Prediction of Fracture Nonunion Leading to Secondary Surgery in Patients with Distal Femur Fractures - Statistical Analysis Plan

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INTRODUCTION

Background and rationale

Distal femur fractures account for 0.4% of all fractures.[1] The overall incidence is around 8.7/100,000/year.[2] The majority of distal femur fractures are fragility fractures occurring in women with increasing incidence with age.[1,2]. These fractures occur due to high energy trauma such as traffic or sport accident for younger patients, but already falling from a standing position causes similar fractures in elderly people.[3] Total knee replacement surgeries are on the rise, leading to more osteoporotic periprosthetic distal femur fractures.[4] A high one-year mortality rate of 25–38% in elderly people over 60 years old with distal femur fractures is comparable to the mortality of proximal femur fractures.[5–10]

The modern treatment options for distal femur fractures consist of lateral locking plates and retrograde nailing.[11] The operative treatment aims to restore the articular surface and maintain the limb alignment and length with stable fixation.[12,13] The operative treatment can be challenging due to osteoporotic bone and pre-existing implants in knee and hip, possibly limiting the treatment options. A constrained knee prosthesis is an option in very distal and severely comminuted fractures or fractures with a loose knee prosthesis.[11,13] The non-surgical treatment with a cast leads generally to unsatisfactory results but it is an relevant option for patients with unacceptably high surgical risks.[13]

One of the most common and disabling complication following distal femur fracture is nonunion, leading to demanding reoperations and delayed healing. Distal femur fractures treated with a locking plate are associated with decreased and asymmetric callus formation.[14] The exact incidence of nonunion varies in the literature. However, diverse studies document high non-union rates (10–22%) with modern lateral locking plates.[15–23] A recent meta-analysis reported a nonunion rate of only 6% in distal femur fractures treated with a lateral locking plate.[24] Distal femur fracture nonunion can lead to mechanical failure of the plate.[25,26] In a literature review, 75% of implant failures occurred three months after operation due to plate fatigue secondary to delayed union and continuous movement of the fracture site.[26]

Risk factors for non-union

Distal femur fracture nonunion has a multifactorial background involving different patient-, injury- and treatment-related risk factors. The patient- and injury-related risk factors for non-union described in the literature include obesity [23,27], diabetes [15], infection [6,23,27], smoking [19] and open fracture [15,18,23,25,27]. A predictive algorithm in the study by Rodriquez et al showed that with these four risk factors–obesity, infection, titanium plate instead of stainless steel plate, and open fracture–the risk for nonunion was 96% and the absence of these factors reduced the risk to 4%.[23]

Fracture comminution has been identified as a risk factor for distal femur fracture nonunion in two studies.[17,21] However, one study found no correlation between the length of comminution and nonunion.[25] Lateral locking plate constructs may not have adequate stability in fractures with severe medial comminution. In comminuted fractures the medial fracture gap above 5mm may increase the risk for fracture nonunion.[19] A retrospective study showed 9,3% plate failures after lateral locked plating of distal femur fractures, and plate failures occurred average 186 days (range 85-400 days) after operation reflecting the probability of nonunion in these fractures. Open fractures, medial metaphyseal comminution and higher length of the comminution were associated with plate failures.[22]

Knee prostheses in periprosthetic distal femur fractures may limit the fracture treatment options, complicate the operation and affect the fracture healing. There was no significant differences between periprosthetic and non-periprosthetic fractures regarding the union-rates (83,8% vs. 78,9%) in a retrospective study.[21] One study showed periprosthetic fractures to be associated more often with failed hardware than non-periprosthetic fractures.[25] A recent national database study with a large cohort of patients indicates no differences in mortality, reoperation and major complications between periprosthetic and native distal femur fractures.[28] Patients with periprosthetic fracture had a higher rate of wound complications.[28]

Distal femur fracture nonunion rate might be lower in elderly patients with low-energy injuries. A recent study from Sweden showed only 4% nonunion in a geriatric study population with a median age of 79.[29] In their study, no patients over 80 years underwent surgical intervention for nonunion. Patients with nonunion were younger and had open fractures more commonly, reflecting the higher trauma energy.[29] On the other hand, another study with a geriatric study population (average age 78 ± 9.5 years) showed 24% nonunion rate. Age did not predict the development of nonunion.[6]

Additionally, there has been discussion in the recent literature about the stiffness of the plate construction that affects the healing environment and micromotion in the fracture site. A few studies investigated different plate fixation variables as a risk factor for nonunion.[15,16] The plate material can affect the rigidity of fixation. Stainless steel plates appeared as a risk factor for nonunion compared to titanium plates.[16,23] There was less callus formed with fractures treated with a stainless steel plate compared with titanium plate.[17] The plate length, the screw selection and the screw placement in the plate can affect the construction rigidity. Constructs with a plate length > 9 holes appeared to fail less likely compared to shorter plates.[15] The plate constructs with all locking screws have been reported to be 2.9 times more likely to develop a nonunion compared to the plate constructs with both locking and nonlocking screws.[30] In addition, healed distal femur fractures had more empty plate holes adjacent to fracture site compared to fractures that did not heal.[17] The mini-invasive plate insertion spares the blood circulation to the periosteum. The submuscular plate insertion reduced nonunion rate in distal femur fractures instead of open reduction.[21,25]

This study explores the predictive value of previously identified explanatory risk factors for a distal femur fracture nonunion and identifies patients who are at risk for distal femur fracture nonunion after lateral locked plating. In a predictive model, there is no need to consider the causality of the individual risk factors which is a common caveat in studies exploring potential risk factors for a given outcome.[31] This prediction model could be applied into clinical practice to identify and advise patients with known risks before operation and to more carefully follow-up patients with an elevated risk for fracture nonunion.

Our plan is to publish this study in two consecutive articles: the first article examines the patient- and injury- related factors and the second article examines the role of different treatment related factors in the prediction of distal femur fracture nonunion. To avoid selective reporting and to improve the transparency of the data collection and analysis phases of these two studies, we decided to write this statistical analysis plan before any statistical analyses were conducted. The study results will be reported according to The Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) -statement.[32]

Objectives and hypotheses

The objectives of the first study:

- To determine the rate of secondary surgery due to fracture nonunion of AO/OTA type A and C distal femur fractures treated primarily with lateral locking plate
- To evaluate how accurately the previously identified patient- and injury-related risk factors predict a distal femur fracture nonunion

The objective of the second study:

- To evaluate how accurately the previously identified treatment-related risk factors predict a distal femur fracture nonunion
- To evaluate a secondary prediction model combining the treatment-related risk factors and the three most important patient- and injury-related predictive factors from the first study

STUDY METHODS

This study is a retrospective cohort study conducted in level 1 trauma centre at the Helsinki University Hospital with a catchment population of around one million for these fractures. After receiving permission from our institutional review board, we identified all patients with a distal femur fracture treated at our institution between 2009 and 2018 using the electronic patient record system. Both of our future articles regarding the prediction of distal femur fracture non-union will use the same patient data.

The detailed inclusion and exclusion criteria are shown in Table 1. We included patients aged 16 years or older with traumatic distal femur fractures. The first surgical procedure had to be performed at our institution in 1 month (≤ 31 days) after trauma. Patients with a stress fracture, a pathological fracture, epicondylar or subchondral fracture, or ligament sprains such as ACL, PCL, MCL or LCL avulsion injuries, were excluded. We included in these studies The AO Foundation/Orthopaedic Trauma Association (AO/OTA) classification 33A- and 33C-type fractures [33] treated with a lateral locking plate. Only distal lateral anatomic locking plates for distal femur were included and any other unconventional plates used in the distal femur were excluded. Those fractures treated with a lateral and medial plate (double plating-method) or with lateral plate and femur nail together were excluded. We excluded patients treated with a retrograde or an antegrade femoral nail, a constrained prosthesis, femoral amputation, non-surgical treatment and patients who died before the final treatment. We excluded the operatively treated unicondylar fractures (AO/OTA classification 33B,) because the fixation methods and principles used for the operative treatment for B-type fractures differ from the A- and C-type fractures.

The first author examined all femur fracture X-rays included in the study. A fracture was classified as a distal femur fracture if a part of the fracture site was located on a metaphyseal area of distal femur. Metaphyseal area of distal femur was defined with a square-method as proposed by Urs Heim.[34,35]

We excluded the patients whose follow-up was too short to define the final healing status of the fracture. The patients who had a radiological or clinical union of the fracture site during the follow-up, and the patients who had any surgical intervention to promote the bony union were accepted to this study.

We defined a fracture as nonunited only when a patient had a surgical intervention to promote bony union in the fracture site. In addition, a reoperation done for a plate failure at least 3 months after operation and without a new trauma is assumed in this study to occur because of a nonunion of the fracture.

The radiological union in the x-ray is defined as a bridging callus consolidation on three out of four cortices of fracture site and vanishing of fracture lines during the follow up. If the radiological follow-up ended before the fracture was radiologically united in x-rays, we followed up the patients from electronic patient records of all medical specialties and general medicine at least 12 months after operation and examined their ambulating status and other problems regarding the fracture site. If there were no clinical signs of problems with distal femur fracture such as pain during gait or pain on the fracture site, and those patients did not come back to our institution after 1 year at least, we assumed that the fracture has been healed and those patients were included in the study. Our institution Helsinki university hospital is the only place in our catchment area where distal femur fractures are treated and based on that we assumed that those patients, who had problems with healing such as non-union or plate failure, will return to the Helsinki university hospital for reoperation.

Surgical treatment

The two different plate types used in this study were DePuy Synthes 4,5mm VA-LCP Curved Condylar Plate (Stainless steel) and DePuy Synthes Less invasive stabilization system (LISS) for LCP-DF-plate (Titanium alloy). The fractures included in this study were operated by the senior orthopaedic trauma surgeons or orthopaedic residents. The plate type, screw types and proximal fixation used in the operation were chosen by the treating surgeon. The methods for proximal fixation were 4.5mm locking- and cortical screws and with peri-implantary fractures also cables and 3.5mm proximal locking attachment plates were used. The fracture fixations were performed both with absolute or relative stabilization techniques according to treating surgeon’s preference. There were no proper data available from the surgical records if the operation was performed with a mini-invasive or an open technique. There were not any standardized postoperative protocols for weight-bearing or a cast or an orthosis use. Usually, the non-weight-bearing period was 6-10 weeks after operation. After that patients normally continued with half-weight-bearing, and the weight-bearing as tolerated was allowed from the weeks 10 to 12 depending how the fracture was healed. Typically, the follow-up visits were at 6 and 12 weeks at the outpatient clinic and after that if deemed necessary.

Table 1. Inclusion and Exclusion criteria used in the study.

Inclusion

- Age > 16 years
- AO/OTA type A or C distal femur fracture
- Fracture located on the metaphyseal area of the distal femur (square method)
- Operative treatment in the Helsinki University Hospital with a distal femur anatomic lateral locking plate
- Operative treatment within 1 month after trauma
- Operative treatment between years 2009 and 2018

Exclusion

- Stress fracture
- Pathological fracture
- An epicondylar or subchondral fracture
- A ligament sprain in distal femur
- Treatment with a double-plating method or with both plate and nail
- Non-surgical treatment and patients who died before the treatment
- Treatment with an unconventional plate (other than distal femur plate)
- Patients whose follow-up criteria not fulfilled

Data collection

The details of the data used in this study are shown in Table 2.

The principles of the injury-related factors are as follows. Distal femur fractures were classified according to the AO/OTA classification system 2007.[33] High energy trauma was defined as a motor-vehicle accident or a fall from a height of >1m. Low-energy trauma was defined as a fall from a height of < 1m such as a fall from the same level or a fall from a chair or a bed. All fractures were classified as open or closed injuries. Open fracture was defined as a fracture with an open wound or break in the skin near the broken bone. The definition for a periprosthetic fracture in this study was a distal femur fracture above a knee prosthesis. Segmentally comminuted fractures were defined as A3, C2 and C3- fractures according to the AO/OTA-classification. The definition for medial fracture comminution was that more than one fracture line reached the medial cortex on the antero-posterior x-ray forming one or more loose bone fragments on the medial side. Fracture zone length was measured from the postoperative x-rays where the fracture was reduced. The known plate length in millimetres was used to correctly calibrate the x-ray.

The principles of the treatment-related factors are as follows.

1. The x-ray was calibrated using the plate length
2. Plate length in millimetres: Measured as the plate shaft holes first and then in millimetres given from the manufacturer
3. Plate working length: Defined as a distance from the nearest proximal screw to the nearest distal screw on each side of the fracture
4. Empty holes adjacent the fracture site (i.e., on the intact part of the femur)

5. Plate span ratio: defined as a ratio of the plate length to the fracture length
6. Proximal plate length: Defined as number of plate holes proximal to the fracture lines in X-ray
7. Proximal fixation mode: locking screws, locking + cortical screws (hybrid), cortical screws, cables with or without screws
8. Proximal cortices: Defined as the number of proximal cortices fixed with screws or cables above the fracture segment. One cable is defined to correspond to a bicortical screw (i.e., purchase of 2 cortices). The sufficient proximal fixation is defined as a purchase of 8 or more cortices (e.g., minimum of 4 bicortical screws) and a purchase of less than 8 cortices is defined as not sufficient.
9. The number of locking screws in the plate crossing the fracture segment

Table 2. Data set used in the study.

Patient-related factors (Study I)

- Age at the date of injury
- Sex
- Body mass index
- Diabetes
- Smoking

Injury-related factors (Study I)

- AO/OTA[a] classification
- Periprosthetic fracture above a knee prosthesis
- Open/closed fracture
- Trauma energy
- Fracture zone length
- Segmental comminution (AO/OTA A3, C2, C3)
- Medial comminution of the fracture

Treatment-related[b] factors (Study II)

- Plate length in millimetres
- Plate working length
- Empty holes adjacent the fracture site
- Plate span ratio
- Proximal plate length
- Proximal fixation mode
- Proximal cortices
- Locking screws in the fracture segment

[a] AO/OTA = The AO Foundation/Orthopaedic Trauma Association

[b] See text for definition

STATISTICAL PRINCIPLES

Our statistical analysis is based on predictive approach, and we will follow guidelines from Harrell and Heinze et al.[36,37] We will use logistic regression since our outcome is binary. Our analysis will be three-fold as outlined above. In the first analysis, we will model risk of nonunion using patient- and injury-related variables. In the second analysis, we will use treatment-related variables. The third analysis will be a combined model which include 3–4 most important variables from the first analysis combined with the 3–4 most important from the second model.

Background knowledge based on previous literature was used to form initial set of variables which may be predictive for nonunion. Variable missingness is assessed. We assume Missing Completely at Random (MCAR) for any missing data and multiple imputation is used. Imputation is based on both predictors and outcome variable. Redundancy analysis is then performed to assess any collinearity between predictors and data reduction is performed if reasonable. Binary variables with very high skewness are critically assessed and excluded from final variable set if seen feasible. Model fitting will be done with imputed datasets. For fitted models, overall R2 is estimated and used to interpret the applicability of baseline predictors. Variable importance is also assessed using Wald chi-squared test minus degrees of freedom. Calibration plots will be printed for all three models. Multiplicity is not considered since we are not focused in single regression coefficients nor we have specific multiple testing. When appropriate, 95% confidence intervals will be calculated, and associated p-values calculated. Analysis is done with RStudio using rms package.

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