The Impact of Fracture-Related Infection on Quality of Life and Complications

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Abbreviations

AO/OTA	Arbeitsgemeinschaft für Osteosynthesefragen/Orthopaedic Trauma Association
ASA	American Society of Anaesthesiologists
BMI	Body Mass Index
CCI	Charlson Comorbidity Index
DFIR	Dutch Fracture Infection Registry
EQ-5D-5L	Five-level EuroQol five-dimension
FRI	Fracture-Related Infection
IFI	Accuracy of Medical Imaging for Suspected FRI
IQR	Interquartile range
ISS	Injury Severity Score
METC	Medical Ethics Review Committee
PFNA	Proximal Femoral Nail Antirotation
PROMIS	Patient Reported Outcomes Measurement Information System
QoL	Quality of Life
SD	Standard Deviation
SF-36	Short Form 36
SIRS	Systemic Inflammatory Response Syndrome
SPSS	Statistical Package for the Social Sciences
UMCU	University Medical Centre Utrecht
VAS	Visual Analogue Scale

Abstract

BACKGROUND By gaining insight into the Quality of Life (QoL) and occurrence of complications, critical facets in the care for patients with Fracture-Related Infection (FRI) can be mitigated. Therefore, the aims of this study were to 1) determine the QoL in FRI patients in comparison to non-FRI patients and 2) describe the incidence of complications in this cohort.

METHODS An ambidirectional cohort study was conducted in a level 1 trauma centre between January 1st 2016 and November 1st 2021. All patients who underwent surgical stabilisation of an isolated long bone fracture were eligible for inclusion. Patients with an injury severity score ≥16 or incomplete follow-up were excluded. QoL was assessed through the use of five-level EuroQol five-dimension questionnaires twelve months post-injury.

RESULTS A total of 134 patients were included, of whom 38 (28%) FRI patients and 96 (72%) non-FRI patients. FRI patients scored significantly worse on the QoL assessment regarding the average index (p=0.007), and the subjects' mobility (p=0.00), daily activities (p=0.010) and pain (p=0.009). During the median follow-up of 14.5 months (interquartile range 9.5-26.5), patients developed other complications besides FRI in 42% (n=56) of cases. A higher complication rate was reported in FRI patients (74%), compared to non-FRI patients (29%), with a total of 56 and 36 individual complications, respectively.

CONCLUSION FRI patients have a decreased QoL and a higher overall complication rate (74%) in comparison to non-FRI patients (29%). As a result of this study, FRI patients can be better counselled regarding the potential physical and mental consequences of their disease.

Introduction

Fracture-Related Infections (FRIs) are one of the most challenging complications after fracture surgery [1]. As a result of extensive treatment and long-term consequences of the infection, FRI tend to impact the economy substantially due to high healthcare costs and increased absenteeism from work [2]. Besides these socioeconomic effects, FRI also affects the patient's daily life and functioning status [3].

Quality of Life (QoL) and mental health have become increasingly important regarding the treatment of diseases and healthcare in general. In an attempt to objectify the QoL, EuroQol five-dimension (EQ-5D) questionnaires are commonly used to analyse the QoL based on various subjects [4,5]. By implementing a QoL assessment, critical facets of healthcare can be improved, in particular the provision of information, choice of treatment, facilitation of communication and outpatient aftercare [6,7]. In addition, a QoL assessment could expose and prioritise underlying problems with regard to disease management strategies [7]. EQ-5D questionnaires are also used in trauma and subsequently in patients with FRI. Recent literature demonstrated a significant decrease with regard to the QoL in FRI patients [2,8,9]. These studies reported poorer outcomes in FRI patients concerning the physical functioning, mental health status and pain interference [2,8,10]. Unfortunately, the patient populations of these studies are either heterogenous, not generally applicable or relatively small [2,8,10]. Hence, validation on a larger scale is necessary before results of QoL assessments can be implemented in FRI patient care.

In comparison with QoL, adverse outcomes after trauma- and orthopaedic surgery have been studied over a longer period of time. Several studies are available that have analysed the occurrence and consequences of complications such as nonunion, malunion, infections and pain after fracture surgery [11–13]. In addition, a lower QoL was depicted in patients who had developed either of these complications [14]. However, the available data on the occurrence and impact of complications in FRI patients is limited. In general, identification of postoperative complications leads to surgical quality improvement and should therefore be encouraged [15].

In order to improve future care of FRI patients, it is necessary to get an in-depth view regarding the QoL and to gain more insight into the development of complications in this population. Therefore, the aims of this study were to 1) determine the QoL in

FRI patients in comparison to non-FRI patients and 2) describe the incidence of additional complications in both FRI and non-FRI patients.

Methods

Study design

An ambidirectional cohort study was conducted in the University Medical Centre Utrecht (UMCU), a level 1 trauma centre in the Netherlands. A waiver was granted by the Medical Ethics Review Committee (METC-number 21/734) of the UMCU.

Patient population

Patients of at least 18 years of age who were treated with surgical stabilisation of a fracture of a long bone between January 1st 2016 to November 1st 2021 were eligible for inclusion in this study. Fractures of the humerus, forearm, femur, tibia or fibula were classified as long bone fractures. Exclusion criteria were, firstly, patients with an inadequate availability of data including failure to complete the QoL questionnaire. Secondly, to avoid confounding, multitrauma patients with an Injury Severity Score (ISS) of ≥16 [16] and patients with a periprosthetic or pathologic fracture were excluded.

Study outcomes

The primary endpoint of this study was to determine the QoL in FRI patients in comparison to non-FRI patients. The secondary endpoint was to describe the incidence of complications in both FRI and non-FRI patients.

Definitions of terms

FRI was defined as the presence of at least one confirmatory FRI criterion, according to the *FRI-consensus criteria*, which are a fistula or wound break-down communicating with the bone or implant, the presence of pus, two positive microbiological cultures with the same pathogen and histological signs of infection [17]. Recurrence of FRI was deemed as the re-appearance of at least one confirmatory FRI criterion after full completion of the initial FRI treatment. Infection control was described as absence of 1) amputation, 2) death related to the FRI, 3) confirmatory criteria and 4) ongoing FRI treatment during the last follow-up consultation.

A complication was defined as an adverse event that had either developed during the initial admission or (outpatient) follow-up as a result of treatment of the fractured long bone, leading to a change in treatment or irreversible damage [15]. Due to the study subject being FRIs, this was exempted as a complication to draw an

equivalent comparison between the FRI and non-FRI patients. The complications were divided into the following categories: nonunion, malunion, implant failure, error in technique, re-fracture, soft tissue problem, compartment syndrome, postoperative haemorrhage, deep venous thrombosis, amputation of the affected limb, persisting pain, anaemia and electrolyte disturbances, respiratory failure, infection other than FRI, Systemic Inflammatory Response Syndrome (SIRS), paralytic ileus, cardiac arrhythmia, urine retention, delirium, pressure ulcus and other not further specified complications. Complications were scored according to the Clavien-Dindo classification, whereas a grade I complication is a modest postoperative deviation requiring no or minor pharmacological treatment, grade II requires treatment with pharmacological drugs or interventions other than allowed for grade I complications, grade III complications need surgical intervention, grade IV is classified as organ failure and grade V as demise of the patient [18].

Regarding the complication nonunion, a comprehensive consensus definition is missing [19]. For this study, a nonunion was defined as failure of progression of bone-healing within the expected time frame [20] including ongoing clinical impairment. Malunion was defined as a consolidated fracture which has healed in a non-anatomical position, thereby increasing the risk of adverse functional outcome. Error in technique was described as a surgical deficiency that had either caused malalignment, malposition or insufficient stability of the affected implant/bone in such a degree that revision surgery was indicated.

Data collection

Data from three databases was retrieved, including two prospective FRI databases, namely the Accuracy of Medical Imaging for Suspected FRI (IFI-trial) [21] database and the database of the Dutch Fracture Infection Registry (DFIR) [22], and the retrospective UMCU FRI database. Only FRI patients who had at least three deep tissue cultures taken were included in these databases. For all databases, the data capturing program Castor EDC (Castor Electronic Data Capture, v2022.5.1.0) [23] was used. In addition, electronic patient files were reviewed to create a control group of consecutive non-FRI patients treated with a surgical stabilisation procedure between January 1st 2016 to November 1st 2021. All collected data used for this study was pseudonymised. Data was both prospectively and retrospectively collected, as the

outcomes of the EQ-5D questionnaires were obtained prospectively, whereas demographic data was gathered both prospectively and retrospectively.

Data with regard to patient demographics, sex, age, Body Mass Index (BMI), substance abuse, American Society of Anaesthesiologists (ASA) classification [24] and Charlson Comorbidity Index (CCI) [25] were collected. Fracture and trauma characteristics were identified according to the ISS [16], Arbeitsgemeinschaft für Osteosynthesefragen/Orthopaedic Trauma Association (AO/OTA) fracture classification [26] and Gustilo-Anderson classification [27]. The follow-up and course of the disease were described according to the length-of-stay, occurrence of complication(s), need for re-operation(s) and re-admission(s), and fracture consolidation. Additional data concerning the treatment and follow-up of FRI patients included time to onset of the infection, recurrence rate and infection control rate.

In order to determine the QoL of trauma patients, PROMIS (Patient Reported Outcomes Measurement Information System) five-level EQ-5D(-5L) questionnaires were used. The EQ-5D-5L consisted of five questions concerning the topics of mobility, self-care, daily activities, pain, anxiety and depression, including a Visual Analogue Scale (VAS) regarding the patients' general health. Patients could indicate a score on a dichotomised scale of one to five with regard to the five aforementioned subjects, a score of one was considered as absence of problems related to the specific topic, whilst a score of five was deemed as excessive inconvenience. In addition to the scores per subject, the average of the index [28] of all subjects was reported as well. General health was assessed based on a VAS of zero to one hundred, with zero as the worst conceivable health and one hundred the best. In the UMCU, as standard-of-care, EQ-5D questionnaires are sent to all trauma patients admitted via the Emergency Department at a time-point of twelve months post admission. In addition, patients seen in the outpatient clinic or admitted directly to the trauma unit without an admission via the Emergency Department, received the EQ-5D questionnaires at multiple time points post-injury as part of the IFI and DFIR trials. For this study, the questionnaires of twelve months post-injury were collected. The transmission and collection of the QoL assessments was administered to Network Acute Care Central Netherlands (Netwerk Acute Zorg Midden-Nederland) [29] and the author (M.B.) of the present study. Reminders were sent within three weeks or after one month of failure to complete the EQ-5D questionnaire, respectively.

Statistical analysis

All data analyses were conducted in Statistical Package for the Social Sciences (SPSS®) statistics (version 26.0, Armonk, NY, USA: IBM Corp.). Data was presented as dichotomised variables in counts and percentages (n (%)), or as continuous variables in median and interquartile range (IQR) or in mean and standard deviation (SD) according to the normality distribution of the variable. Regarding the baseline characteristics and QoL analyses, FRI patients and patients with complications were compared to a control group. In case of dichotomised variables, Chi-Squared tests or Fisher's exact tests were performed depending on the estimated cell size. Independent t-tests or Mann-Whitney U tests were performed for continuous variables, based on the normality test of the variable. The level of statistical significance was set at $p < 0.05$.

Results

Baseline characteristics

In total, 513 unique patients were identified who were eligible for inclusion in this present study. Ultimately 134 patients were included, of whom 38 (28%) FRI patients and a control group of 96 (72%) non-FRI patients. The majority of patients (63%, n=325/513) were excluded as a result of failure to complete the EQ-5D questionnaire, herewith a response rate of 37% was reported. The baseline characteristics of the respondents who were included in this study and a group of non-respondents who met all inclusion criteria and did not meet exclusion criteria, are presented in Appendix 1. Non-respondents were significantly younger and healthier, had a lower ISS and shorter duration of admission compared to respondents. Besides, FRI was more often reported among the respondents. A synopsis of the complete in- and exclusion process is available in Figure 1.

An overview of the baseline characteristics of the patients in this cohort is available in Table 1. The cohort consisted of predominantly males (62%, n=83), with a median age of 52.0 years (IQR 32.0-63.0). Majority of the patients were classified as ASA 1 (46%, n=61) along with a median CCI index of 1.0 (IQR 0.0-3.0). Most injuries were caused by low energy trauma's (58%, n=78), with a corresponding median ISS of 9.0 (IQR 4.8-10.0). Fractures were most often located at the tibia/fibula (57%, n=76) and a third of the patients had an open fracture (31%, n=42), which demonstrated to be more prevalent in FRI patients contrary to non-FRI patients (61%, n=23/38 vs. 20%, n=19/96). In particular, Gustilo-Anderson grade III fractures were more common in the FRI group versus the control group of non-FRI patients (32%, n=12/38 vs. 9% n=9/96). The median follow-up duration was 14.5 months (IQR 9.5-26.5), FRI patients had a significantly longer follow-up (22.7 (IQR 13.3-30.5) as opposed to non-FRI patients (12.6 (IQR 8.1-22.4). During this follow-up, 53 (40%) patients were re-admitted and 66 (49%) patients were re-operated after the initial fracture fixation operation. Higher re-admission (95%, n=36/38 vs. 18%, n=17/96) and re-operation (97%, n=37/38 vs. 30%, n=29/96) rates were reported among FRI patients compared to non-FRI patients. In 60% (n=61/102) of patients, complete fracture consolidation was achieved after one year, with complete consolidation in 30% of FRI patients (n=10/33) and in 74% of non-FRI patients (n=51/69).

A more in-depth view of FRI patients is presented in Table 2. The average onset of FRI was 17.5 days (IQR 11.0-41.8). During follow-up, recurrence of FRI occurred in 26% (n=10) and overall infection control was achieved in 92% (n=35) of cases.

QoL assessment (EQ-5D-5L questionnaires)

The QoL of FRI and non-FRI patients was assessed based on the six topics mobility, self-care, daily activities, pain, anxiety and depression, and general health. In comparison to non-FRI patients, FRI patients scored significantly worse regarding the subjects' mobility (p=0.00), daily activities (p=0.010) and pain (p=0.009) (Table 3). In addition, the median index of FRI patients was significantly (p=0.007) higher compared to non-FRI patients (1.9 (IQR 1.4-2.7) vs. 1.6 (IQR 1.2-1.9)). The topics self-care (p=0.064) and anxiety and depression (p=0.24), including the general health score (p=0.31), were unsignificant components of the QoL analysis. A visual overview of the results of the QoL assessment is presented in Figure 2.

Another QoL assessment was executed to describe the difference in QoL between patients with and without the development of other complication(s). Patients with other complications scored significantly worse with regard to the topic mobility (p=0.026). The results of this comprehensive QoL assessment are available in Appendix 2.

Occurrence of complications

In this cohort, 56 patients (42%) developed at least one other complication besides FRI, during the admission or follow-up due to treatment of a fractured long bone (Table 4). These 56 patients developed, apart from FRI, 92 other complications with a median of one complication (IQR 1.0-2.0) per patient. The development of other complications was more common (p=0.00) in FRI patients (74%, n=28/38) compared to non-FRI patients (29%, n=28/96). Overall, 56 complications were reported in 38 FRI patients contrary to 36 complications in 96 non-FRI patients, with a median of 1.0 (1.0-2.0) other complication per FRI patient and 0.0 (IQR 0.0-1.0) other complications per non-FRI patient (p=0.00). The complications nonunion (26%, n=24/92), infection other than FRI (14%, n=13/92) and implant failure (10%, n=9/92) were the most frequently described in the total study cohort. With regard to FRI patients, the complications nonunion (30%, n=17/56), infection other than FRI (16%, n=9/56) and implant failure (11%, n=6/56) were most often reported, whereas non-FRI patients encountered the

complications nonunion (19%, n=7/36), error in technique (19%, n=7/36) and infection other than FRI (11%, n=4/36) more frequently. In addition, the proportion of the complication malunion was more substantial in non-FRI patients compared to FRI patients (8%, n=3/36 vs. 2%, n=1/56). Other complications that were not further specified in Table 4, are delay in diagnosis and cessation of the operation due to unforeseen logistic circumstances. Most complications (49%, n=45/92), in both FRI (46%, n=26/56) and non-FRI patients (53%, n=19/36), were scored as grade III according to the Clavien-Dindo classification, requiring a re-operation to treat the complication. Moreover, out of the 21 non fracture-related complications in FRI patients, 9 (43%) complications occurred before and 12 (57%) complications after onset of the FRI.

Discussion

This study describes the QoL and the occurrence of postoperative complications in FRI patients in an attempt to quantify the impact of FRI in a variety of long bone fractures on daily life. The QoL of FRI patients was determined to be significantly worse regarding the topic's mobility, daily activities, pain and the average index compared to non-FRI patients. In addition, a high burden of postoperative complications was demonstrated. In a total of 56 patients, 92 complications besides FRI were identified with a median of one complication per patient. Patients with FRI were more prone to develop other complications in comparison with non-FRI patients (74%, n=28/38 vs. 29%, n=28/96). The most reported complications in this cohort were nonunion, infection other than FRI and implant failure, respectively. The results of this study and its possible implications regarding daily practice will be discussed below.

Firstly, the decreased QoL in FRI patients with a long bone fracture is in accordance with the results of previously conducted studies [2,8,30]. However, due to the use of different outcome measurement systems in these studies, namely PROMIS with focus on several domains [2] and the (German) Short Form 36 (SF-36) [8], it can be difficult to compare the results in an unequivocal approach. Besides, dissimilar time-points regarding the collection of the QoL assessment were reported and, most importantly, different control groups were used, such as non-FRI patients with a long bone fracture [2], normative health data of the general national population [8,30] and complicated vs. uncomplicated osteomyelitis [30]. In addition, the scored domains are not equally affected in each study. Iliaens et al. reported a significantly worse physical functioning and pain interference [2], Walter et al. demonstrated substandard scores regarding physical, mental and general health [8], and Hotchen et al. reported an overall inferior QoL in patients with complicated osteomyelitis [30], whereas the present study demonstrated worse scores with regard to mobility, daily activities, pain and the average index. Besides studies that affirmed our findings, one recently published article could not confirm a decreased QoL in patients with FRI, which might be related to a different composition and size of the studied groups, as only patients with osteomyelitis who encountered treatment failure were included [31].

In addition, in this cohort the QoL of patients with complications was only significantly lower regarding the modality mobility, no compelling difference was reported concerning the average index. These findings suggest that not the complications reduce the QoL in our cohort, but that the decreased QoL seems to be

related to the FRI in particular. Our results are in consonance with recent literature, whereas De-Las-Heras-Romero et al. reported no significant impact of complications on the QoL in patients with an intra-articular pilon fracture [32].

Secondly, this present study demonstrated a complication rate of 74% in FRI patients and 29% in non-FRI patients, and described nonunion (18%, n=24/134), infection other than FRI (10%, n=13/134) and implant failure (5%, n=7/134) as the most common complications. These results are inconsistent with the reported outcomes of Meeuwis et al. [33]. Their study described a complication rate of 19.8% and wound infections (4.2%), loss of reduction or fixation (3.7%) and error in osteosynthesis (1.8%) as the most frequently disclosed complications in a general fracture population [33]. Nonunion was present in only 1% of their cases, this considerable difference might be explained due to the use of different definitions regarding nonunion, as no definition was elaborated in their study. Additionally, there were substantial differences in the composition of both study populations, such as the inclusion period, the number of open fractures and the large group of FRI patients included in our cohort [33,34]. Other studies analysed specific fracture sites, such as the hip [35], tibia plateau [13] and ankle [36]. These studies reported acute urinary retention, reduction of knee motion and postoperative wound problems as relatively common complications [13,35,36]. Besides reduction of motion at the affected fractured site, the aforementioned complications were also demonstrated in this present cohort, although in a different frequency.

In addition to the general complication analysis, the subgroup of FRI patients was analysed separately. To our knowledge, the occurrence of other complications in FRI patients in particular has not been studied before, hence these results can be interpreted as new data. Apart from the FRI, a complication rate of 74% was reported in the subgroup of FRI patients. The most prevalent other complications in FRI patients were nonunion, infection other than FRI and implant failure.

Furthermore, noticeable differences were the contribution of error in technique and malunion as complications in non-FRI patients compared to FRI patients. Unfortunately, a comprehensive explanation regarding the higher reported prevalence of error in technique in non-FRI patients is absent. Previous findings by Meeuwis et al. suggested that an older age might contribute to the more frequent manifestation of technical errors [33]. However, this finding cannot be confirmed in our cohort due to a median older age of FRI patients compared to non-FRI patients (56.0 vs. 49.5).

Considering the low frequency of malunion in FRI patients, this might be explained due to the scarcity of consolidated fractures in this subgroup (30% vs. 74%) which is a requirement to diagnose malunion. Another explanation could be the fact that FRI patients had undergone more revisions and therefore any previously existing malposition of the fixation devices or fracture position might have been corrected before consolidation took place.

Moreover, 43% of the non-fracture related complications in FRI patients occurred prior to the onset and 57% after the onset of FRI. Due to the limited number of non-fracture related complications in this cohort, it is difficult to correlate these outcomes to a specific cause. Presumably, the increased occurrence of non-fracture related complications after onset of the FRI might be associated with the strong pro-inflammatory immune response caused by the infection [37].

Complementary to the general study outcomes, prominent baseline characteristics will be briefly discussed. The complete consolidation rate after one year was significantly lower in FRI patients (30%) compared to non-FRI patients (74%). These numbers are in contrast to the results of Rupp et al., whereas consolidation rates of 89.7% and 84.7% were reported in FRI patients treated with and without a multidisciplinary team, respectively [38]. The low consolidation rate among FRI patients in our cohort might be related to the high incidence of nonunion. The overall consolidation rate is not described in our cohort, hence it is possible that a higher consolidation rate was achieved after surgical interventions to treat the nonunion and a longer period of time that had elapsed. Besides, an increased length-of-stay, a higher number of re-admissions and more re-operations were reported in the subgroup of FRI patients. These outcomes can be explained due to the extensive treatment, most often involving new operations and subsequent intravenous administration of antibiotics, which is associated with FRI [3]. The increased initial length-of-stay is likely affected by a large group of early FRI patients in this study, since a median onset of FRI of 17.5 days (IQR 11.0-41.8) was reported.

This ambidirectional study is subject to certain limitations. Firstly, since PROMIS was used to determine the QoL, the results of this assessment could be influenced by response and non-response bias, respectively. With the use of the standardised EQ-5D questionnaire and the subsequent utilisation of reminders, the likelihood of these forms of bias was reduced. However, significant differences between respondents and non-respondents were reported in this cohort, especially concerning the age, ASA

classification and severity of the trauma. This corresponds with previously conducted QoL assessments in trauma patients and suggests that the current findings are not haphazard [39,40]. As a consequence, this study is not generalisable to the entire fracture population. In addition, compared to studies of both Gunning et al. and van der Vliet et al., originating from the same institute, our reported response rate is significantly lower (37% vs. 59% and 77%, respectively) [41,42]. This difference could be explained due to the composition of population [41], time of administration of the questionnaire (median of completion of the questionnaire six years post-injury) and the use of reminders by telephone [42]. Secondly, due to the retrospective review of the severity of complications, the assessment might be subject to misclassification bias. However, due to the strict use of definitions this bias is thought to be limited. Lastly, as a result of the relatively small size of the cohort, it was not possible to correct for potential confounders that might have influenced the QoL.

In conclusion, our study provides insight into the expected consequences in daily life after developing FRI. As a result of this study, FRI patients can be better counselled regarding the potential physical and mental consequences of their disease. FRI patients can be informed that they are more likely to endure challenges in daily life due to a decreased QoL and that a 74% chance of developing a postoperative complication was seen in this cohort.

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Tables and Figures

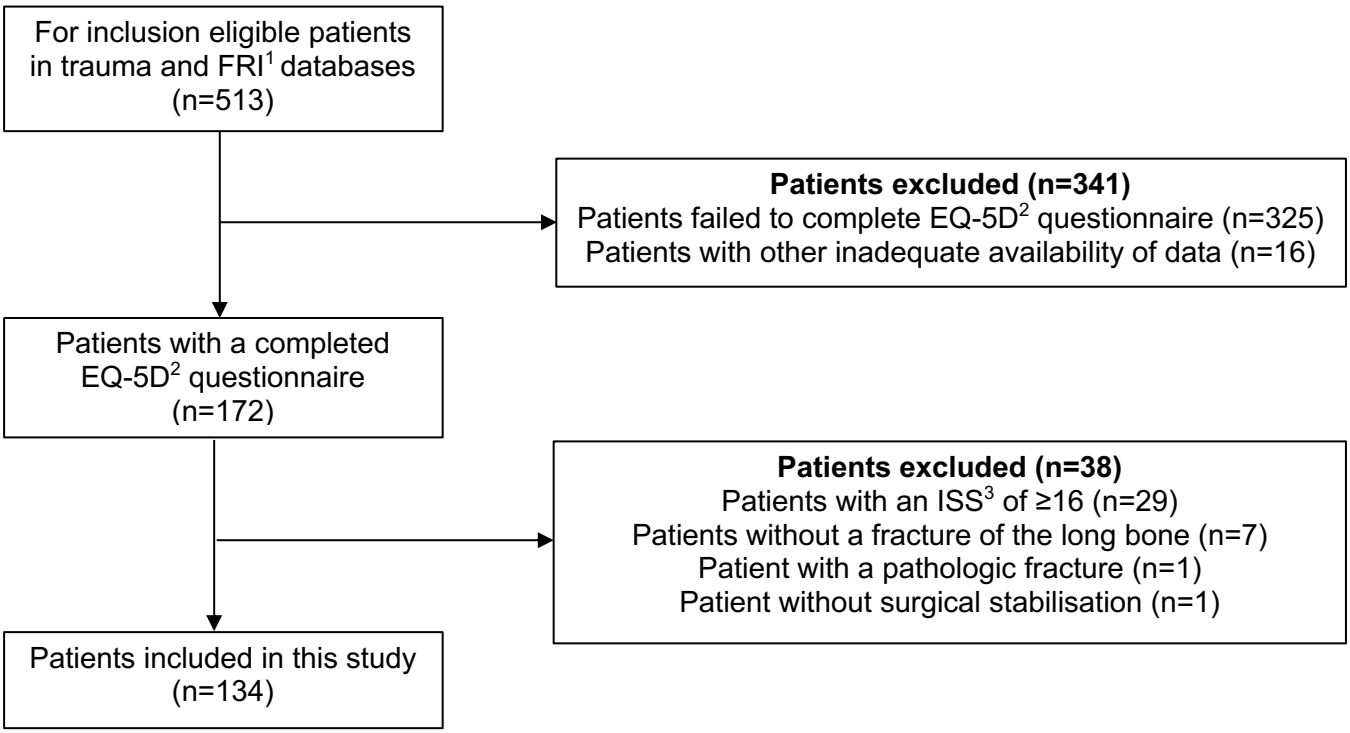

Figure 1. In- and exclusion process.

[1] Fracture-Related Infection, [2] EuroQol five-dimension, [3] Injury Severity Score.

Table 1. Baseline characteristics.

	All patients (n=134)	No FRI [1] (n=96)	FRI [1] (n=38)	p-value
Patient characteristics				
Sex (male)	83 (62%)	60 (63%)	23 (61%)	0.85
Age (years)	52.0 (32.0-63.0)	49.5 (31.3-63.5)	56.0 (36.5-63.0)	0.26
Body Mass Index (kg/m^2) (n=126)	24.8 (23.0-27.5)	25.1 (23.0-27.6)	24.6 (23.0-27.5)	0.93
Substance abuse				
Nicotine (n=114)	38 (33%)	30 (40%)	8 (21%)	0.059
Drugs (n=112)	10 (9%)	8 (11%)	2 (5%)	0.49
ASA classification [2]				0.40
ASA 1	61 (46%)	40 (42%)	21 (55%)	
ASA 2	57 (43%)	44 (46%)	13 (34%)	
ASA 3	16 (12%)	12 (13%)	4 (11%)	
Charlson Comorbidity Index	1.0 (0.0-3.0)	1.0 (0.0-3.0)	1.0 (0.0-2.0)	0.51
Fracture and trauma characteristics				
Injury Severity Score	9.0 (4.8-10.0)	9.0 (4.0-10.0)	9.0 (5.0-11.5)	0.24
High-energy trauma	56 (42%)	37 (39%)	19 (50%)	0.25
Crush injury	10 (7%)	5 (5%)	5 (13%)	0.15
(Additional) injuries				**0.008**
One fracture one extremity	64 (48%)	51 (53%)	13 (34%)	
Multiple fractures same extremity	6 (5%)	6 (6%)	0 (0%)	
Multiple fracture different extremities	13 (10%)	5 (5%)	8 (21%)	
Other [3]	51 (38%)	34 (35%)	17 (45%)	
Fracture location				0.097
Humerus	7 (5%)	6 (6%)	1 (3%)	
Forearm	18 (13%)	14 (15%)	4 (11%)	
Femur	33 (25%)	28 (29%)	5 (13%)	
Tibia/fibula	76 (57%)	48 (50%)	28 (74%)	
Open fracture	42 (31%)	19 (20%)	23 (61%)	**0.00**
Gustilo-Anderson classification (n=42)				1.00
Type I	10 (24%)	5 (26%)	5 (22%)	
Type II	10 (24%)	5 (26%)	5 (22%)	
Type III	21 (50%)	9 (47%)	12 (52%)	
Type unknown	1 (2%)	0 (0%)	1 (4%)	
Implant used at index operation				0.083
G-nail, PFNA [4] or similar	8 (6%)	6 (6%)	2 (5%)	
Intramedullary nail	47 (35%)	39 (41%)	8 (21%)	
Plate	72 (54%)	46 (48%)	26 (68%)	
Screws or k-wires	4 (3%)	3 (3%)	1 (3%)	
External fixation	3 (2%)	2 (2%)	1 (3%)	
Disease course and follow-up				
Length-of-stay (days) (n=130)	7.5 (4.8-13.3)	6.5 (4.0-11.0)	15.0 (5.8-38.0)	**0.001**
Need for re-operations [5]	66 (49%)	29 (30%)	37 (97%)	**0.00**
Need for re-admissions [5]	53 (40%)	17 (18%)	36 (95%)	**0.00**
Follow-up duration (months)	14.5 (9.5-26.5)	12.6 (8.1-22.4)	22.7 (13.3-30.5)	**0.002**
Fracture consolidation (n=102)	61 (60%)	51 (74%)	10 (30%)	**0.00**

Dichotomised variables: n (%)
Continuous variables: median (IQR [6])

[1] Fracture-Related Infection, [2] American Society of Anaesthesiologists, [3] All other additional injuries that could not be specified to one of the previously stated categories, [4] Proximal Femoral Nail Antirotation, [5] Including Fracture-Related Infection re-operations and re-admissions, excluding planned removal of implant(s) only, [6] Interquartile range.

Table 2. Characteristics of FRI [1] patients.

	FRI [1] (n=38)
Time to onset of infection (days)	17.5 (11.0-41.8)
Follow-up duration (months)	22.7 (13.3-30.5)
Average number of re-operations	3.0 (2.0-6.0)
Average number of re-admissions	2.0 (1.0-3.3)
Recurrence of FRI [1]	10 (26%)
Infection control at last follow-up visit	35 (92%)
Dichotomised variables: n (%)	
Continuous variables: median (IQR [2])	

[1] Fracture-Related Infection, [2] Interquartile range.

Table 3. Quality of Life assessment Fracture-Related Infection.

	All patients (n=134)	No FRI [1] (n=96)	FRI [1] (n=38)	p-value
Mobility				**0.00**
1 – No problems	49 (37%)	39 (41%)	10 (26%)	
2 – Mild problems	50 (37%)	40 (42%)	10 (26%)	
3 – Moderate problems	22 (16%)	15 (16%)	7 (18%)	
4 – Severe problems	10 (8%)	1 (1%)	9 (24%)	
5 – Extreme problems	3 (2%)	1 (1%)	2 (5%)	
Self-care (n=133)				0.064
1 – No problems	98 (74%)	75 (79%)	23 (61%)	
2 – Mild problems	23 (17%)	14 (15%)	9 (24%)	
3 – Moderate problems	7 (5%)	4 (4%)	3 (8%)	
4 – Severe problems	4 (3%)	1 (1%)	3 (8%)	
5 – Extreme problems	1 (1%)	1 (1%)	0 (0%)	
Daily activities (n=133)				**0.010**
1 – No problems	43 (32%)	34 (36%)	9 (24%)	
2 – Mild problems	57 (43%)	44 (46%)	13 (34%)	
3 – Moderate problems	22 (17%)	14 (15%)	8 (21%)	
4 – Severe problems	8 (6%)	2 (2%)	6 (16%)	
5 – Extreme problems	3 (2%)	1 (1%)	2 (5%)	
Pain and discomfort (n=133)				**0.009**
1 – No pain	34 (26%)	27 (28%)	7 (18%)	
2 – Mild pain	65 (49%)	51 (54%)	14 (37%)	
3 – Moderate pain	26 (20%)	13 (14%)	13 (34%)	
4 – Severe pain	6 (5%)	2 (2%)	4 (11%)	
5 – Extreme pain	2 (2%)	2 (2%)	0 (0%)	
Anxiety and depression (n=133)				0.24
1 – No symptoms	88 (66%)	64 (67%)	24 (63%)	
2 – Mild symptoms	37 (28%)	25 (26%)	12 (32%)	
3 – Moderate symptoms	5 (4%)	5 (5%)	0 (0%)	
4 – Severe symptoms	2 (2%)	1 (1%)	1 (3%)	
5 – Extreme symptoms	1 (1%)	0 (0%)	1 (3%)	
Average index score (n=131)	1.6 (1.2-2.2)	1.6 (1.2-1.9)	1.9 (1.4-2.7)	**0.007**
General health (n=133)	75.0 (61.0-85.0)	75.0 (65.0-85.0)	75.0 (57.5-80.0)	0.31
Dichotomised variables: n (%)				
Continuous variables: median (IQR [2])				

[1] Fracture-Related Infection, [2] Interquartile range.

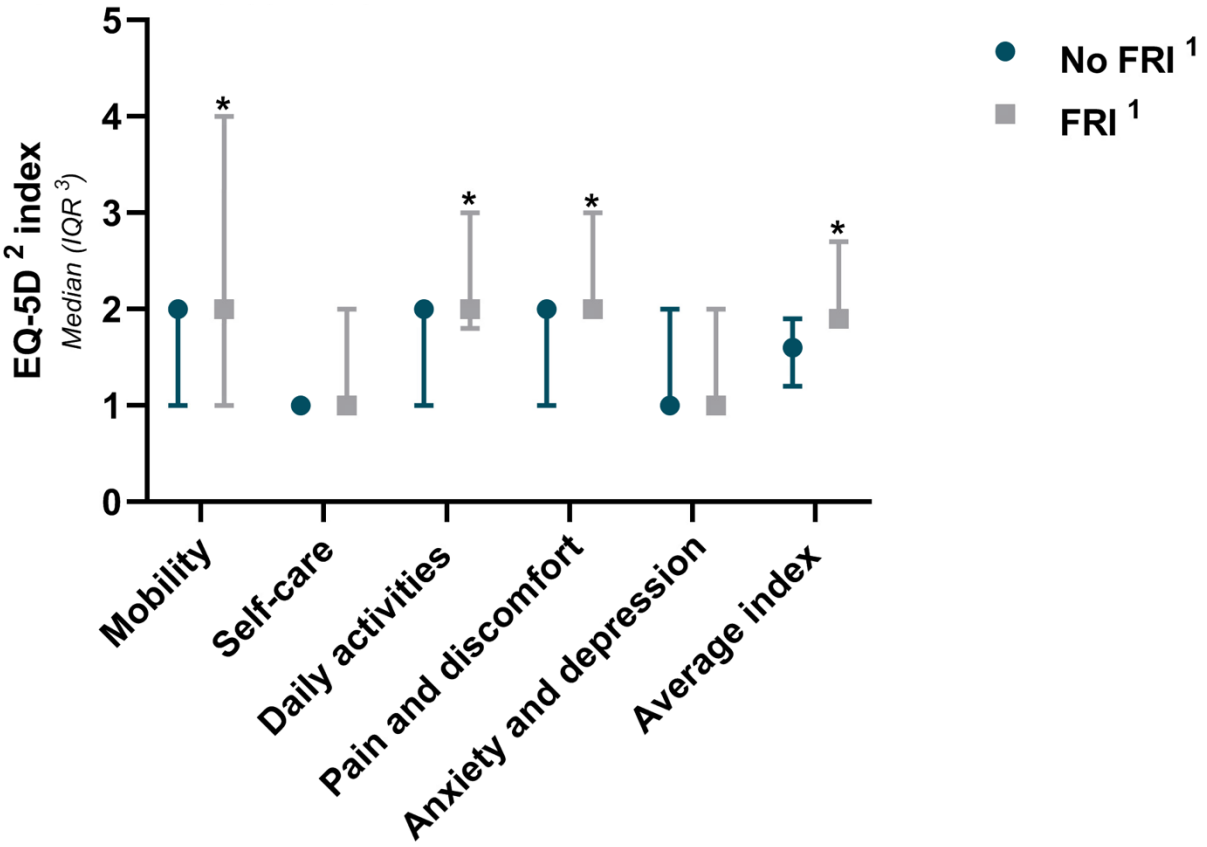

Figure 2. Visual overview of the Quality of Life assessment.

[1] Fracture-Related Infection, [2] EuroQol five-dimension, [3] Interquartile range, * Statistically significant variables.

Table 4. Occurrence of complications [1].

	All patients (n=134)	No FRI [2] (n=96)	FRI [2] (n=38)
Development of complication(s)	56 (42%)	28 (29%)	28 (74%)
Total amount of complications	92	36	56
Average amount of complications per patient	0.0 (0.0-1.0)	0.0 (0.0-1.0)	1.0 (0.0-2.0)
Type of complications (n=92)			
Nonunion	24 (26%)	7 (19%)	17 (30%)
Malunion	4 (4%)	3 (8%)	1 (2%)
Implant failure	9 (10%)	3 (8%)	6 (11%)
Error in technique	8 (9%)	7 (19%)	1 (2%)
Re-fracture	1 (1%)	0 (0%)	1 (2%)
Soft tissue problem	3 (3%)	2 (6%)	1 (2%)
Compartment syndrome	1 (1%)	0 (0%)	1 (2%)
Postoperative haemorrhage	4 (4%)	2 (6%)	2 (4%)
Deep venous thrombosis	2 (2%)	0 (0%)	2 (4%)
Amputation	1 (1%)	0 (0%)	1 (2%)
Persisting pain	6 (7%)	2 (6%)	4 (7%)
Anaemia and electrolyte disturbances	3 (3%)	2 (6%)	1 (2%)
Respiratory failure	1 (1%)	0 (0%)	1 (2%)
Infection [3]	13 (14%)	4 (11%)	9 (16%)
SIRS [4]	1 (1%)	0 (0%)	1 (2%)
Paralytic ileus	1 (1%)	0 (0%)	1 (2%)
Cardiac arrhythmia	1 (1%)	0 (0%)	1 (2%)
Urine retention	5 (5%)	1 (3%)	4 (7%)
Delirium	1 (1%)	0 (0%)	1 (2%)
Pressure ulcer	1 (1%)	1 (3%)	0 (0%)
Other [5]	2 (2%)	2 (6%)	0 (0%)
Clavien-Dindo classification (n=92)			
Grade I	28 (30%)	12 (33%)	16 (29%)
Grade II	15 (16%)	5 (14%)	10 (18%)
Grade III	45 (49%)	19 (53%)	26 (46%)
Grade IV	4 (4%)	0 (0%)	4 (7%)
Grade V	0 (0%)	0 (0%)	0 (0%)

Dichotomised variables: n (%)
Continuous variables: median (IQR [6])

[1] Complications that had either developed during the initial admission or (outpatient) follow-up excluding Fracture-Related Infection, [2] Fracture-Related Infection, [3] All infections other than Fracture-Related Infection, [4] Systemic Inflammatory Response Syndrome, [5] Other complications that could not be further specified, [6] Interquartile range.

Appendix

Appendix 1. Baseline characteristics respondents versus non-respondents.

	All patients (n=288)	Respondents (n=134)	Non-respondents (n=154)	p-value
Patient characteristics				
Sex (male)	168 (58%)	83 (62%)	85 (55%)	0.28
Age (years)	45.0 (28.3-59.0)	52.0 (32.0-63.0)	40.0 (27.0-55.0)	**0.001**
Body Mass Index (kg/m^2) (n=273)	24.9 (22.8-27.8)	24.8 (23.0-27.5)	24.9 (22.4-28.3)	0.77
Substance abuse				
Nicotine (n=246)	91 (37%)	38 (33%)	53 (40%)	0.29
Drugs (n=241)	26 (11%)	10 (9%)	16 (12%)	0.41
ASA classification [1]				**0.002**
ASA 1	152 (53%)	61 (46%)	91 (59%)	
ASA 2	116 (40%)	57 (43%)	59 (38%)	
ASA 3	20 (7%)	16 (12%)	4 (3%)	
Charlson Comorbidity Index	0.0 (0.0-2.0)	1.0 (0.0-3.0)	0.0 (0.0-1.0)	**0.00**
Fracture and trauma characteristics				
Injury Severity Score	9.0 (4.0-9.0)	9.0 (4.8-10.0)	4.0 (4.0-9.0)	**0.00**
High-energy trauma	104 (36%)	56 (42%)	48 (31%)	0.066
Crush injury	18 (6%)	10 (7%)	8 (5%)	0.47
Fracture location				**0.001**
Humerus	20 (7%)	7 (5%)	13 (8%)	
Forearm	67 (23%)	18 (13%)	49 (32%)	
Femur	59 (21%)	33 (25%)	26 (17%)	
Tibia/fibula	142 (49%)	76 (57%)	66 (43%)	
Open fracture	71 (25%)	42 (31%)	29 (19%)	**0.019**
Gustilo-Anderson classification (n=71)				0.089
Type I	20 (28%)	10 (24%)	10 (35%)	
Type II	22 (31%)	10 (24%)	12 (41%)	
Type III	29 (39%)	21 (50%)	7 (24%)	
Type unknown	1 (1%)	1 (2%)	0 (0%)	
Implant used at index operation				**0.004**
Dynamic Hip Screw	1 (0%)	0 (0%)	1 (1%)	
G-nail, PFNA [2] *or similar*	12 (4%)	8 (6%)	4 (3%)	
Intramedullary nail	79 (27%)	47 (35%)	32 (21%)	
Plate	180 (63%)	72 (54%)	108 (70%)	
Screws or k-wires	13 (5%)	4 (3%)	9 (6%)	
External fixation	3 (1%)	3 (2%)	0 (0%)	
Disease course and follow-up				
Fracture-Related Infection	53 (18%)	38 (28%)	15 (10%)	**0.00**
Length-of-stay (days) (n=284)	5.0 (1.0-10.0)	7.5 (4.8-13.3)	2.0 (1.0-6.0)	**0.00**
Need for re-operations [3]	113 (39%)	66 (49%)	47 (31%)	**0.002**
Need for re-admissions [3]	93 (32%)	53 (40%)	40 (26%)	**0.016**
Follow-up duration (months)	12.5 (7.1-21.9)	14.5 (9.5-26.5)	10.9 (5.7-16.1)	**0.00**

Dichotomised variables: n (%)
Continuous variables: median (IQR [4]*)*

[1] American Society of Anaesthesiologists, [2] Proximal Femoral Nail Antirotation, [3] Including Fracture-Related Infection re-operations and re-admissions, excluding planned removal of implant(s) only, [4] Interquartile range.

Appendix 2. Quality of Life assessment based on occurrence of complications.

	All patients (n=134)	No complication (n=78)	Complication (n=56)	p-value
Mobility				**0.026**
1 – No problems	49 (37%)	29 (37%)	20 (36%)	
2 – Mild problems	50 (37%)	36 (46%)	14 (25%)	
3 – Moderate problems	22 (16%)	8 (10%)	14 (25%)	
4 – Severe problems	10 (8%)	4 (5%)	6 (11%)	
5 – Extreme problems	3 (2%)	1 (1%)	2 (4%)	
Self-care (n=133)				0.55
1 – No problems	98 (74%)	61 (78%)	37 (67%)	
2 – Mild problems	23 (17%)	12 (15%)	11 (20%)	
3 – Moderate problems	7 (5%)	3 (4%)	4 (7%)	
4 – Severe problems	4 (3%)	2 (3%)	2 (4%)	
5 – Extreme problems	1 (1%)	0 (0%)	1 (2%)	
Daily activities (n=133)				0.089
1 – No problems	43 (32%)	28 (36%)	15 (27%)	
2 – Mild problems	57 (43%)	34 (44%)	23 (42%)	
3 – Moderate problems	22 (17%)	13 (17%)	9 (16%)	
4 – Severe problems	8 (6%)	1 (1%)	7 (13%)	
5 – Extreme problems	3 (2%)	2 (3%)	1 (2%)	
Pain and discomfort (n=133)				0.58
1 – No pain	34 (26%)	21 (27%)	13 (23%)	
2 – Mild pain	65 (49%)	40 (52%)	25 (45%)	
3 – Moderate pain	26 (20%)	13 (17%)	13 (23%)	
4 – Severe pain	6 (5%)	2 (3%)	4 (7%)	
5 – Extreme pain	2 (2%)	1 (1%)	1 (2%)	
Anxiety and depression (n=133)				0.98
1 – No symptoms	88 (66%)	52 (67%)	36 (66%)	
2 – Mild symptoms	37 (28%)	21 (27%)	16 (29%)	
3 – Moderate symptoms	5 (4%)	3 (4%)	2 (4%)	
4 – Severe symptoms	2 (2%)	1 (1%)	1 (2%)	
5 – Extreme symptoms	1 (1%)	1 (1%)	0 (0%)	
Average index score (n=131)	1.6 (1.2-2.2)	1.6 (1.2-2.0)	1.6 (1.4-2.4)	0.22
General health (n=133)	75.0 (61.0-85.0)	75.0 (60.8-85.0)	72.0 (61.0-80.0)	0.30
Dichotomised variables: n (%)				
Continuous variables: median (IQR [1])				

[1] Interquartile range.