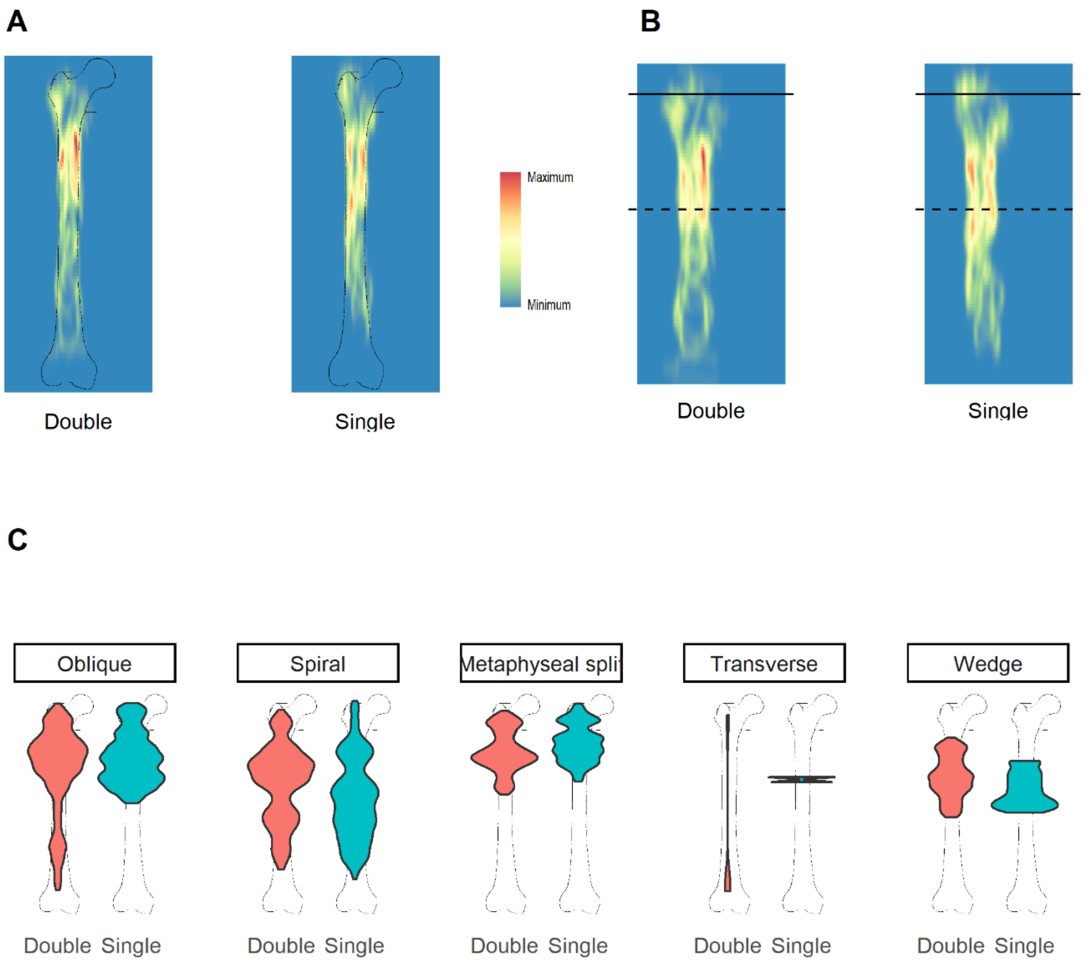


Figure 6-9 Univariate comparison of fracture position by stem taper with triple taper stems excluded (n=2). Figures show fracture density on a standardised anteroposterior femoral template (A), normalised to stem length in-situ (B) and on a normalised femoral template for each fracture type (C).

6.3.2.8 Univariate comparison by stem metaphyseal cross-sectional shape

There were just 21 cases with a stem which had an oval metaphyseal cross-sectional shape and one case where the metaphyseal cross-sectional shape was not known. Patients who fractured around a stem with oval metaphyseal cross-sectional shape were older (84.3 years [IQR 77.2 to 89.0] versus 77.8 years [IQR 69.0 to 82.1], p<0.01), had a greater proportion of hemiarthroplasty constructs (66.7% versus 19.4%, p<0.01). These patients also had more stems which had a grit blasted surface finish

(66.7% versus 10.7%, p<0.01) and single taper (100.0% versus 47.1%, p<0.01, Table 6-9).

Distribution of UCS between groups was similar but there were fewer metaphyseal split fractures around stems which had an oval metaphyseal cross-sectional shape (4.8% versus 14.6%, p=0.05).

Table 6-9 Univariate numerical comparison of fracture pattern by metaphyseal cross sectional shape.

Variable	Level	oval	rectangular	p
n		21	103	
Age (median [IQR])		84.3 [77.2, 89.0]	77.8 [69.0, 82.1]	0.008
Gender (%)	*Female*	12 (57.1)	61 (59.2)	1
	Male	9 (42.9)	42 (40.8)	
Construct type (%)	*Total hip replacement*	7 (33.3)	83 (80.6)	<0.001
	Hemiarthroplasty	14 (66.7)	20 (19.4)	
Collar (%)	*Collarless*	7 (33.3)	44 (42.7)	0.58
	Collared	14 (66.7)	59 (57.3)	
Surface coating (%)	*Grit blasted*	14 (66.7)	11 (10.7)	<0.001
	Non-grit blasted	7 (33.3)	92 (89.3)	
Taper (%)	*Single*	21 (100.0)	48 (47.1)	<0.001
	Double	0 (0.0)	52 (51.0)	
	Triple	0 (0.0)	2 (2.0)	
Metaphyseal cross-sectional shape (%)	*Oval*	21 (100.0)	0 (0.0)	<0.001
	Rectangular	0 (0.0)	103 (100.0)	
UCS (%)	*B1*	7 (33.3)	37 (35.9)	0.174
	B2	7 (33.3)	46 (44.7)	
	B3	1 (4.8)	9 (8.7)	
	C	6 (28.6)	11 (10.7)	
Fracture type (%)	*Oblique*	10 (47.6)	50 (48.5)	0.048
	Spiral	6 (28.6)	35 (34.0)	
	Metaphyseal split	1 (4.8)	15 (14.6)	
	Transverse	3 (14.3)	2 (1.9)	
	Wedge	1 (4.8)	1 (1.0)	

Note: One stem where the cross-sectional shape was unknown was not included in the analysis. Numbers with percentage of each variable given in parentheses unless otherwise stated. IQR indicates interquartile range, Grit blasted indicates a stem which has a grit blasted surface finish without additional coatings and UCS indicates Unified classification system.

The greatest concentration of fractures for both groups was around subtrochanteric region of the femur and the distal half of the femoral stem (Figure 6-10).

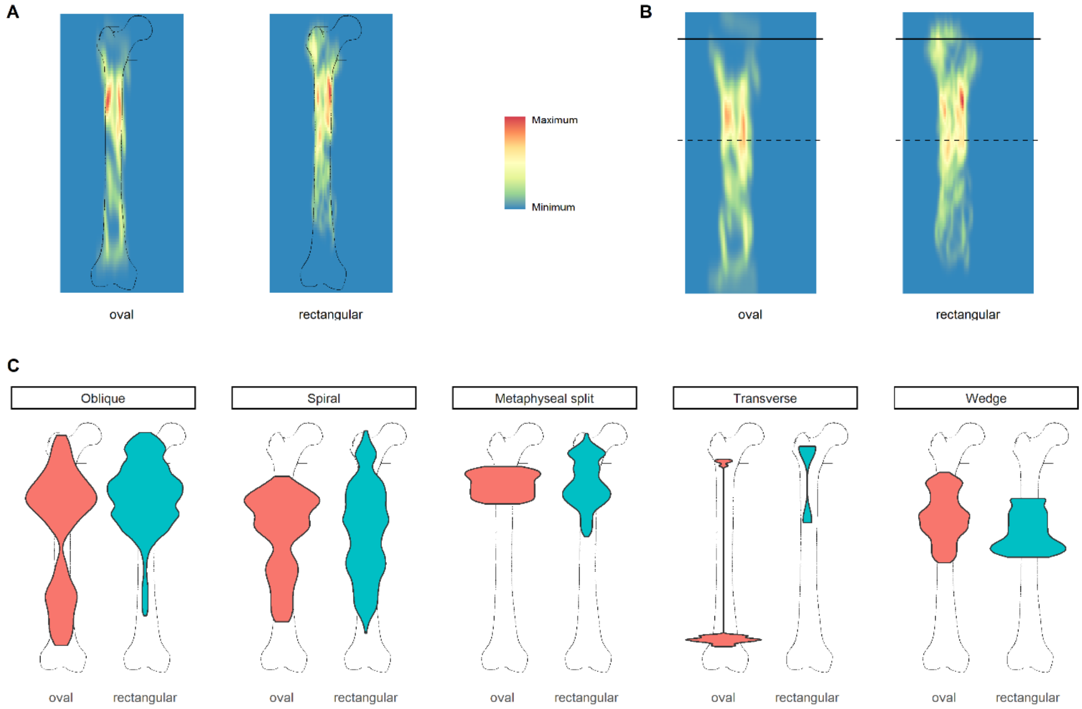


Figure 6-10 Univariate comparison of fracture position by metaphyseal cross-sectional shape. Figures show fracture density on a standardised anteroposterior femoral template (A), normalised to stem length in-situ (B) and on a normalised femoral template for each fracture type (C).

6.3.3 Modelling fracture position

Univariate linear regression modelling of fracture centroid position on the normalised femur indicated that a more distal fracture location is significantly associated with increasing age, female gender, POPFF after 90 days, hemiarthroplasty constructs, stem collar (borderline p =0.07), a fully grit blasted surface finish and an ovaloid cross sectional metaphyseal stem shape (Table 6-10). The largest significant univariate estimated effect on fracture centroid position was late POPFF (difference of 14% on a normalised femur distally) followed by hemiarthroplasty constructs and ovaloid metaphyseal cross-sectional shape (both with displacement of 10% on a normalised femur).

When the variables were combined into a multivariate model which had the largest adjusted R^2 value, variables associated with a significant change in fracture centroid position were associated with female gender, late POPFF and hemiarthroplasty constructs. The largest significant multivariate estimated effect on fracture centroid position was late POPFF (displacement of 15% on a normalised femur distally).

Table 6-10 Univariate and multivariate fixed effect estimates of explanatory variables on the fracture centroid position on the normalised femur.

Variable	Level	Fracture position (mean [SD])	Univariate coefficient (95% CI, p)	Multivariate coefficient (95% CI, p)
Age	[43.0,101.6]	0.3 (0.2)	0.00 (0.00 to 0.01, p=0.002)	-
Gender	Male	0.3 (0.1)	-	-
	Female	0.4 (0.2)	0.08 (0.02 to 0.14, p=0.006)	0.09 (0.02 to 0.16, p=0.019)
Early POPFF	Within 90 days	0.2 (0.1)	-	-
	90 days or later	0.4 (0.2)	0.14 (0.05 to 0.24, p=0.004)	0.15 (0.07 to 0.24, p=0.001)
Implant construct	Total hip replacement	0.3 (0.1)	-	-
	Hemiarthroplasty	0.4 (0.2)	0.10 (0.04 to 0.16, p=0.002)	0.12 (0.04 to 0.21, p=0.003)
Collar	Collarless	0.3 (0.1)	-	-
	Collared	0.4 (0.2)	0.05 (-0.01 to 0.11, p=0.073)	-
Taper	Single	0.3 (0.2)	-	-
	Double	0.3 (0.2)	-0.01 (-0.07 to 0.05, p=0.656)	-
	Triple	0.2 (0.0)	-0.18 (-0.42 to 0.05, p=0.128)	-
Surface finish	Not fully grit blasted finish	0.3 (0.1)	-	-
	Fully grit blasted finish	0.4 (0.2)	0.09 (0.02 to 0.17, p=0.011)	-
Metaphyseal cross-sectional shape	Rectangular	0.3 (0.1)	-	-
	Ovaloid	0.4 (0.2)	0.10 (0.03 to 0.18, p=0.009)	-

Multivariate model metrics: cases excluded due to missing data = 53, Log-likelihood = 34.42, AIC = -58.8, R-squared = 0.28, Adjusted R-squared = 0.25

Note: Value given is the mean fracture centroid position (standard deviation). Multivariate model with the largest adjusted R-squared value was chosen using exhaustive search. Coefficients indicate the change in fracture centroid position associated with a single unit change in the explanatory variable for a single variable (univariate) and when included with other variables (multivariate). SD = standard deviation, 95% CI indicated 95% confidence interval of the coefficient, p indicates the likely hood that the true effect is zero.

6.3.4 Modelling fracture type

The only significant univariate fixed effect which decreased the odds ratio of metaphyseal splitting fracture (versus oblique fracture) was female gender (OR 0.32, p<0.05, Figure 6-11). Significant univariate fixed effects which increased the odds of a spiral fracture (versus oblique fracture) included hemiarthroplasty constructs (OR 4.09, p<0.05) and Early POPFF (5.06, p<0.05). Significant univariate effects which increased the odds of transverse fracture (versus oblique fracture) was oval metaphyseal cross-sectional shape (OR 7.5, p<0.05). There was no statistically significant univariate relationship demonstrated with wedge fractures.

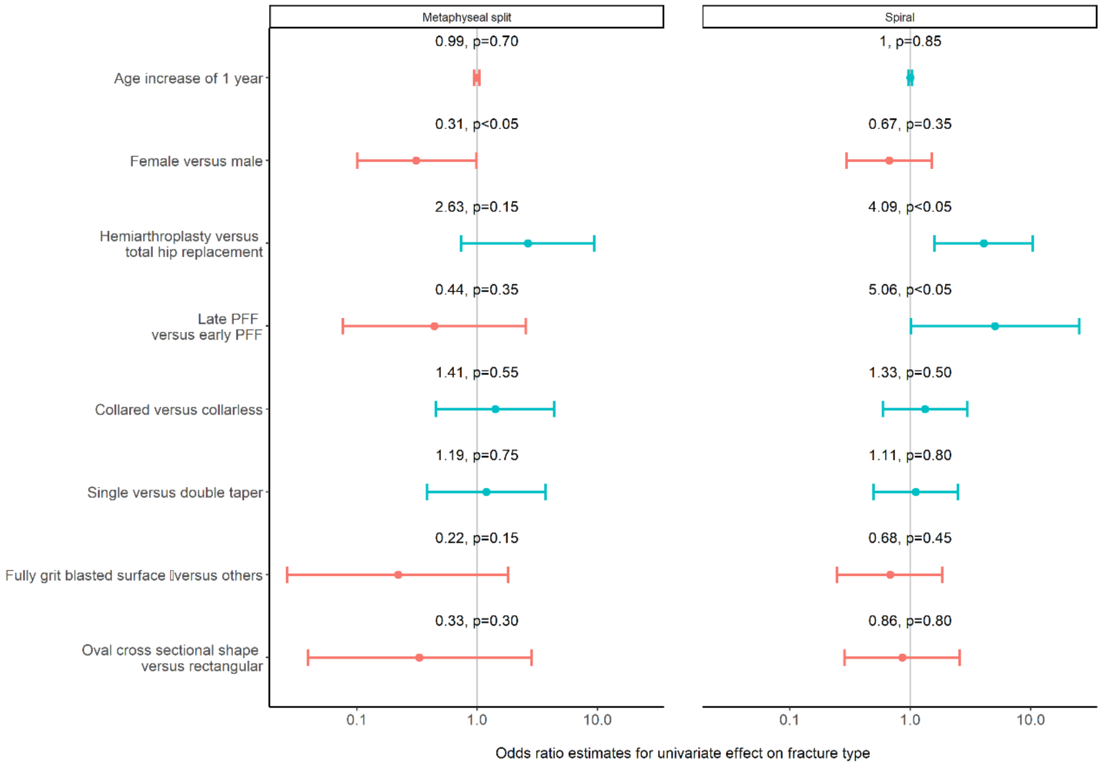


Figure 6-11 Univariate regression of each variable on the odds ratio (OR) of fracture type (versus oblique fracture). Labels indicate the odds ratio with p value above a graphical representation of odds ratio (dot) and 95% confidence interval (error bar). Red colour indicates OR of less than one (decreasing odds) and blue colour indicates OR of greater than one (increasing odds).

The most important variables were early POPFF versus late POPFF followed by hemiarthroplasty construct versus total hip replacement, as determined by a relevant feature selection algorithm. Addition of other variables reduced the accuracy of the model. The final model had an accuracy (SD) of 0.66 (0.17), meaning that based on the final variables the model could accurately predict the fracture type 66% of the time. Hemiarthroplasty (versus total hip replacement) was associated with an increased odds of spiral versus oblique fracture type (OR 4.3 [95% CI 1.2 to 15.3], p<0.05) and Late POPFF (versus early POPFF) was associated with an increased odds of spiral versus oblique fracture type (OR 5.6 [95% CI 1.1 to 28.6], p<0.05) and there was an association between late POPFF and a reduced odds of metaphyseal split fractures, although this effect was not significant (Figure 6-12).

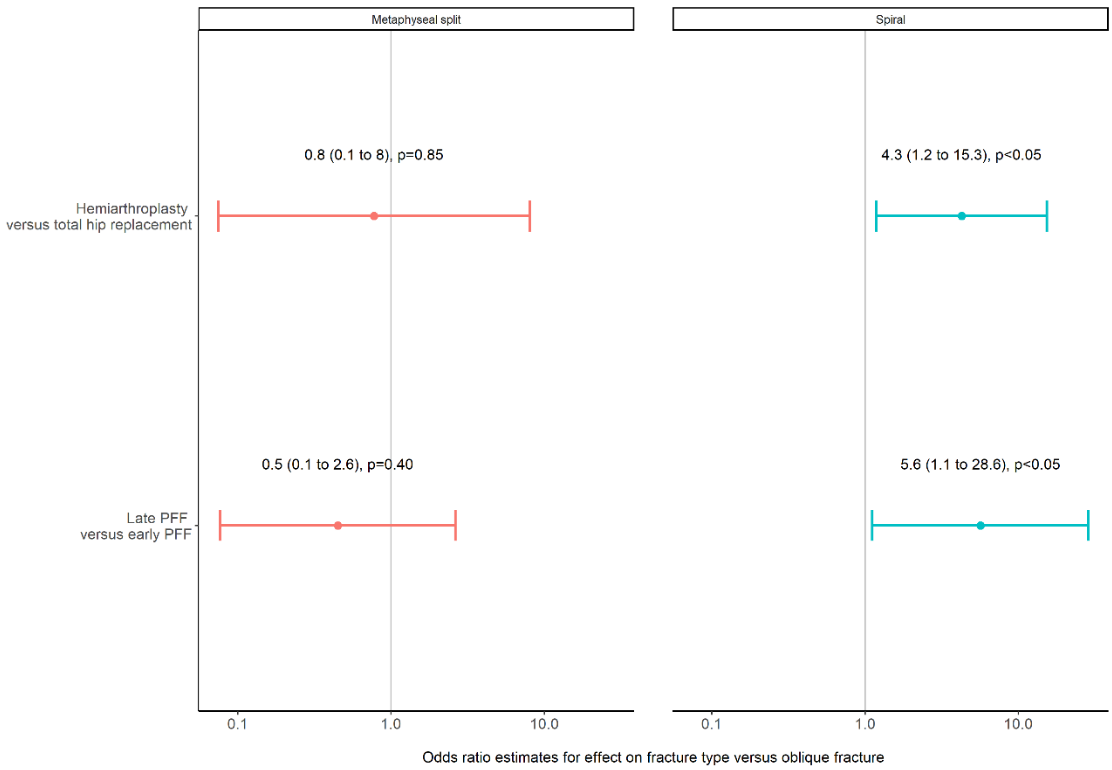


Figure 6-12 Fixed effects of variables of greatest importance on odds of fracture type (versus oblique fracture) in final multinomial logistic regression model.

6.4 Discussion

Most fractures occurred in the subtrochanteric region of the femur around the distal half of the femoral stem. Fracture position along the femoral axis was more distal with older patients, females and POPFF occurring after 90 days. The most common fracture pattern was oblique and spiral. Fracture patterns tended to occur in specific anatomical location and were associated with hemiarthroplasty constructs and time to fracture.

Almost nine out of ten fractures were UCS B type with the majority being B2 fracture types, which is in agreement with large studies in the published literature (Khan, T. et al., 2017; Abdel et al., 2016b). Most fractures occurred within the first 0.6 of a year following implantation and a third of which occurred within 90 days of hip replacement. This finding supports the assertion that a large proportion of fractures around a cementless femoral stem tend to occur within the first few months following surgery (Gromov et al., 2017; Thien et al., 2014), and is in agreement with the findings in this thesis based on large scale analysis of revision for periprosthetic femoral fracture from the NJR.

6.4.1 Fracture location

Fractures were most common in the subtrochanteric area of the femur and around the distal half of the femoral stem. The methods used are novel and direct comparison with other results is not possible but the results are broadly in agreement with Vancouver grades given in the literature (Khan, S. and Kyle, 2019; Abdel et al., 2016b; Chatziagorou et al., 2019a; Finlayson et al., 2019). This study also demonstrated that fractures types occurred within specific regions of the normalised femur. Notably, transverse fractures occurred around the femoral metaphysis and wedge fractures were centred on the stem tip, where there is likely to be a relatively abrupt change in modulus of elasticity between the flexible femoral diaphysis and the relatively stiffer metaphysis or stem respectively. Much of the changes observed by univariate comparison appear to be due to a change in spiral and or oblique fractures location. This new observation would not have been identified using conventional means given that the precise location of fractures would not have been evident when using the UCS classification.

Early fractures occurred more proximally than late fractures and were almost exclusively around the femoral stem. This may suggest that the press-fit stem-femur construct creates a focal point for fracture. This may be related to the generation of hoop stresses in the proximal femur, which reduce the tolerance of the femoral cortex to further loads which may occur during injury (Abdul-Kadir et al., 2008).

Fractures after 90 days were associated with a more distal location of approximately 15% of total femoral length and a greater density of spiral and oblique fractures in the distal diaphysis. This result represents a new and more accurate finding than would be possible using existing methods. As the cementless implant undergoes osseointegration there is an increase in strength and transference of shear stress as bone grows (Gao et al., 2019). When the stem is in a press-fit state, without associated bony growth, relative movement between the implant and bone are more likely and may allow implant movement relative to the femur and fracture. Fracture mechanics may differ before and after 90 days as a function of recovery of muscle function since and experimental study has shown that muscle action of the enveloping muscle groups may reduce the global strain values in an intact human femur (Simões et al., 2000).

It is possible that features associated with a more distal fracture configuration and less likely to lead to revision surgery. Implant design characteristics which were associated with a more distal fracture position were calcar collar, decreasing stem body taper, non-grit blasted surface finish. Interestingly, these relationships agree with the findings of the preceding registry study which found that these features were associated with a reduced risk of early periprosthetic fracture revision. This is the first time such a relationship has been quantified and provides the first signal that links registry-based observations with changes in real world fracture mechanics.

The final model demonstrated that a more distal fracture position was associated with female gender, hemiarthroplasty constructs and late fracture. The fixed effects were well beyond the expected error associated with the image processing methods (see preceding chapter) and are likely to represent real effects. Large scale registry studies have demonstrated that UCS C fractures are more common in women and older patients (Chatziagorou et al., 2018). This may reflect the greater risk of diaphyseal fractures in females versus males in native femur fractures (Ng et al., 2012) and the increased risk of diaphyseal fracture relative to trochanteric fractures in females versus males, which has been observed in elderly populations (Sine et al., 2019). The majority of strength in the femur is derived from the surrounding cortical bone (Holzer et al., 2009) and cortical thickness is the strongest single predictor of fracture loads in native femur models (Pottecher et al., 2016; Napoli et al., 2012). Reduction in cortical thickness and quality are most pronounced in women and those with neck of femur fractures (Osterhoff et al., 2016; Dorr et al., 1993; Napoli et al., 2012). It is possible that females and those with a history of hip fracture experience a greater loss of diaphyseal bone strength relative to metaphyseal bone strength than men and those with a history of hip osteoarthritis. This may precipitate a greater frequency of diaphyseal fracture relative to proximal metaphyseal fracture.

6.4.2 Fracture type

Half of fractures were oblique types occurring in the proximal half of the femur adjacent to the stem and a third were spiral types, occurring from the proximal to distal metaphyseal-diaphyseal junction. Only a small proportion of fractures were wedge or transverse types. This is in line with the current evidence which has suggested a majority of fractures are broadly oblique or spiral (Abdel et al., 2016b; Fenelon et al., 2019). In the native femur, oblique fractures in the proximal metaphysis and subtrochanteric region may be initiated by a rotational moment around a posterior greater trochanter impact (Keyak, 2000), whilst spiral fractures of the femoral shaft are typically caused by rotational loads (Gitajn, I. and Rodriguez, 2011). Rupprecht and colleagues suggested that rotational mechanisms lead to fracture around a cemented polished taper femoral stem in all cases, and pictures of fractures suggest an oblique pattern (Rupprecht et al., 2011). These results demonstrate that spiral fractures, which are likely to be caused by rotational loads, occurred along the length of the femur. Differences may be accounted for by implant mechanics since the polished taper stem, used by Rupprecht and colleagues, did not have a direct bond to the surrounding cement mantle and is able to move independently of the femur and cement mantle. In POPFF terms, a polished taper cemented stem may be analogous to a press-fit stem in very strong bone (cement). A similar concentration of oblique fractures around the stem can be seen in early fractures, where the cementless stem is held in the femur by press-fit and may move independently of the femur under high loads. For late fractures, where relative movement between the stem and femur is less likely, axial and rotational loads may be transferred across the stem-bone interface to the surrounding femur, leading to rotational fractures which are distal to the femoral stem.

Univariate modelling demonstrated that metaphyseal split versus oblique fractures were three times more likely in males and there was a weak association between increased odds of metaphyseal split fracture and total hip replacement, early POPFF, stems which were not fully grit blasted or rectangular in cross-sectional shape. Metaphyseal split fractures may be more likely under high loads (Demey et al., 2011), which may be more likely to occur during injuries where the proximal femur is of greater strength. Males may have been at greater risk of metaphyseal split fractures because they are likely to be heavier than females and are able to impart greater axial loads on the stem femur construct. Fracture loads are also likely to be greater in thicker, stronger bone of men (Dorr et al., 1993) and those with total hip replacement (rather than hemiarthroplasty). Greater required loads to initiate fracture in these cases may lead to a higher relative proportion of metaphyseal split fractures. Early POPFF may be a risk factor because prior to osseointegration the stem and femur may move independently, as already discussed. Stems with thicker modern mineralised coatings are likely to have greater levels of interference fit (Abdul-Kadir et al., 2008) and many of the stems with rectangular shape in this study had a horizontal stepped surface shape (Corail, DePuy Synthes) or an pronounced shelf (Furlong HAC, JRI), which may also increase transmission of stresses on the surrounding metaphyseal bone precipitating higher energy fracture during axial loading.

Univariate and multivariate modelling demonstrated strong associations between late POPFF and hemiarthroplasty constructs and increased odds of spiral versus oblique fractures. Spiral versus oblique fractures were five times more likely for late POPFF versus early POPFF and four time more likely following hemiarthroplasty versus total hip replacement. This is in agreement with the argument that late POPFF, where osseointegration is more likely, leads to greater transfer of shear stresses from stem to the femur and the subsequent rotational forces result in a larger proportion of spiral fractures rather than an oblique fracture around the stem (Rupprecht et al., 2011). Hemiarthroplasty constructs are likely to be a surrogate marker for neck of femur fracture and poorer bone strength relative to patients with total hip replacement. It may be that the relative loads required to cause a spiral fracture in patients with poorer bone quality is less resulting in a greater proportion of spiral fractures relative to oblique fractures.

6.4.3 Limitations

Primarily this study is limited by a small overall sample size, which reduces the power of conclusions and modelling methods. Missing time to POPFF was responsible for a large loss in sample size during multivariate modelling caused by poor patient recall, failure to record an exact primary surgery date and patients being treated for POPFF who did not undergo primary surgery in the same hospital, so that no available images of primary surgery available to determine the date of implantation. Given the strength of early POPFF as a predictor of fracture features in this study, further studies should seek to carefully determine the time of primary surgery such that larger samples can be analysed in future study. A small overall sample size precluded the useful analysis of variables occurring with low frequency in the study and reduced the power of associated modelling. Despite the significant positive findings, the variability between patients was large and overall, the linear models were poor predictors of fracture position. This may be because of the range of fractures which can occur secondary to variation in injury mode, anatomical variation between patients or unmeasured important differences in implant design and usage such as appropriate implant sizing and position. Given the complexity of the task the number of predictors could well grow beyond what is feasible to model and careful variable selection is required in future work to balance the number of predictors and the sample size. Greater power could be achieved by a much larger sample size or including more relevant predictors. Despite small sample size the accuracy of the final multinomial model was good but may also improve with greater sample sizes. This study only used anteroposterior images which may reduce the accuracy of fracture type. In addition, three-dimensional fractures are analysed in two dimensions which result in some loss of accuracy in determining fracture position and fracture type, particularly when oblique fractures are viewed out of plane. Two-dimensional data was expressed using one-dimension violin plots of fracture distribution along the length of the femoral axis, which prevents the reporting of fracture position across the width of the femur.

6.4.4 Conclusions

This small exploratory study has demonstrated that fracture location and pattern vary significantly between patients and may be dependent on patient gender, bone quality and the likelihood of osseointegration at the cementless stem bone interface. Early POPFF tend to occur almost exclusively around the distal half of the femoral stem and are predominantly oblique, metaphyseal split and spiral types. Early POPFF are likely to occur as a result of a range of fracture mechanisms, which may predominantly be a combination of axial loading and rotational forces. The manual segmentation method in this study has allowed for more accurate fracture analysis than conventional methods, which in turn has facilitated analysis of factors which affect the characteristics of POPFF for the first time. This information will be an important for the future analysis of fracture patterns and evaluation of implant performance relative to POPFF.

Chapter 7 Biomechanical testing of calcar collar using simulated periprosthetic femoral fracture model.

This chapter will describe biomechanical studies which tested the hypotheses developed so far in the thesis. Part one of this study forms the basis of the publication:

Lamb JN, Baetz J, Messer-Hannemann P, Adekanmbi I, van Duren BH, Redmond A, West RM, Morlock MM, Pandit HG. *A calcar collar is protective against early periprosthetic femoral fracture around cementless femoral components in primary total hip arthroplasty: a registry study with biomechanical validation.* **Bone and Joint Journal** 101-B (7):779-786 Jul 2019.

Chapters Three and Four identified important variables which may predict a change in the risk of periprosthetic fracture of the femur (POPFF) using a national observational dataset and then performed an exploratory analysis to define fracture patterns in a cohort of patients with POPFF to estimate the likely mechanism of fracture leading to POPFF. This chapter aims to test the hypotheses which have been created thus far using experimental methods. Part one of this chapter outlines the resistance to simulated POPFF between otherwise identical collared and collarless cementless stems. Part two assesses the validity of the use of composite bone models in POPFF testing by comparing the results of cadaveric and composite femur testing using identical methods. Finally, part three assesses the effect of collar contact on the resistance to fracture around collared cementless stems to validate the hypothesis proposed in Part one.

7.1 Comparison of collared and collarless stem in simulated early POPFF using a paired cadaveric femurs.

7.1.1 Introduction

Periprosthetic fractures are a rare but potentially devastating event leading to an increased risk of death (Gitajn, I.L. et al., 2017; Bhattacharyya et al., 2007), reduction in mobility and an increased risk of reoperation and revision (Phillips, J.R. et al., 2011). Chapter Four has shown that most fractures occur in the early post-operative period, prior to osseointegration of the femoral stem and a range of implant design features have a significant effect on the risk of POPFF in this initial post-operative phase.

A reduced risk of fracture was strongly associated with stems which had a calcar collar, a fully grit-blasted or roughened surface finish (versus porous or mineralised porous surface finishes), a rectangular metaphyseal cross-sectional shape and a stem body which was tapered in two planes (versus triple taper), but causation could not be inferred without validation by other methods. Design features which are extra osseous may be an appropriate target for reduction in POPFF since later adoption may be less likely to cause unintended consequences on stem performance during normal use. Such a potential target is a medial calcar collar, which may reduce risk of fracture by preventing relative movement between the stem and proximal femur during injury. This may make the calcar collar a good starting point for biomechanical validation of the hypotheses proposed thus far in this thesis.

Early POPFF around cementless stems most commonly cause a Vancouver $A_{1\text{-}2}$ fracture type or 'new B_2' (fracture of calcar with lesser trochanter) (Gromov et al., 2017; Taunton et al., 2015; Van Houwelingen and Duncan, 2011; Van Eynde et al., 2010; Capello et al., 2014). These fracture patterns suggest a torsional mechanism (Van Eynde et al., 2010). These hypotheses were corroborated in chapter 6, which demonstrated that early POPFF are likely to occur as a result of a combination of axial and rotational loading. Such an approach has been used previously in the literature to produce fractures around cemented polished taper femoral stems (PTS) (Ginsel et al., 2015; Morishima et al., 2014). Given that there are similarities in the relative movement of a PTS and a cementless stem prior to osseointegration, it is likely that a similar approach will produce fractures closely represent the most common position and fracture type during early POPFF.

Fracture loads between patients are not comparable due to differences in age and bone mineral density (Jakubowitz et al., 2009a), within patient (paired) comparison may provide more robust results (Thomsen et al., 2008; Jakubowitz and Seeger, 2015). This approach is most useful when comparing binary groups such a calcar collar versus no calcar collar.

The aim of this study is to experimentally quantify the difference in maximum load to fracture between collared and collarless cementless stems.

7.1.2 Methods

This study was performed in collaboration with the Professor Michael Morlock and his team at the Department of Biomechanics, Hamburg University of Technology, who provided expertise in experimental design and facilities for specimen preparation, storage and testing. Implants were supplied by DePuy Synthes (DePuy Synthes UK, Leeds).

7.1.2.1 Specimens and preparation

This study was performed in accordance with local ethical guidelines and regulations of Hamburg University School of Medicine. Biomechanical assessment of the effect of calcar collar on pre-osseointegration POPFF was performed by comparing maximum moment to fracture between collared and collarless Corail (DePuy Synthes, Leeds, UK) implants which are identical in every way apart from the presence of a calcar collar. To minimise cost of precious donated fresh frozen femora a small sample size was used. Five pairs of fresh frozen human female femora were dissected within 48-hours post-mortem, frozen at -20°C (2 freeze-thaw cycles per specimen), and defrosted overnight before biomechanical testing and kept moist using saline solution and plastic wrapping (Table 7-1). One pair of femora was excluded due to IOPFF and one pair due to adhesive failure between implant head and load applicator during mechanical testing.

Table 7-1 Donor demographics for female femora used in biomechanical testing.

Trial	Collar	Age (years)	Height (cm)	Side	BMD [gHA/cm³]
1	Yes	67	154	Right	1.35
1	No	67	154	Left	1.31
2	No	85	157	Right	1.08
2	Yes	85	157	Left	1.08
3	No	76	158	Right	1.33
3	Yes	76	158	Left	1.42

Note: BMD indicates bone mineral density measured in grams of hydroxyapatite per cubic centimetre.

The author performed all preparation and fixation to minimise variability. Femora were stripped of soft tissue and scanned using a 16-row Computer tomography scanner (CT, Brilliance 16 CT; Philips Healthcare, Hamburg, Germany) with a solid calibration phantom (Bone Density Calibration Phantom; QRM, Möhrendorf, Germany) to assess comparative bone mineral density between pairs (Lewiecki et al., 2009) and screen for pre-existing fractures and/or bony disease. Femora were prepared using standard equipment as per manufacturer's guidelines. Calcar reaming was performed on each femur and primary stability was assessed manually for each stem. Stem size was selected when the largest possible broach achieved rotational stability in the proximal femora on manual rotational stability assessment. Prior to stem implantation a plastic replica implant identical to the final implant was inserted into the cavity to reduce CT artefact and CT scanning was repeated to look for IOPFF. In each pair, one femur was implanted with a Corail collarless stem and the other with a Corail collared stem (both stems DePuy [standard offset, 135 degrees], Leeds, UK) of equal size and offset (Figure 7-1). Stem stability was assessed manually, and collar contact was confirmed when the implant was fully seated. CT scanning was repeated to ensure correct implant placement and exclude IOPFF. CT images were analysed using FIJI (ImageJ v1.52, NIH, USA).

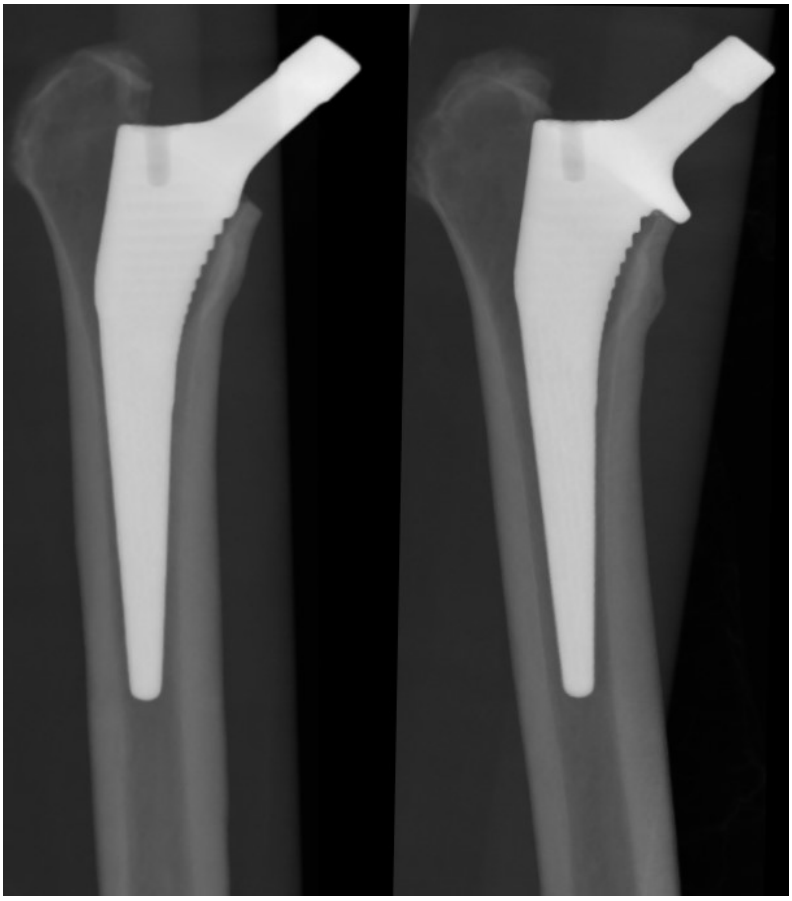


Figure 7-1 Reformatted CT demonstrating anteroposterior view of specimens immediately after implantation with a Corail femoral stem.

7.1.2.2 Experimental setup

The test set up was adapted from previous methods (Morishima et al., 2014). A mixed axial and rotational method was chosen because this has previously been shown to reproduce POPFF at the level of the stem (Morishima et al., 2014; Ginsel et al., 2015; Jakubowitz and Seeger, 2015) and is likely to be a common mechanism of injury in early POPFF around cementless stems (Chapter Six). Specimens were embedded distally in polymethylmethacrylate inside steel pots and stabilised with reinforcing screws to prevent axial rotation of the femur. Specimens were aligned in six degrees of varus in the coronal plane and vertical in the sagittal plane. Depth was adjusted so 40mm of diaphysis remained between the stem tip and the fixative. A 32mm CoCr head (DePuy, Leeds, UK) was fitted to the stem and each specimen was secured in a materials testing machine (MTS 858.2; Eden Prairie, MN, USA). The prosthetic head was fixed to the load applicator with adhesive (Figure 7-2). A vertical load was applied to the specimen to simulate single leg stance (1500N) for ten seconds to allow bedding in and stabilisation of stem press-fit (Kannan et al., 2014). Axial loading was maintained at 1500N and the head was rotated internally through 45^0 in one second to simulate a traumatic event and obtain more realistic mechanical properties of the proximal femur (Courtney et al., 1994). Video recording at 5000 Hz (CamRecord 5000, Optronis, Kehl, Germany) and 60Hz during trials (GoPro 4, GoPro, California, USA) and CT-scanning after fracture were performed to identify fracture patterns.

Figure 7-2 Experimental set up in the materials testing machine prior to fracture protocol.

7.1.2.3 Statistical methods

The maximum torsional moment prior to failure of the specimen was compared between samples. Due to the small number of specimens, no test for significance was computed.

7.1.3 Results

Maximum torsional moment prior to fracture in all femur pairs was greater for the collared implant versus a collarless implant (Figure 7-3).

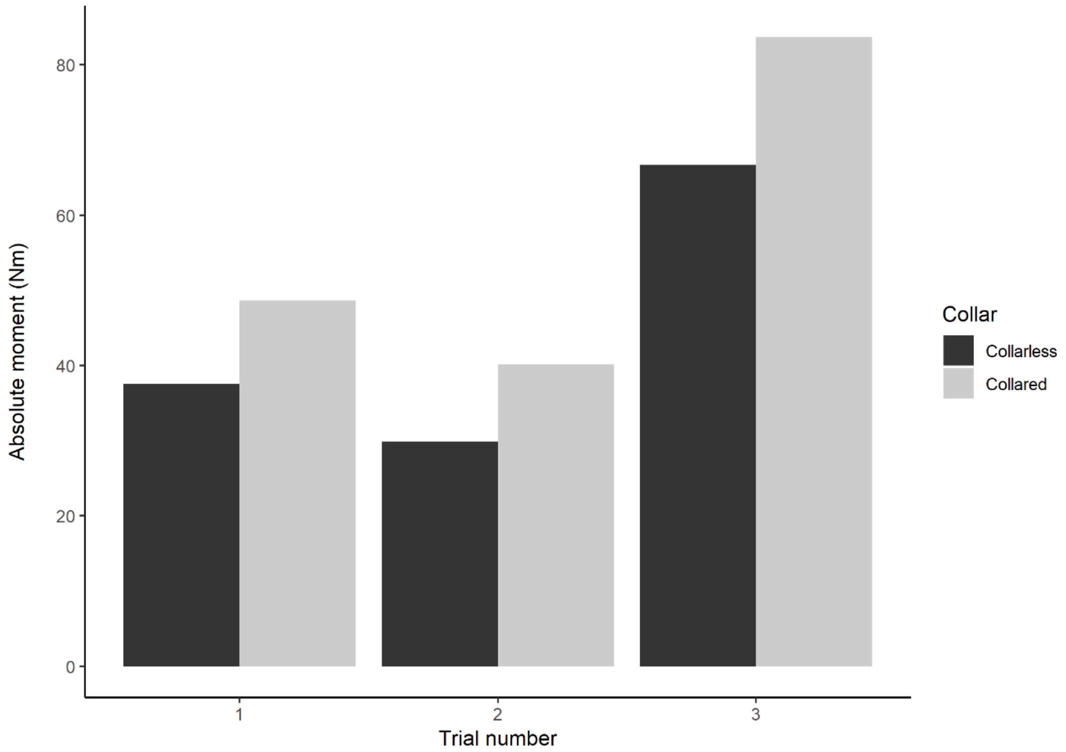


Figure 7-3 Comparison of maximum fracture toque between trials for each pair of human cadaveric femora.

Collarless stems deformed the trabecular bone adjacent to the stem body during rotational moment application until the implant engaged with the cortex and produced smaller fractures of the posterior calcar. The collared implants rotated less within the femur, until the posterior collar engaged with the cut edge of the cortex and then moved in this position with the femur until a fracture occurred (Figure 7-4). Collared stems produced larger fractures compared to collarless stems (Figure 7-4 and Figure 7-5).

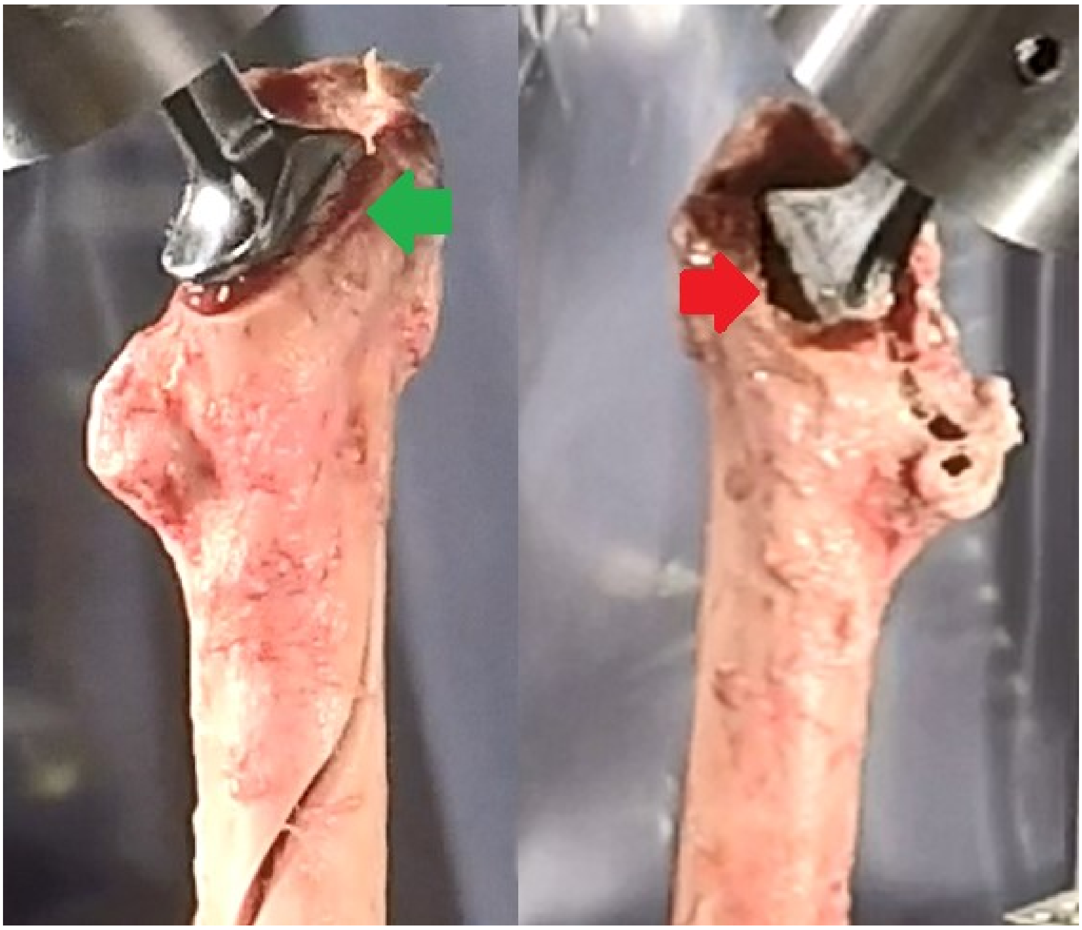


Figure 7-4 Fracture patterns from still views of 60Hz video footage on the first frame where the fracture is visible. Both the collared stem (left) and collarless stem (right) are undergoing internal rotation away from the centre of the Figure. A gap between the implant and trabecular bone is most pronounced on adjacent to the anterior surface of the collarless stem (red arrow) versus the collared stem (green arrow), suggesting larger amounts of relative movement between the collarless stem and femur.

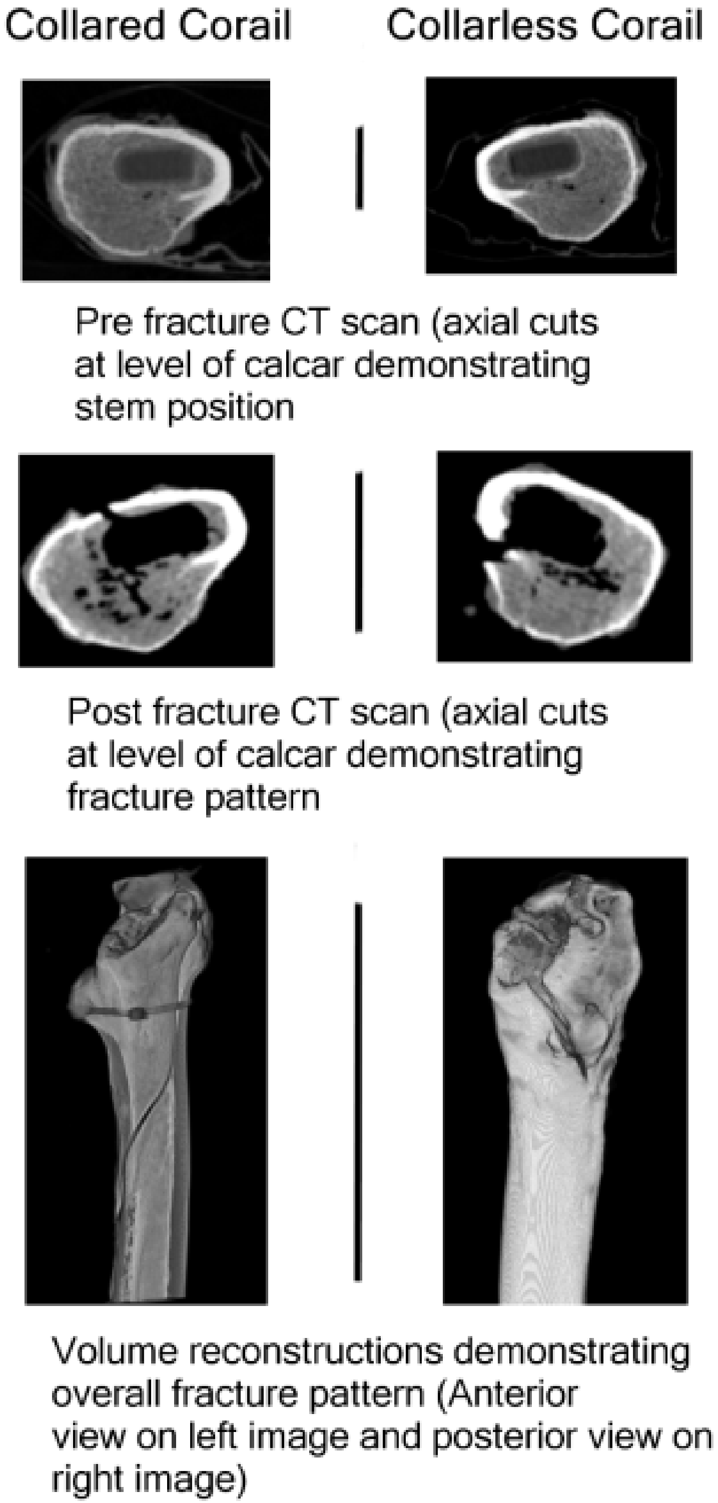


Figure 7-5 CT scans of the cadaveric femoral trials. Note: Left images are from a femur in the collared group and right images are of a femur form the collarless group. Top images represent axial sections at the level of the calcar cut after preparation of the femoral cavity around a polymer implant. Middle images are axial sections following fracture at the level of the calcar cut. Bottom images are volume reconstructions demonstrating the overall fracture pattern.

7.1.4 Discussion

Biomechanical testing produced a mixture of oblique and spiral fracture patterns in the proximal femoral cortex, which matched early in-vivo periprosthetic fracture patterns and was similar to those reported in the literature (Gromov et al., 2017; Taunton et al., 2015) and those described in Chapter 6. This study confirmed that POPFF with a collarless stem occurs with less force than an otherwise identical collared stem.

Cortical bone is anisotropic and strongest when loaded in compression (Mirzaali et al., 2016; Osterhoff et al., 2016). A medial calcar collar has been shown to increase the fracture load during axial and rotational loads using quasi-static methods (Demey et al., 2011). During rotational injury at more realistic rates of loading the collar can load the calcar in compression increasing the force required for a fracture. When the calcar collar is positioned flat on a neck cut which is 45 degrees to the stem body, the calcar collar will act like a screw thread and cause the stem to move out of the femoral cavity if the stem is rotated. This may have the effect of further decreasing the load on the trabecular bed inside the femoral cavity. The calcar possibly acts as a check-rein which prevents excessive peri-prosthetic trabecular deformation in rotational injuries and may improve the resistance to trabecular deformation after high energy injuries which do not cause cortical fracture.

These mechanisms are likely to increase the force required to cause a POPFF around a collared implant versus collarless implants. Since this work was completed (and published), the results have been replicated in a much larger sample of paired cadaveric femurs by Johnson and colleagues (Johnson, A. J. et al., 2020). Their methods were similar and combined a combination of vertical load (68kg) and 45 degrees of rotation in one second. They found that the peak torque to fracture was significantly greater (median difference of 29Nm) for collared versus collarless stems in matched femora.

This work significantly increases the likelihood that there is a real difference between the behaviours of collarless and collared stems during simulated early POPFF.

7.1.4.1 Limitations

Paired femora were used to match biomechanical trials on likely confounders. Simulation of the soft tissues or other possible fracture mechanisms should also be investigated to allow comparison to more realistic *in vivo* joint forces. The findings of the biomechanical study are limited by small numbers and that only one implant design investigated. It still needs to be shown that the results can be generalised to other stem designs, even so this seems reasonable, since the observed effect can be explained biomechanically. Despite the overwhelming evidence that calcar collar causes an increase in the force required to fracture, the effect of calcar contact on the force required to fracture was not specifically measured. Further study is required to demonstrate that calcar contact is the exact mechanism by which this process is enacted.

7.1.4.2 Conclusions

This study demonstrated that the force required to cause a simulated early POPFF is greater when a collared cementless femoral stem is used. These results also suggested a plausible biomechanical mechanism via which a calcar collar reduced the risk of early POPFF, which will need validation with further testing. Given the predicted rise in POPFF rates, the use of a medial calcar collar may help to improve future cementless stem survival by reducing the risk of early POPFF.

7.2 Comparison of Rotational Periprosthetic Fracture of the Femur in Composite Osteoporotic Femur versus Human Cadaveric Specimens: A Validation Study.

7.2.1 Introduction

Biomechanical studies use a range of methodology with the choice of specimen largely between composite (Ginsel et al., 2015; Morishima et al., 2014; Klasan et al., 2019; Jones, C. et al., 2015) and cadaveric femurs (Harris et al., 2010; Johnson, A. J. et al., 2020; Rupprecht et al., 2011). The majority of studies, regardless of specimen choice use fracture loads (axial load or torque) at the moment of fracture as the primary outcome (Jakubowitz and Seeger, 2015).

Cadaveric samples can offer realistic fit, loading and fracture patterns but these benefits are offset by the large between-sample variation which occurs when testing groups of cadaveric specimens and the associated complexities associated with tissue handling, storage and ethical regulation (Jakubowitz and Seeger, 2015). Variability can be overcome using pairwise comparison of results in bilateral femur pairs (Johnson, A. J. et al., 2020), but this limits the experiment to the testing binomial variables. Composite femurs are a valid and highly uniform specimen choice when comparing whole bone composite femurs to whole bone cadaveric specimens (Jakubowitz and Seeger, 2015; Gardner et al., 2010) and do not require ethical approval or specialised handling and storage techniques to use effectively. As a result, they form the basis of much experimental testing. Validation has largely focused on the mechanical properties of the complete femur and in the field of POPFF, relies on a single study comparing composite femur models to a single cadaveric femur trial (Jones, C. et al., 2015).

The aim of this study was to compare in-vitro results of POPFF simulated methods using composite femur specimens to results using cadaveric specimens utilising identical loading protocols described in Section 7.1.

7.2.2 Methods

To assess the validity of a composite femur model, results from tests using fresh frozen femur specimens were compared to results from tests using an osteoporotic femur composite model. The methods and testing of specimens from the fresh frozen cadaver trials are described in section 7.1.2.

7.2.2.1 Specimen preparation

7.2.2.1.1 Cadaveric specimens

This study was performed in accordance with local ethical guidelines and regulations of Hamburg University School of Medicine and the University of Leeds. Preparation was been described in section 7.2.2 for femurs which were tested in pairs. To maximise sample size and use of precious resources, this study includes all femurs which were tested and excluded from the study described in section 7.1 because one of the pairs failed or was unsuitable for testing.

7.2.2.1.2 Composite femur preparation

Composite femurs (Osteoporotic femur, SawBones, WA) contained 10 PCF low-density cancellous, thin walled low-density cortical shell, overall length 45.5 cm, and 16 mm hollow canal (SawBones, 2020). `Osteoporotic femur` models are intended to mimic the specific biomechanical properties of an osteoporotic femur and were selected since they were likely to more closely match those in the cadaveric testing group. Pre-operative implant size selection and neck cut to recreate preoperative offset and leg length was planned using proprietary software (IMPAX Orthopaedic Tools, Agfa Healthcare) following plain anteroposterior radiographs with a 25mm diameter scaling ball. Femurs were prepared and implanted according to manufacturer's guidance to minimise variability using the methods described in 7.12.

After preparation, distal femoral resection was performed so that 40mm of specimen remained between the stem tip and the distal fixative. Specimens were fixed into steel pots using a rapid setting resin fixative (cadaveric femurs: polymethylmethacrylate and composite femurs: G&B Epoxy Acrylate Resin, G&B Fissaggi, UK) in an identical alignment to those in the cadaveric group. Femurs were implanted with an appropriately sized fully coated cementless femoral stem with and without a medial calcar collar (Corail, DePuy Synthes, Leeds UK) in accordance with manufacturer guidelines and underwent visual inspection (composite femurs) or CT (cadaveric specimens) to screen for intraoperative fractures.

7.2.2.2 Experimental setup

The test set up was adapted from previous methods (Morishima et al., 2014) and the exact details were described in 7.1.2.

For composite femora tests, the potted specimen was secured distally into a clamp which was secured to the base of the materials testing machine and the specimen position was adjusted in two planes to ensure precise positioning. Simulated POPFF were conducted using an identical loading regimen in a material testing machine (cadaveric femurs: MTS 858.2; Eden Prairie, MN, USA and composite femurs: ElectroPuls E10000, Instron, USA). In composite femur trials rotation was applied to the femoral head using a custom clamp that additionally ensured that the rotation axes was aligned to the femoral axes (Figure 7-6Figure 7-7).

Figure 7-6 Experimental set up for simulated POPFF testing using a composite \`osteoporotic\` femur.

Fracture torque and rotational displacement were measured and torsional stiffness (rotary displacement divided by torque) and rotational work prior to fracture were estimated (area under rotatory displacement torque curve). Fractures types were described and were classified according to the UCS (Duncan and Haddad, 2014) and each trial was recorded to establish fracture mechanism using video camera equipment (cadaveric GoPro 4, GoPro, California, USA and composite femurs used GoPro Hero 8, GoPro, California, USA).

7.2.2.3 Statistical methods

Comparisons between cadaveric and composite femur groups were conducted using a Mann-Whitney U test, with significance set at $p<0.05$. Comparisons were stratified by implant collar, since the study reported in 7.1 and another published trial has demonstrated that this is likely to affect mechanical properties prior to fracture (Johnson, A. J. et al., 2020)(Johnson, Aaron J. et al., 2019).

7.2.3 Results

The baseline demographics for cadaveric femur donors are shown in Table 7.2.

Table 7-2 Demographics of cadaveric femur donors.

Variable	Result
n	9
Age (median [IQR])	76.00 [69.00 to 81.00]
Height (median [IQR])	158.00 [157.00 to 167.00]

Note: IQR denotes interquartile range

Results demonstrated statistically similar values for fracture torque, fracture displacement and torsional stiffness for cadaveric and composite femurs (Table 7-3).

Table 7-3 Biomechanical results for trials with cadaveric and composite femur specimens.

Implant	Variable	Group composite femur	Group cadaveric femur	p
Collarless	*n*	6	4	
	Rotational displacement at fracture in Rad (median [IQR])	0.33 [0.32, 0.34]	0.44 [0.41, 0.46]	0.2
	Torque at fracture in N.m (median [IQR])	45.12 [39.13, 48.09]	41.91 [35.67, 51.35]	0.67
	Rotational work in N.m.Rad (median [IQR])	5.21 [4.25, 6.04]	10.51 [9.71, 12.57]	0.01*
	Torsional stiffness in N.m/Rad (median [IQR])	138.79 [122.53, 140.59]	113.33 [74.46, 151.52]	1
Collared	*n*	6	5	
	Rotational displacement at fracture in Rad (median [IQR])	0.29 [0.27, 0.31]	0.50 [0.37, 0.55]	0.07
	Torque at fracture in N.m (median [IQR])	48.41 [42.60, 50.27]	48.63 [44.62, 58.61]	0.72
	Rotational work in N.m.Rad (median [IQR])	5.76 [4.92, 6.64]	15.38 [14.01, 17.05]	0.01*
	Torsional stiffness in N.m/Rad (median [IQR])	158.36 [152.61, 163.54]	147.05 [97.41, 153.03]	0.1

Note: Rad indicates radians, N is Newtons, m is metres and IQR is interquartile range. * indicates statistical significance at $p<0.05$

Results in the cadaveric tests displayed a greater variability in results versus composite femur results. There was a trend for a greater rotational displacement at fracture in the cadaveric group, but this failed to reach statistical significance. This observation lead to a non-significant increase in torsional stiffness for all cadaveric specimens (p range 1.0 to 0.1) and a significantly greater rotational work prior to fracture in cadaveric versus composite femurs (collarless stems: 10.51 [9.71 to 12.57] versus 5.21 [4.25 to 6.04], p =0.01 and for collared stems: 15.38 [14.01 to 17.05] versus 5.76 [4.92 to 6.64], p =0.01).

The median (IQR) fracture torque was greater for collared versus collarless stem trials in cadaveric femurs (48.63 [44.62, 58.61] versus 41.91 [35.67, 51.35]) and in composite femurs (48.41 [42.60, 50.27] versus 45.12 [39.13, 48.09]), although in composite femurs the relative difference in median fracture torque was smaller.

Fracture resulted in UCS B2 fractures in all trials. Subjective assessment of fracture pattern demonstrated similar patterns of fracture in cadaveric and composite femur testing (Figure 7-7 and Figure 7-8), although there was subjectively greater velocity of the fracture fragments from the composite femur specimens in comparison to the cadaveric specimens.

Figure 7-7 Comparison of collarless fracture pattern between human cadaveric specimens (top row) and osteoporotic sawbones (bottom row). Fracture occur in a similar position on the proximal femur. Fracture fragment acceleration is noticeably less in the cadaveric versus composite models.

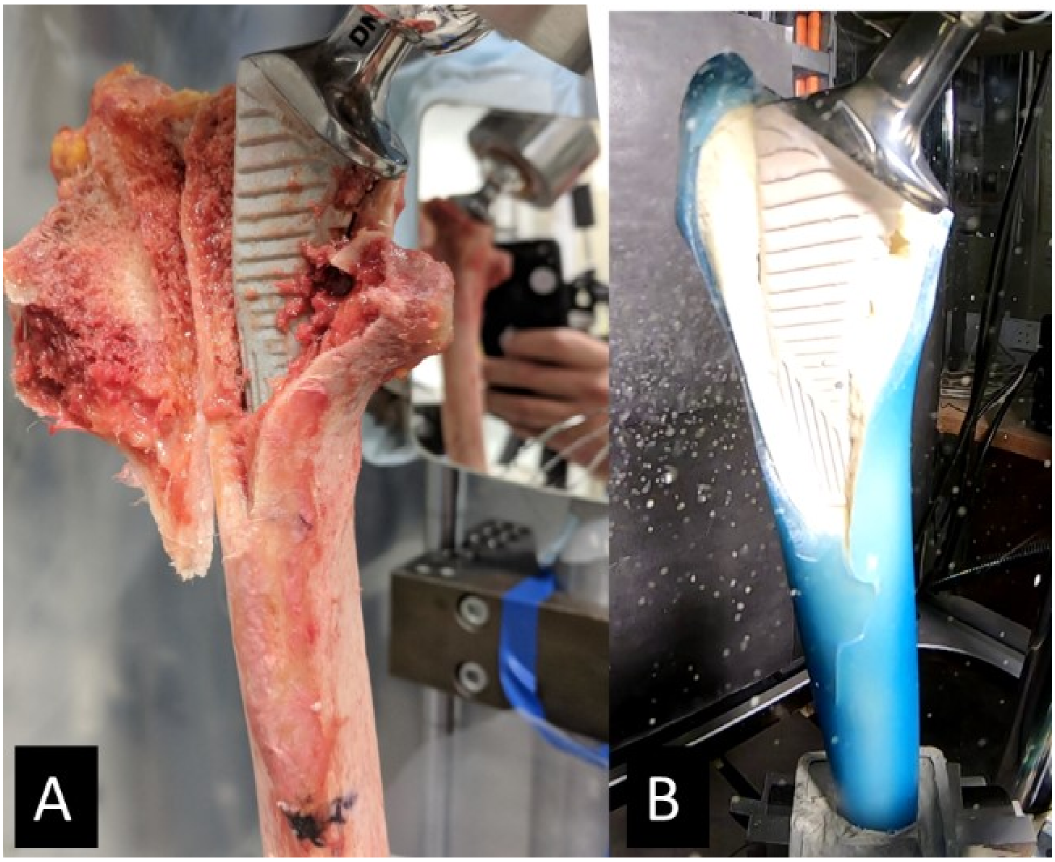


Figure 7-8 An example of fracture patterns which occurred after collared cementless stem trials with cadaveric specimen (A) and composite femur specimen (B).

7.2.4 Discussion

This study has demonstrated comparable fracture torque and fracture patterns between composite femur and cadaveric femur trials. Rotational work in cadaveric femurs was greater than that recorded in composite femurs with the same loading regimen. This was largely because cadaveric femur trials fractured at a greater median rotational displacement, but this difference did not reach statistical significance.

This study confirms that the results obtained with composite femur specimens are largely comparable to those results from testing using cadaveric femur trials, with some important differences. Whilst the fracture torque was comparable between composite and human femurs the composite femurs appear to be stiffer than cadaveric counterparts and fracture occurred at smaller angular displacements in comparison to cadaveric specimens. Whole human femur stiffness follows a rate dependent relationship (Courtney et al., 1994), with strength and stiffness increasing with loading rate. The stiffness of whole composite femurs has been found to be constant over a range of loading rates (Zdero et al., 2010) and comparable to human specimens in torsional and axial loading (Gardner et al., 2010). When the stem is placed under axial load, the stem can move independently of the femur under high loading rates as seen in section 7.1 and published elsewhere (Johnson, A. J. et al., 2020). The implant-femur construct stiffness is dependent on the mechanical properties of the stem, the stem-bone interface and the bone. The internal foam of the composite femur is homogenous and does not represent the variation seen in mechanical strength and mineral density within human femurs (Oftadeh et al., 2015). This may make the stiffness of foam adjacent to the stem greater than that which is seen in human specimens and reduce relative stem-femur displacement under high load conditions. In addition the coefficient of friction between a stem and artificial bone is dissimilar to human trabecular bone (Grant et al., 2007) and may lead to differing results when loads are transferred across the stem-bone interface. During preparation of the cadaveric femurs it was noted that the foam did not behave in a similar way to normal trabecular bone. The Corail hip system uses an impaction broaching technique to prepare the femur for implantation (Vidalain et al., 2011). The broaching technique was not easy to replicate in the composite femur and the foam did not appear to compress against the broach in a similar way. In addition, foam particles which are broached tended to fall into the void in the central portion of the composite femur specimen. Absence of a compressed trabecular layer in the composite femur is likely to change the stem-bone interface mechanics and may account for some differences in rotational stiffness seen in this study.

Previous studies assessing neck of femur fracture patterns in composite femur models have found fracture patterns which are both consistent with cadaveric and embalmed femurs (Topp et al., 2012; Jones, C. et al., 2015) unrealistic patterns (Bir et al., 2016) and also unrealistic stability when the mechanical properties of `fixed` composite femur fractures are tested (Basso et al., 2014). In this study, the pattern of fracture between composite and human femurs in an axial loading model was very similar and in agreement with a small study including just one cadaveric trial (Jones, C. et al., 2015). This would suggest that the failure mechanism is similar between composite and human femurs during axial loaded POPFF simulations.

For researchers hoping to use similar composite femur specimens mentioned in this study it is worth commenting on the practical constraints. The Osteoporotic composite femur specimens had a very thin cortical shell which in comparison to the cancellous foam were incredibly fragile and in future work, care should be taken during manipulation, preparation and implantation of the femur since inadvertent fracture is much more likely than standard composite femurs which represent normal adult anatomy.

7.2.4.1 Limitations

The main limitation in this study is small sample sizes in both cadaveric and composite femur groups. Given the precious resource which cadaveric samples represent, this is a common drawback of biomechanical testing. The small sample sizes reduce the power of our comparisons and further work should seek to validate composite femur models with larger sample sizes. This study did not objectively quantify relative motion between stem and femur, which would have enabled interesting comparison of implant behaviour during rotational loading. Future work should seek to integrate methods which allow accurate quantification of implant displacement and foam deformation. This study only compares the results with a torsional loading model.

Even though this model has been used previously and produces clinically valid fracture patterns around cementless stems, testing should also look to validate the use of composite femurs with a range of loading methods.

7.2.4.2 Conclusions

Given the reduced variability of results and comparable fracture torque and the similarity in fracture patterns from the fracture trials using composite samples versus cadaveric femurs, the use of composite femur models is a reasonable choice within certain limitations.

7.3 Calcar-Collar Contact during Simulated Periprosthetic Femoral Fractures Increases Resistance to Fracture and Depends on the Initial Separation on Implantation: A Composite Femur in vitro study

7.3.1 Introduction

A strong association between the presence of a medial calcar collar and a reduced risk of revision surgery for periprosthetic fracture of the femur within 90 days of implantation has been demonstrated, which has subsequently been validated by the first study in this chapter and another subsequently published study (Johnson, A. J. et al., 2020). A suggested hypothesis is that a medial calcar collar may act to reduce relative movement between the implant and the proximal femur during rotational injuries, through calcar collar contact (CCC). This was observed when comparing collared to collarless stems, but it is possible that such an observation may be due to unknown differences in stem mechanical properties because of the presence of a medial calcar collar. To validate the former hypothesis, the impact of removal of CCC on the resistance to POPFF around collared stems will need to be assessed. In addition, a medial calcar collar may not be well seated on the cut surface of the calcar in clinical practice (Markolf et al., 1980) or a small gap may be the intention of the stem designers to improve press-fit in some collared stem designs (Smith & Nephew, 2020). The effect of increasing initial separation on the resistance to POPFF is not defined. It is important for surgeons to understand what difference this may make to the proposed benefits of a medial calcar collar during an injury which may lead to periprosthetic fracture of the femur. The aims of this study are to:

1- Estimate the effect of calcar collar contact on periprosthetic fracture mechanics using a collared fully coated cementless femoral stem.

2- Estimate the effect of initial calcar collar separation on the likelihood of calcar collar contact during in vitro periprosthetic fracture.

7.3.2 Methods

To assess the effect of CCC on pre-osseointegration POPFF, three groups of six composite femurs (Osteoporotic femur, SawBones, WA) with increasing calcar-collar gap in each group, were subjected to the POPFF simulation technique described in section 7.1 and the maximum moment prior to fracture was compared.

7.3.2.1 Specimen preparation

Pre-operative implant size selection and neck cut to recreate preoperative offset and leg length was planned using proprietary software (IMPAX Orthopaedic Tools, Agfa Healthcare) following plain anteroposterior radiographs with a 25 mm diameter scaling ball. Stem implantation was performed according to manufacturer's guidance to minimise variability. Neck resection was standardised in all cases to a level at which calcar contact could be achieved according to pre-operative templating. To simulate a distribution of failure to achieve CCC, the neck resection was increased between groups using the manufacturer supplied calcar mill attached to a size 10 broach inserted into the femoral cavity to a line marked on the femoral neck according to the group (group one = no additional resection, group two = 3 mm additional resection, group three = 6 mm additional resection). Specimens were prepared and fixed into steel pots in an identical method to that described in the second study in this chapter. Femurs were implanted with a fully coated collared cementless femoral stem (Corail KA size 12, DePuy Synthes, Leeds UK) in accordance with manufacturer guidelines and inspected visually for intraoperative fractures. Prior to each trial, the distances between anterior (ACC) and posterior (PCC) collar and the calcar were measured using feeler gauges or a micrometre for gaps above 1 mm.

7.3.2.2 Experimental setup

The potted specimen was secured to the base of the materials testing machines as described in the second study in this chapter (Figure 7-9).

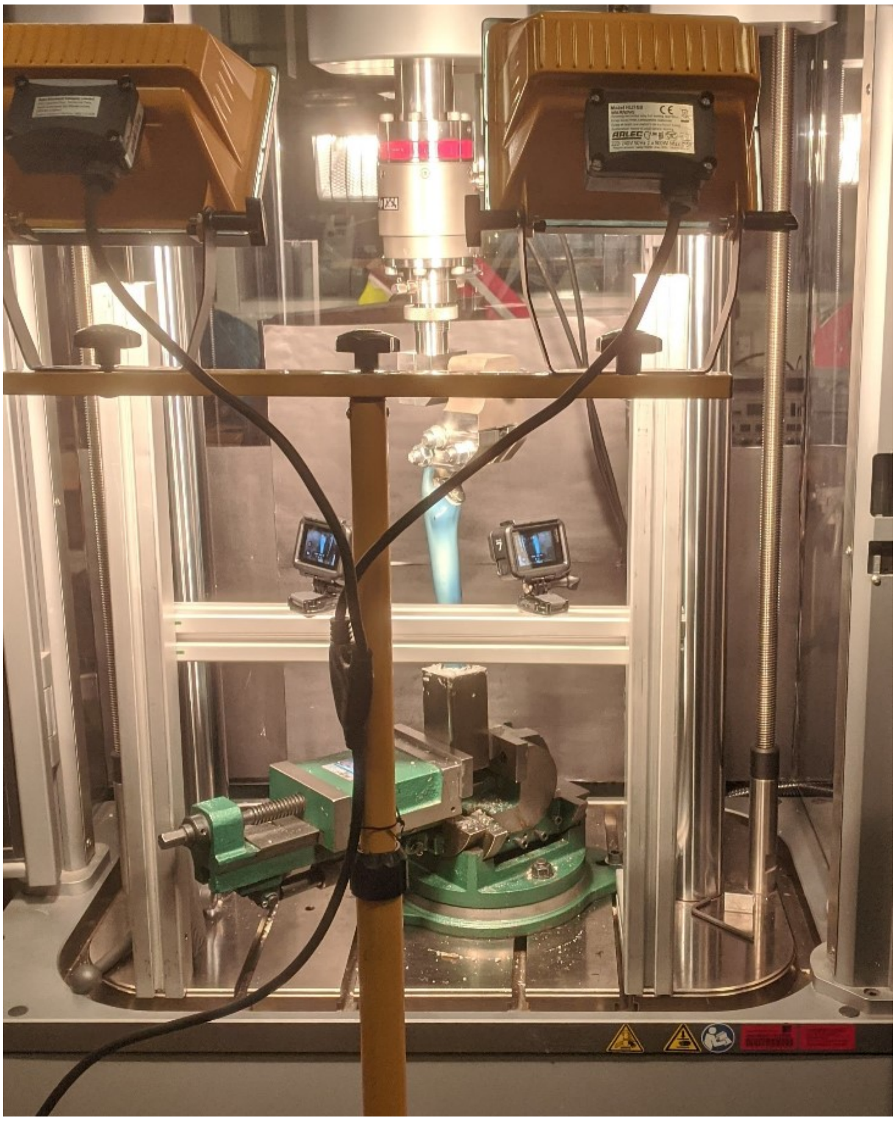


Figure 7-9 Experimental set up with camera position and lighting.

Periprosthetic fractures of the femur were simulated in a material testing machine (ElectroPuls E10000, Instron, USA) using the methods described in 7.1.2. This involved initial axial load of 1500 N followed by the application of a rotation (45 degrees) until fracture.

Fracture torque and rotational displacement were measured and torsional stiffness (rotary displacement divided by torque) and rotational work prior to fracture were estimated (area under rotatory displacement torque curve). CCC prior to fracture was defined as visible contact between any part of the collar and the calcar prior to the appearance of a fracture on high-speed camera footage.

7.3.2.3 Statistical methods

Results between trials where calcar contact did and did not occur where compared using Mann-Whitney U tests. The ACC and PCC were compared between trials where the CCC was and was not achieved. Logistic regression estimated the odds ratio with 95% confidence interval of failing to achieve CCC for a given ACC or PCC. Statistical significance was set to $p<0.05$.

7.3.3 Results

7.3.3.1 Effect of calcar collar contact

Where CCC occurred versus where no CCC occurred, median (interquartile range [IQR]) fracture torque was greater (47.33 [41.03 to 50.45] Nm versus 38.26 [33.70 to 43.60] Nm , p= 0.05, Figure 7-10), median (IQR) rotational displacement was less (0.29 [0.27 to 0.39] rad versus 0.37 [0.33 to 0.49] rad, p= 0.07, Figure 7-11), median torsional stiffness (IQR) was greater (151.38 [123.04 to 160.42] rad.Nm^{-1} versus 96.86 [84.65 to 112.98] rad.Nm^{-1}, p <0.01, Figure 7-12) and median (IQR) rotational work was similar (5.88 [4.67, 6.90] J versus 5.31 [4.40, 6.56] J, p= 0.6, Figure 7-13).

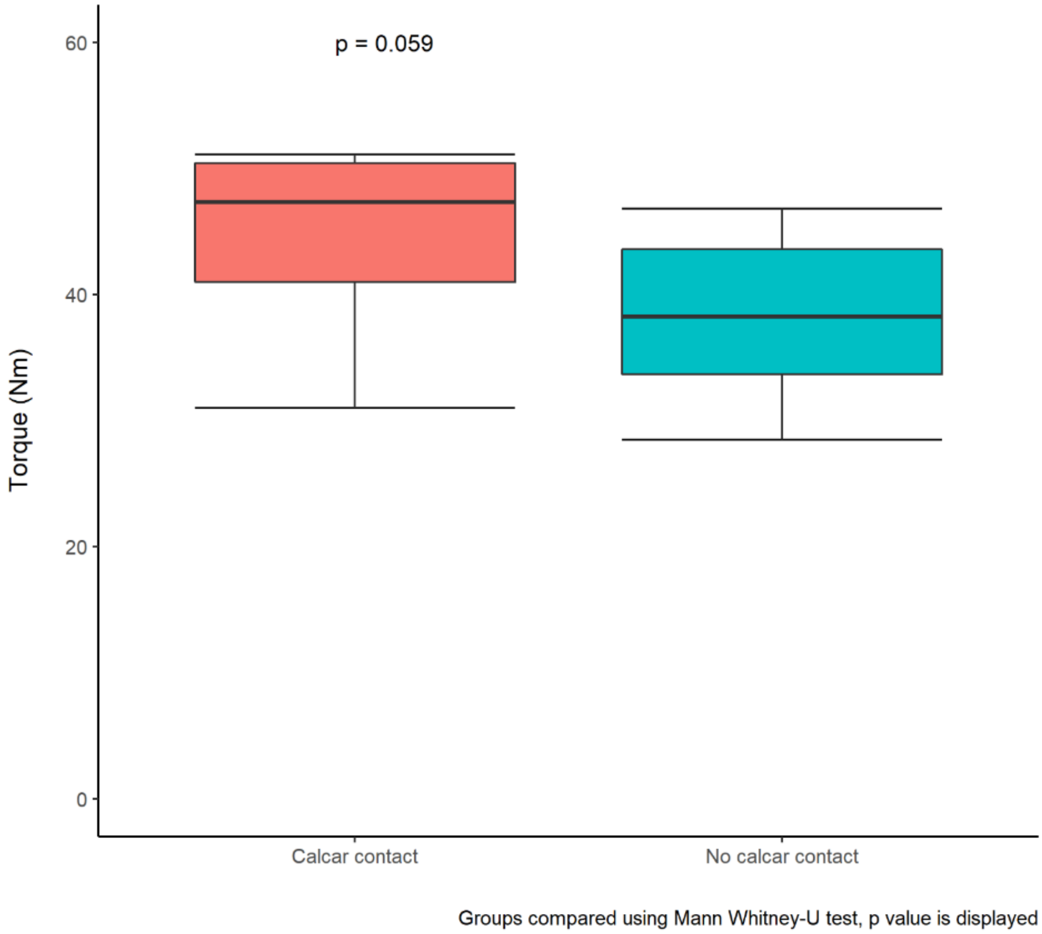


Figure 7-10 Maximum fracture torque prior to fracture stratified by calcar collar contact.

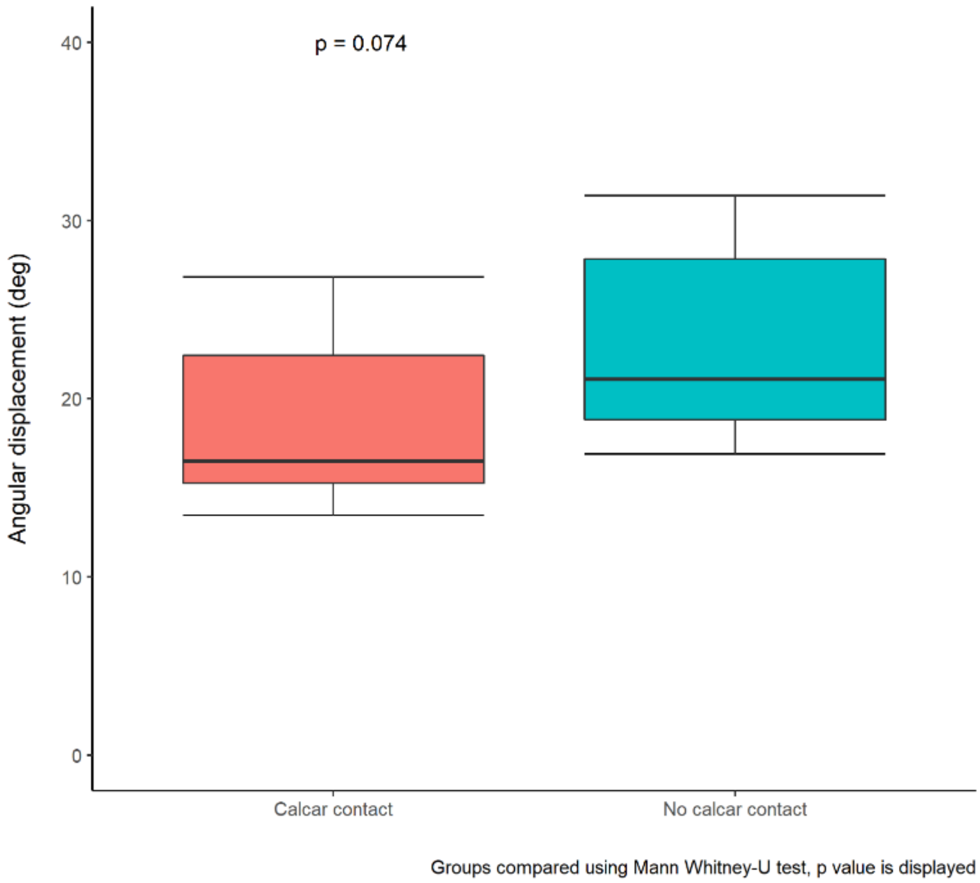


Figure 7-11 Angular displacement prior to fracture stratified by calcar collar contact.

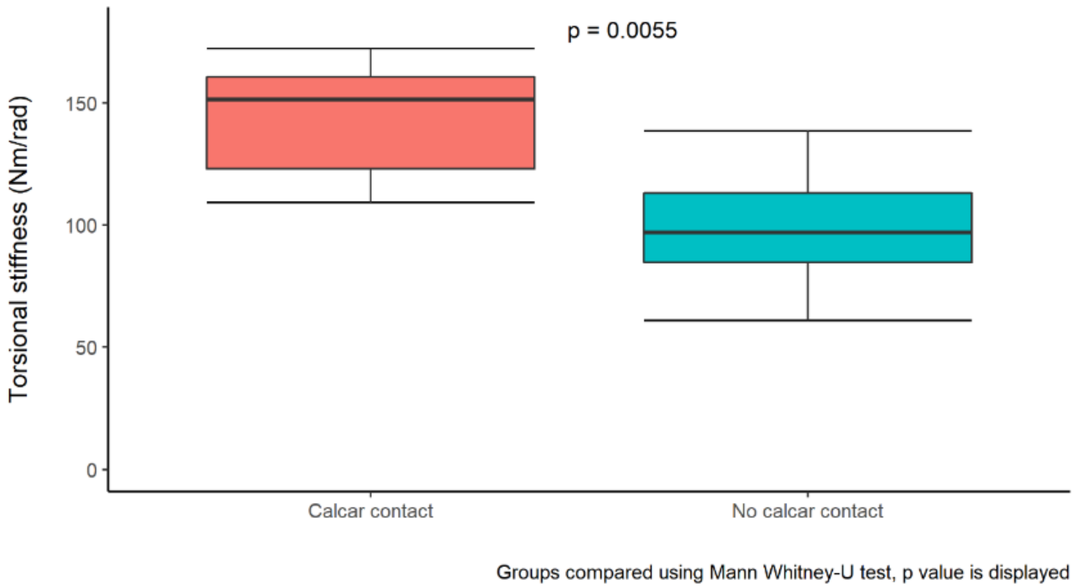


Figure 7-12 Torsional stiffness from initiation of angular displacement to fracture stratified by calcar collar contact.

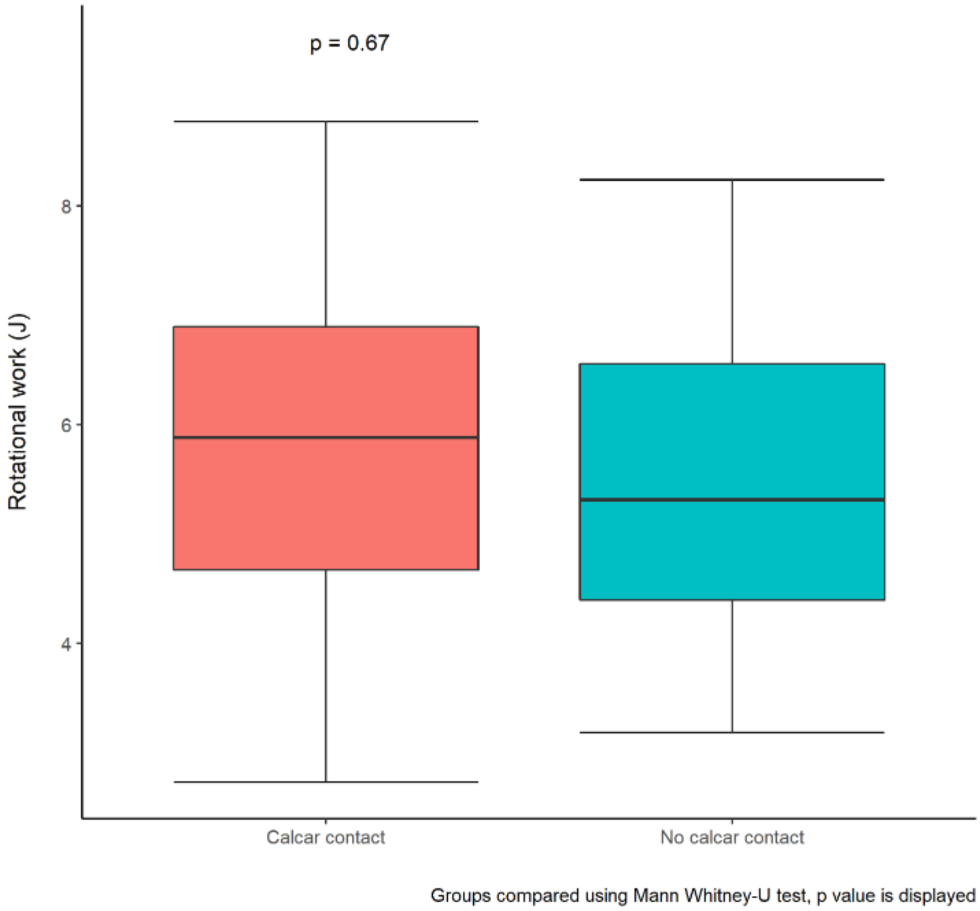


Figure 7-13 Rotary work from initiation of angular displacement to fracture stratified by calcar collar contact.

7.3.3.2 Effect of initial separation

CCC was achieved prior to fracture in all cases in group one, 50% in group two and 0% in group three. The median (range) ACC for those trials where CCC was achieved was 0.40 (0.00, 3.37) mm versus 6.15 (3.06 to 6.88) mm, where CCC was not achieved ($p < 0.01$). The median (range) PCC for those trials where CCC was achieved was 0.85 (0.00 to 3.71) mm versus 5.97 (2.23 to 7.46) mm, where CCC was not achieved ($p < 0.01$). Binomial logistic regression estimated OR of failure to obtain CCC increased 3.8-fold (95% CI 1.6 to 30.2, $p < 0.05$) for each millimetre of PCC. When the odds of CCC were modelled with ACC, the ACC was not a significant predictor of CCC (OR

0.02, [95% CI 0.00 to 0.48, p =0.2). The model predicted that 95% chance of successful CCC was associated with a PCC of one millimetre or less.

7.3.4 Discussion

Fracture torque and construct stiffness increased when a collared cementless stem contacted the femoral calcar prior to fracture versus a collared stem with no CCC. The odds of CCC decreased with increasing initial calcar collar separation at the time of implantation.

Increased fracture torques for collared versus collarless stems have been demonstrated in two independent biomechanical studies using different methodology (Johnson, A. J. et al., 2020). This is the first experimental evidence demonstrating that CCC prior to fracture is crucial to significantly increased fracture torque and construct stiffness. As demonstrated in section 7.1, the stem rotates and tips posteriorly in our trials and the posterior edge of the calcar collar could be seen to contact the calcar surface. It is likely that CCC leads to load transfer from the stem to the relatively stiff cortex polymer, which deforms rather less than the medullary foam, whereas when there is no CCC, the stem loads adjacent foam which deforms more easily under load and reduces the overall stem-femur construct stiffness. This work confirms that CCC rather than the presence of a calcar collar *per se*, is a key mechanism which acts to increase resistance to rotational POPFF mechanisms.

The odds of achieving CCC prior to fracture decreased with increasing initial calcar-collar separation. In this study the PCC and not the ACC was a significant predictor of the CCC. This is likely to be because the trial used internal rotation (stem head moves posterior relative to anatomical axis), which lead to engagement of the posterior collar and calcar. If the rotary displacement was reversed that ACC distance is likely to contact the calcar and in this situation the ACC will become a significant predictor of

CCC. Not all POPFF with rotational mechanism are caused by internal rotation of the stem relative to the femur and surgeons should ensure that the ACC and PCC are both minimised to increase likelihood of CCC during rotational injuries. During simulated POPFF there is a less than 95% chance of CCC during the trial when the PCC was 1mm or above.

Uniformity in composite femur specimens is a distinct advantage in terms of a reduction in variability and absence of regulatory burden. Whilst the use of composite femur analogues are broadly comparable to human femurs (Gardner et al., 2010), they may not exhibit comparable rate dependent change in stiffness (Zdero et al., 2010), which occurs in human femurs (Courtney et al., 1994). Composite femurs are an advantage in scenarios where variations in methods and materials between laboratories may prevent reproduction of experimental results, however it prevents direct immediate comparison between results using composite femurs and clinical practice. In addition, the testing of intramedullary implants also brings into question the validity of homogenous foam in composite femurs as a substitute for human cancellous bone. It is likely that the behaviour of the stem inside a homogenous foam is different to the behaviour in a human femur, which varies in mechanical properties in both length along the femur and also across the axial cross-section (Yang et al., 2012; Oftadeh et al., 2015). In addition the coefficient of friction between a stem and artificial bone is dissimilar to human trabecular bone (Grant et al., 2007). The homogenous foam inside a composite femur represents the average for non-cortical femoral component such that the overall mechanical properties of the femur are like a human femur. In human femora the trabecular bone strength is likely to be less in the femoral neck and subtrochanteric region than in the femoral head (Oftadeh et al., 2015), but in the composite femur they are the same, which may make the implant unnaturally stable during simulated POPFF. Whilst these discrepancies may prevent perfect translation of these findings into clinical practice with absolute confidence, given the underlying mechanism has been demonstrated in cadaveric samples (section 7.1), these results represent a mechanism which are likely to be replicated with human femurs. Given these constraints, one might expect that in human femurs the relative movement between stem and femur would be greater, and that the real PCC which might be associated with a 95% chance of successful CCC is slightly larger.

7.3.4.1 Limitations

The main limitation of this study is the use of composite bones to model implant behaviour during POPFF. Despite this being a previously adopted approach (Ginsel et al., 2015; Morishima et al., 2014; Fottner et al., 2017; Klasan et al., 2019; Pepke et al., 2014; Schmidutz et al., 2017), further studies using fresh frozen cadaveric specimens are required for clinical validation of these results. Torsional stiffness was estimated without precise measurements of size and length of femur and compared directly between specimens despite the small differences in specimen length due to small differences in neck cuts. The effect of this on stiffness estimates is likely to be negligible given the small differences between composite femurs and small changes in length due to differences in neck cut and should not affect the overall conclusions. This study did not simulate POPFF occurring around an osseointegrated stem because a validated model of simulated in vitro osseointegration does not exist. This study utilised a combined axial-rotational loading methodology, which created fracture patterns similar most fracture patterns occurring in early POPFF. Further work is required to test these hypotheses using a range of loading mechanisms which more accurately represent the complete picture of injuries which might occur during POPFF. Since a large proportion of POPFF occur within the first 90 after implantation, when osseointegration is unlikely to be complete, our experiments still represent a clinically relevant model.

7.3.4.2 Conclusions

These results demonstrate that calcar-collar contact and not a calcar collar *per se*, is crucial to maximising the protective effect of a medial calcar collar on the risk of post-operative periprosthetic fractures of the femur. Increased separation between collar and calcar reduced the likelihood of calcar collar contact during a simulated periprosthetic fracture of the femur. Surgeons should aim to achieve a calcar-collar distance of one millimetre or less following implantation to ensure calcar collar contact during periprosthetic femoral fracture and to reduce the risk of fracture.

Chapter 8 Summary, future perspectives and concluding remarks

8.1 Summary

This thesis described the investigation of risk factors leading to POPFF after hip replacement using a cementless femoral stem. A novel method was used to summarise fracture patterns occurring during POPFF and estimated the likely fracture mechanisms responsible for POPFF in general and early POPFF specifically. The effect of calcar collar was investigated using *in vitro* simulation, which demonstrated a protective effect of a calcar collar related specifically to calcar-collar contact prior to fracture.

Chapter Two included a thorough overview of the salient issues surrounding POPFF in the literature including epidemiology, effects on morbidity and mortality, health economics and an overview of risk factors for POPFF including identification of specific gaps across the breadth of research. A need for a detailed understanding of stem design related risk factors, fracture mechanisms and biomechanical validation were outlined.

Chapter Three described two studies using the National Joint Registry dataset to investigate the relationship between IOPFF and future outcomes and risk factors associated with IOPFF during hip replacement. This was the first analysis to comprehensively identify outcomes and risk factors of specific anatomical subtypes of IOPFF and link the occurrence of any IOPFF to the risk of future mortality. The first analysis identified a strong association between the occurrence of each anatomical subtype and the risk of subsequent POPFF revision surgery and identified a particularly large effect following calcar and shaft fractures specifically. The second estimated the fixed effects and interactions of variables on risk of any IOPFF and each anatomical subtypes. Risk of IOPFF was increased in patients with left hip disease, female patients, patients at the extremes of age and patients with non-osteoarthritic hip disease. Risk reduction may be achieved with a posterior approach, use of cementless implants and the use of computer guided surgical techniques.

Chapter Four described a retrospective study using a large national dataset outlining the patient, surgical and implant related risk factors associated with POPFF occurring within 90 days of implantation. This study used a novel approach by which cases were linked to implant design data using implant catalogue codes in the NJR dataset in order to identify specific cementless stem design features associated with increased risk of POPFF. The study concluded that increased risk of early POPFF was associated with stems which were collarless, had mineralised or non-mineralised porous coatings and were triple tapered.

Chapter Five outlined the development of a novel radiographic analysis technique to describe fracture pattern, location and phenotype. This work represents the first ever attempt to accurately quantify fracture patterns in such a way that more detailed analysis of fracture mechanism and its associated influencing factors can be performed. The accuracy and reliability associated with each step of a manual segmentation process was assessed. The final methods were able to identify fracture location to within 10mm maximum error, with acceptable reproducibility between raters. This method was then used in Chapter Six to quantify and analyse fracture patterns in a cohort of 125 fractures occurring following hip replacement with a cementless femoral stem.

Chapter Six used the novel manual segmentation technique to describe a series of POPFF occurring after hip replacement with a cementless stem. This is the first study to accurately describe fracture patterns according to patient and implant characteristics. Factors associated with more distal fracture patterns were female gender, late POPFF and hemiarthroplasty constructs. Spiral fracture type was five times more likely when POPFF occurred after 90 days and when a cementless stem was used as a hemiarthroplasty construct for neck of femur fracture. POPFF within 90 days of primary surgery occurred exclusively around the femoral stem and we predominantly oblique and spiral type fractures of the proximal femur, suggesting a mixed axial and rotational aetiology. This finding enabled the selection of appropriate in vitro biomechanical methodology during subsequent hypothesis testing.

Chapter Seven described the testing of the effect of a medial calcar collar on the resistance of the stem femur construct to POPFF in a mixed axial-rotational loading biomechanical model. Identical collared and collarless stems were assessed in paired cadaveric femora. Torque required to fracture a collared stem was greater than that for collarless stems in all trials. Further analysis in composite femurs confirmed a causal relationship between calcar contact and the increased force required to fracture. A 95% likelihood of calcar contact is demonstrated if the collar is no further than 1 mm from the calcar on implantation during the experiment.

8.2 Future perspectives

This thesis has developed the field of POPFF prevention through identification of factors relating to both risk of IOPFF and POPFF respectively using a range of novel approaches. The priorities for future work in the field of IOPFF prevention should include estimation of the incidence of occult fractures following THR and implant features and surgical techniques which alter the risk of IOPFF. The priorities in the field of direct POPFF prevention should include testing the effect of implant surface coating and implant shape of the risk of POPFF. Following this it may then be possible to develop a cementless femoral stem with a very low risk of POPFF, which may be tested in clinical trials to examine the effect of POPFF risk prospectively. There is also scope for further development of research methodology used in this thesis. For example the development of implant design databases and image analysis techniques. This section will outline future directions in these domains.

8.2.1 Intraoperative periprosthetic femoral fractures

The reason for greater risk of POPFF following seemingly uneventful THR using a cementless femoral stem is still unknown. Yun and colleagues identified that there was a large undiagnosed rate of occult IOPFF following cementless femoral stem insertion, which may precipitate POPFF in the early post-operative period (Yun et al., 2019). Future studies should seek to reproduce these findings following THR with a range of different cementless and cemented stem types. This work could be performed as a prospective observational clinical study in patients undergoing primary THR. Such a study should aim to observe the outcomes of these patients within the first year of surgery so that the effect of occult fractures on the natural history of POPFF can be measured. Identification of occult fractures occurring during cementless femoral stem implantation and would be a vital step in understanding the mechanism responsible for increased risk of POPFF after THR using a cementless femoral stem. Following this a focused analysis of risk factors leading to occult fractures could be undertaken with a view to identifying useful interventions.

This study identified that the use of computer guided surgery was associated with a large reduction in the risk of IOPFF during THR. The mechanism of this effect remains unclear and should be investigated to understand whether a reduction in risk arises from the direct use of computer guided methods or that computer guided surgery is a surrogate marker for another direct effect such a surgeon skill or experience. Currently there is little known about what constitutes computer guided surgery as reported in the NJR. The range of practice included in this group could be evaluated with a national audit of computer guided surgery methods used by surgeons reporting to the NJR. Analysis of the results could be used to generate hypotheses, which could then be tested in a prospective trial or biomechanically if this was not feasible.

Cementless stem insertion remains a large source of risk for both IOPFF and POPFF. It is likely that there is a relationship between preparation methods, implant design and risk of IOPFF beyond the cementless-cemented divide which explains risk of IOPFF. The effect of implant design on the risk of IOPFF was not investigated using NJR data because of difficulties ascertaining the exact equipment used when the fracture occurred. A better understanding could be gained by retrospectively reviewing clinical records in a random sub-sample of cases with IOPFF to understand whether IOPFF occurred during preparation of the femur or final implantation. From this data, common features can be identified which could then be used to ascertain the likely cause of IOPFF. If femoral stem implantation is found to be a common key feature, an analysis of implant design features associated with increased risk of IOPFF could be undertaken using a design linked data analysis (Section 4.2) to generate hypotheses which can be explored with further research.

8.2.2 Postoperative periprosthetic femoral fracture

For POPFF, this thesis has demonstrated that the risk of POPFF is lower following implantation with a collared cementless stem. The priority following this is to complete validation of other hypotheses generated in Chapter Four using experimental testing methods similar to those in this thesis (Chapter Seven). Once a robust picture of important design features is obtained the ultimate goal should be to test a femoral stem with these features in a prospective clinical trial to evaluate risk of POPFF versus the currently available stems. The steps in this process are outlined in this Section.

This thesis demonstrated that a medial calcar collar is likely to significantly reduce the risk of early POPFF, however further work is required to validate this finding in other stem types and in collars of different shapes. Testing the protective effect of a calcar collar in stems of different shapes could be performed using identical methods to those described in Chapter Seven and ideally with large groups of paired cadaveric femora. Researchers should take care to test stems which are identical in all features apart from the calcar collar to reduce confounding. In cases where no collared stem version exists (for example, blade type stems), it would be necessary to produce bespoke femoral stems with an added calcar collar. This approach may be justifiable since blade type stems are associated with the greatest risk of POPFF. In addition, many stems have collars with just a medial projection, which may not contact the posterior cortex in a similar way. It is not yet clear whether collars with only a medial projection have a protective effect and requires further investigation.

This work also identified that the risk of POPFF is strongly associated with both mineralised and non-mineralised porous coatings versus grit blast surface finishes, metaphyseal stem body cross-sectional shape and triple tapered stem bodies. Validation of these hypotheses could be performed using a similar approach to those used for calcar collar testing outlined in Chapter Seven. When performing in vitro tests of design variables, care should be taken to test stems which do not differ in any other way. If there are no stems in production, where only the variable of interest differs between stems, stems should be manufactured specifically for testing to reduce the confounding of other design variables.

Once there is high confidence in the validity of these findings the next step in this field of research would be to test the combined effect of these design features in a clinical trial versus cementless stems in current use. The trial should be prospective, randomized and include an initial follow-up period of at least two years to capture a majority of POPFF occurring after primary total hip replacement. Inclusion criteria would have to be carefully judged since the sample size requirements would be proportional to the expected incidence rate of POPFF in the study population. Inclusion of patients at high risk of POPFF using the risk factors identified in Chapter Four would be likely to increase the incidence of POPFF in the study population and reduce the requirement for large sample sizes and study costs.

Whilst this work focused on the 90 days following implantation where a large portion of POPFF occur, there are a large proportion of fractures occurring beyond this point and further work should seek to identify risk factors for POPFF during this period. It is possible that POPFF is more likely to occur around cementless stems which fail to fully osseointegrate and so modelling this relationship is likely to be complex and may need approaches which take into account the competing risks of stem loosening and fracture in late POPFF. A retrospective registry analysis using survival modelling which take into account competing risks may be useful in this case. In this case it may be possible to perform regression on implant design features in a similar fashion to that performed in Chapter Four to identify important features, which can then be tested in prospective experimental trials.

There is evidence that the risk of POPFF following hip replacement with a cemented stem and a polished taper slip stem, is large in certain patients. Given that this is currently the most popular stem design choice in the frailest patients who may also be at the highest risk of POPFF overall, there is likely to be justification for further research in this area. The first steps towards this have been completed (see Appendix B) and will progress in order to understand how the outcomes of patients with a cemented stem might also be improved.

Whilst much risk can be altered with a change in implant choice and methods at the time of primary hip replacement, it is likely that some risk can also be reduced with appropriate patient interventions. In 2020, periprosthetic fractures have come under the auspices of the National Hip Fracture Database in the UK and focus on service improvement and research in this group of patients is likely to increase. With this in mind, researchers should focus on medical and social interventions which may reduce the risk of falling, injury and fracture.

8.2.3 Research methods

This thesis used a novel design linked registry analysis to identify associations between implant design features and the risk of subsequent POPFF. Such approaches utilising large registry datasets could also be used for a range of other outcomes, which lead to large amounts of mortality, morbidity and cost such as infection and dislocation following hip replacement. Similarly, these techniques could be used to understand the risk factors posed by design features in a range of other disciplines including knee, shoulder and ankle arthroplasty. Further work in this area should seek to utilise datasets which include the full spectrum of POPFF outcomes, namely fixation and a small proportion of patients with conservatively managed POPFF. This work can be completed in the UK by making use of linkage between the National Joint Register and Hospital episodes Statistics.

A further extension to this work which may arise given the popularity and rapid development in the field of convolutional neural networks is the integration of image and conventional structured datasets. This would allow variables such as neck cut, implant sizing, implant positioning and bone quality to be investigated in large numbers. An initial approach would include the adaptation of existing radiographic analytic methods to identify key radiographic features of pelvic and femoral radiographs prior to THR, following THR and at the time of POPFF. Such an approach has been utilised in the classification of stem implant brand to an accuracy (area under receiver operating curve) of 0.99, using 170 original AP pelvis radiographs (Kang et al., 2020). The classification task attempted by Kang *et al* was relatively simple in comparison to femoral and pelvic anatomical classification since stem shapes have distinct reliable borders and femoral anatomy is highly variable with less distinct borders on radiographs. It is likely that many more cases of radiographs would be required to obtain a similar accuracy. Once a stable anatomical classifier was trained it could be used across a large volume of data to assess the effect of anatomical and implant variables on risk of POPFF. In the UK, this approach would rely on large scale integration of national image sharing networks and complex confidentiality and data sharing agreements. It may be possible to take advantage of existing image repositories of image data to reduce the administrative burden of creating a de novo image sharing agreement between hospitals in the UK. Although challenging, such analysis is possible using mediums other than radiographs and there is no reason why such approaches could not be used in the not so distant future.

This thesis describes the development and use of an original fracture analysis technique, which allows the description and summary of fracture patterns in two-dimensional space. Further work should seek to improve the accuracy, repeatability and simplicity of this method in both two and three dimensions. Approaches may include automated and semi-automated methods on larger datasets. Automated methods have already been produced for standardised proximal femoral detection on AP radiographs (BoneFinder, Claudia Lindler, University of Manchester) and for femoral shaft fracture classification (Bayram and Çakıroğlu, 2016). A similar approach could be used to identify and classify any fracture. A reliable automated fracture classification method has a large array of applications across trauma and orthopaedics.

It is not difficult to see how automated identification of fracture patterns would be useful in all fields of trauma to predict the risk of future outcomes such as non-union and failure of conservative or operative management. Such an approach would be useful in the initial screening and management of fractures across the field of trauma and potentially have huge cost-saving implications. To achieve this existing image repositories or trauma registries to develop image analysis methods beyond that in this thesis.

This thesis reports *in vitro* techniques to validate hypotheses, which are expensive and time consuming. This may be overcome in future through the development and use of accurate dynamic finite element modelling techniques, which are able to replicate accurate POPFF over a range of mechanisms and reduce the reliance on experimental methods. Such techniques would be incredibly useful when analysing the effect of interference fit, surface coatings and stem body shape on the force required to fracture, which are the next logical targets for biomechanical validation given the findings in this thesis.

The choice of implant is somewhat perplexing, and patients involved in discussion groups often ask, "why not just avoid using cementless stems?". This is obviously a complex problem, but it is reasonable to attempt an answer. Not all cemented stem confer a low risk of POPFF. There is evidence that cemented polished taper slip stems are also associated with an increased risk of POPFF (Mukka et al., 2016). Whilst the risk of POPFF associated with cementless stems is greater than for cemented stems in general, cementless stems perform incredibly well overall and are likely to be of clear benefit in certain subpopulations of patients. In order to maintain those benefits and reduce the risk of associated complications like POFF it is important that the effect of implant design is properly understood and adapted to match the risk of the patient in which the stem is implanted. The current dogma for surgeons is to use one, or perhaps two implants with a high degree of accuracy, in order to reduce the risk of errors and subsequent treatment failure. In most practices this often leads to the surgeon using a certain cementless or a certain cemented stem depending on an often-esoteric set of parameters. Given that more is now understood about the risk of implants selection and design in relation to POPFF, future work should seek to identify what the specific risks or failure are for particular patient subgroups and which implant designs and brands are might minimise these specific risks. Such work should seek to balance the overall risks of revision, function and satisfaction to identify the most likely successful approach.

8.3 Concluding remarks

This thesis described the exploration of factors affecting the risk of POPFF after hip replacement with a cementless stem. Risk of early POPFF, which occur within 90 days of implantation, is associated with increasing age, female gender, increasing frailty, non-osteoarthritis hip disease and stem design features including collarless design, porous and porous-mineralised coatings and triple taper designs. A novel method of radiographic image analysis was developed and then used to identify POPFF fracture patterns. From this data it was estimated that a mixed axial and rotational loading mechanism was responsible for a majority of early POPFF. A mixed axial and rotational experimental technique was then used to simulate early POPFF. This simulated method was used to test the effect of a calcar collar versus no calcar collar on fracture torque. Stems with a collar required a larger torque to fracture than collarless stems and this mechanism was dependent on calcar collar contact prior to the point of fracture. Future research should focus on the testing of hypotheses relating to other important design features of cementless femoral stems which may also alter the risk of POPFF. Other priorities for future research include analysis of large registry datasets with integration of image analysis and other POPFF outcomes (such as ORIF and conservative management) to improve the accuracy of risk prediction. Complementary future work should focus on patient level interventions which may reduce the risk of falls and likelihood of fracture in general and patient specific implant selection.

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Appendix A List of *a priori* interactions

Table Appendix A List of *a priori* interactions

Interactions tested
age : gender
gender : stem fixation
ASA : stem fixation
ASA : lead surgeon grade
ASA : lead surgeon grade : stem fixation
age : stem fixation
age : gender : stem fixation
age : indication
age : indication : stem fixation
cgs : age
cgs : indication
cgs : age : indication
cgs : side
cgs : lead surgeon grade
cgs : approach
cgs : stem fixation
cgs : stem fixation : organisation type
lead surgeon grade : organisation
lead surgeon grade : approach
side : approach *
side : surgeon *
side : surgeon : approach *

Note: \`cgs\` indicates computer guided surgery, ASA indicated American society of anaesthesiologists. * denotes interaction only tested on multivariable model predicting risk of any intraoperative fracture

Appendix B Additional publications

During this PhD project, the candidate made contributions to additional co-authored publications, the details of which are included below:

1. **Lamb JN**, Jain S, King SW, West RM, Pandit HG. Risk factors for revision of polished taper-slip cemented stems for postoperative periprosthetic femoral fracture after primary total hip replacement: A registry based cohort study from the National Joint Registry for England, Wales, Northern Ireland and the Isle of Man. JBJS (America). Sep 2020.

2. Abdual-Rub, Z**, Lamb JN*,** West RM, Yang X, Hu Y, Pandit HG. Unicompartmental Knee Replacement: A Systematic Review and Meta-analysis of Sixty-Four Studies and National Joint Registries. The Knee (Accepted September 2020). * indicates joint first authorship

3. Malik-Tabassum K, **Lamb JN**, Chambers A, West R, Pandit H, Aderinto J. Current State of Undergraduate Trauma and Orthopaedics Training in United Kingdom: A Survey-based Study of Undergraduate Teaching Experience and Subjective Clinical Competence in Final-year Medical Students Journal of Surgical Education, 2020.

4. van Duren B, Royeca JM, Cunningham CM, **Lamb JN,** Brew CJ, Pandit HG. Can the use of an inclinometer improve acetabular cup inclination in total hip arthroplasty? A review of the literature. Hip International. ISSN 1120-7000 (In Press)

5. Takahashi T, Hamilton T, **Lamb J**, Baboolal T, Pandit H. Is Knee joint distraction a viable treatment option for knee OA? - a literature review and meta-analysis The Journal of Knee Surgery 32(08):788-795 Aug 2019

6. **Lamb JN**, Holton C, O'Connor P, Giannoudis PV. Avascular necrosis of the hip BMJ: British Medical Journal 365(8201) Article number l2178 01 Jun 2019

7. van Duren BH, **Lamb JN**, Nisar S, Ashraf Y, Somashekar N, Pandit H. Preservation vs. resection of the infrapatellar fat pad during total knee arthroplasty Part I: A survey of current practice in the UK The Knee 26(2):416-421 Mar 2019

8. Nisar S, **Lamb JN**, Somashekar N, Pandit H, van Duren BH. Preservation vs. resection of the infrapatellar fat pad during total knee arthroplasty part II: A systematic review of published evidence The Knee 26(2):422-426 Mar 2019