INFECTION

Long-term patient-related quality of life after fracture-related infections of the long bones

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Aims
We aimed to evaluate the long-term impact of fracture-related infection (FRI) on patients’ physical health and psychological wellbeing. For this purpose, quality of life after successful surgical treatment of FRIs of long bones was assessed.

Methods
A total of 37 patients treated between November 2009 and March 2019, with achieved eradication of infection and stable bone consolidation after long bone FRI, were included. Quality of life was evaluated with the EuroQol five-dimension questionnaire (EQ-5D) and German Short-Form 36 (SF-36) outcome instruments as well as with an International Classification of Diseases of the World Health Organization (ICD)-10 based symptom rating (ISR) and compared to normative data.

Results
With a mean follow-up of 4.19 years (SD 2.7) after the last surgery, the mean SF-36 score was 40.1 (SD 14.6) regarding the physical health component and 48.7 (SD 5.1) regarding the mental health component, compared to German normative values of 48.4 (SD 9.2) ($p < 0.001$) and 50.9 (SD 8.8) ($p = 0.143$). The mean EQ-5D index reached 0.76 (SD 0.27) with a mean EQ-5D visual analogue scale (VAS) rating of 65.7 (SD 22.7) compared to reference scores of 0.88 ($p < 0.001$) and 72.9 ($p < 0.001$). Mean scores of the ISR did not reveal significant psychological symptom burden, while an individual analysis showed moderate to severe impairments in 21.6% ($n = 8$) of the patients.

Conclusion
Even a mean 4.2 years (SD 2.7) after surgically successful treatment of FRI of long bones, patients report significantly lower quality of life in comparison to normative data. Future clinical studies on FRIs should focus on patient-related outcome measures enabling best possible shared treatment decision-making. Prevention methods and interdisciplinary approaches should be implemented to improve the overall quality of life of FRI patients.

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Keywords: Fracture-related infection, Quality of life, Psychological outcomes

Article focus
- Bone infections after fracture are a devastating complication in trauma surgery.
- Studies assessing patient-reported outcome measures in patients suffering from fracture-related infections are rare, and data of the impact of the challenging treatment in terms of the long-term quality of life after final infection eradication and stable bone consolidation is scarce.

This study investigated whether FRI patients return to a quality of life state comparable to normative data after successful surgical treatment with achieved eradication of infection and stable bone consolidation, and whether reduced psychological wellbeing is a long-term impact of FRI.
Key messages

- Even after a mean of 4.2 years (SD 2.7) after successful treatment of FRI of long bones, patients report significantly reduced quality of life, especially in the physical health component, compared to normative data.
- Moderate to severe psychological symptom burden was found in 21.6% (n = 8) of the patients.
- Infection prevention strategies and interdisciplinary approaches are required.

Strength and limitations

- Outstanding characteristics of this study are the long-term follow-up (mean 4.2 years (SD 2.7)), and the explicit investigation of the psychological impact using an International Classification of Diseases of the World Health Organization (ICD)-10 based symptom rating.
- Limitations are the retrospective design and hence no existing baseline quality of life scores; additionally, the cohort does not allow subgroup analysis for fracture localization and a comparison of treatment strategies.

Introduction

Bone infection is a devastating complication in trauma surgery, putting a high burden on the patients, their families, and healthcare systems. In general, the incidence of long bone fractures is projected to increase, especially in the elderly.1,2 The risk of developing a post-traumatic infection is multifactorial, with reported rates of 1% to 2% for closed fractures ranging up to 30% for Gustilo-Anderson type III open tibia fractures.3 Depending on injury severity, success rates vary between 70% and 90% with a recurrence of the disease in 6% to 9% of the patients.4,5 Several limitations such as immobility up to amputations of the affected limb, prolonged length of stay in hospital, multiple surgeries, side effects of antibiotic medication, and further socioeconomic issues such as job loss are often unavoidable despite a variety of treatment concepts.6,8 Healthcare costs are estimated to be approximately 6.5-times higher than in noninfected cases, with median costs of $108,782 (interquartile range (IQR) $61,841 to $150,972) per patient, mainly driven by the prolonged length of hospital stay.9,10 In the past, research has been hindered by the lack of a consensus definition of post-traumatic bone infection, which has only recently been established by an international expert group with clarification of the term “fracture-related infection” (FRI) for this entity.11 However, the management of FRI remains challenging and requires interdisciplinary approaches as well as multifaceted guidelines. The surgical goal is to eradicate the infection and to restore bone integrity and bone stability, which is achieved by adequate debridement of necrotic bone followed by bone regeneration procedures, which often need two- or even multiple-stage surgery.3,4 Success in the treatment of FRIs is mainly determined from a surgical perspective and there are very few data in the literature so far on patient-reported outcomes after FRI, particularly on the psychological burden of patients. Additionally, sufficient data on the impact of the often challenging treatment and outcome after final infection eradication and bone union are missing. Therefore, the purpose of the current study was to evaluate the long-term physical health state and psychological wellbeing of patients after successful somatic treatment of long bone FRIs.

Methods

Patients and data acquisition. FRIs treated in our department between November 2009 and March 2019 were retrospectively studied. A total of 92 FRI cases of the long bones (humerus, radius, ulna, femur, tibia, or fibula) without additional injuries were identified based on the International Classification of Diseases of the World Health Organization (ICD)-10 code “T84.6, infection and inflammatory reaction due to internal fixation device”.12 Clinical data were retrieved, and FRI was verified in all cases applying the criteria of a recent consensus definition.13 The questionnaires were sent by post and were returned by 43 patients, yielding a response rate of 46.7%. Individuals with multiple fractures (n = 4) and surveys with incomplete data (n = 2) were excluded. Hence, the final cohort included 37 long bone FRI cases with a minimum follow-up of one year. All patients were surgically treated and achieved infection eradication and bone consolidation. There were no missing values for any of the variables. Informed consent was obtained from all individual participants included. The study was approved by the institutional ethics committee of the University Clinic
Mean physical health component score (PCS) and mean mental health component score (MCS) assessed with the German Short-Form 36 (SF-36). The results of the fracture-related infection (FRI) cohort are shown in dark grey. For comparison, the values of the normative data are illustrated in light grey. *Significant difference.

Subdimension scores for patient-related quality of life assessed with the German Short-Form 36 (SF-36). The results of the fracture-related infection (FRI) cohort are shown in dark grey. For a comparison, the values of the normative data are illustrated in light grey. *Significant difference.

Quality of life instruments. Patient-related outcomes and quality of life were assessed using the German Short-Form 36 (SF-36) and EuroQol five-dimension questionnaire (EQ-5D) scores as well as an ICD-10-based symptom rating (ISR).\textsuperscript{14,15} The latter is frequently used in psychosomatic anamnesis evaluating the severity of psychological disorders. It consists of 29 items covering various mental syndromes with subscales for depression, anxiety, obsessive/compulsive disorders, somatoform disorders, and eating disorders.\textsuperscript{16} The EQ-5D is a well-established generic quality of life instrument comprising five questions concerning the functional domains mobility, self-care, everyday life activities, pain/discomfort, and anxiety/depression.\textsuperscript{17} The items were converted into a single EQ index value using German norm data weights (range -0.21 (worst) to 1.00 (best)).\textsuperscript{18} Additionally, the EQ-5D was evaluated using the visual analogue scale (VAS) method.\textsuperscript{19} The widely used SF-36 health survey captures the general health status...
Fig. 3
Percentage of individuals showing severe, mild, or no limitations in the EuroQol five-dimension subdimensions.

Fig. 4
Mean values of the International Classification of Diseases of the World Health Organization-10 based symptom rating scores.

with 36 questions in eight functional domains: physical function, physical role, bodily pain, general health, vitality, social function, emotional role, and mental health. Summary scores for the physical and mental component were calculated using normative data from a German national health interview and examination survey conducted in 1998 with 7,124 participants. Statistical analysis. Data were analyzed using SPSS statistics version 24.0 (IBM, USA). Descriptive statistics were calculated for all variables. Continuous variables were expressed as the mean and standard deviation (SD). Correlations between outcome scores and demographic data were calculated using Pearson’s correlation coefficient. For comparisons between continuous variables, independent-samples t-tests were used after determining the distribution was appropriate for parametric testing by Levene’s test. Significance was set at p < 0.001.

Results
In total, 37 patients (12 women, 25 men; mean age 59.5 years (SD 14.3)) without additional injuries were included in the analysis (Table I). FRIs of the tibia comprised the largest proportion of the cohort (n = 18, 48.7%) followed by femoral FRIs (n = 10, 27.0%). The mean revision rate was 3.8 (SD 2.5; 1 to 12). Overall, 12 patients had open fractures (32.4%): six located at the tibia, five at the femur, and one at the fibula. FRI cases after open fractures required more revision surgeries with a mean of 5.7 (SD 3.0) compared to the revision rate for FRI after closed fractures of 2.9 (SD 1.6) (p = 0.002, independent-samples t-test). The mean BMI reached a value of 27 kg/m² (SD 4.5), seven patients (18.9%) were smokers, and 20 patients (54.1%) reported to be former smokers. Three patients had comorbid hypertension. The mean follow-up time was 4.2 years (SD 2.7) with a minimum of one year (1.1 to 9.7) after the last surgery.

The mean physical health component score (PCS) of the SF-36 was 40.1 (SD 14.6), and the mean mental health component score (MCS) of the SF-36 was 48.7 (SD 5.1). In comparison with normative data from Germany FRI, patients score lower in the physical health component (PCS Norm = 48.4 (SD 9.2), p < 0.001) as well as in the mental health component of the SF-36 (MCS Norm = 50.9 (SD 8.8), both independent-samples t-test: p = 0.143), which depicts 82.9% and 95.7% of the reference summary scores, respectively (Figure 1). The subdomain analysis resulted in mean values of 59.5 (SD 20.8) for physical function, 49.3 (SD 16.7) for physical role, 58.0 (SD 21.9) for bodily pain, 59.8 (SD 22.5) for general health, 59.2 (SD 19.7) for vitality, 76.0 (SD 22.1) for social functioning, 71.3 (SD 19.1) for emotional role, and 71.1 (SD 20.0) for mental health (Figure 2). Hence, FRI patients reached 69.7% for physical function (85.4 (SD 20.7), p < 0.001), 59.9% for physical role (82.3 (SD 32.7), p < 0.001), 86.1% for bodily pain (67.4 (SD 25.9), p = 0.034), 90.0% for general health (66.4 (SD 18.2), p = 0.034), 98.6% for vitality (60.0 (SD 17.8), p = 0.782), 88.0% for social functioning (86.4 (SD 19.9), p = 0.003), 80.0% for emotional role (89.1 (SD 26.7), p < 0.001), and 98.1% for mental health (72.5 (SD 16.7), all independent-samples t-test: p = 0.625) of the normative values.

The mean EQ-5D VAS rating reached 65.7 (SD 22.7), which depicts 90.1% of the score of 72.9 (SD 1.0) obtained from an age-matched reference population (p < 0.001, independent-samples t-test). The mean EQ-5D index value was 0.76 (SD 0.27), reaching 86.3% of the age-matched normative value 0.88 (p < 0.001) calculated based on the European value set and 82.0% of the age-matched normative value 0.92 (p < 0.001, both independent-samples t-test), calculated based on a country-specific time trade-off (TTO) value set. In the subdimensions of the EQ-5D, patients showed limited results especially in mobility, everyday life activities, and pain/discomfort (Figure 3). In total, 40.54% (n = 15) of the patients reported problems with mobility (compared to 15.9% of the German reference), 18.92% (n = 7) with self-care (compared to a norm value of 2.7%), 51.35% (n = 19) with usual activities (vs 9.9%), 75.68% (n = 28) with pain/discomfort (compared to 27.6%), and 27.03% (n = 10) with anxiety/depression (4.3% of the normative population).

The mean total score of the ISR was 0.55 (SD 0.16). The mean ISR subdimension scores reached 0.78 (SD 0.23) for
depression, 0.49 (SD 0.10) for anxiety, 0.37 (SD 0.07) for obsessive/compulsive disorders, 0.49 (SD 0.07) for somatoform disorders, and 0.58 (SD 0.18) for eating disorders, respectively (Figure 4). On average, none of the values of the syndrome scales meets criteria for caseness, i.e. clinically relevant severity of psychological disorders. However, examining the data in more detail, individuals reveal mild to severe symptom burden in the total score of the ISR (n = 11, 29.7%; moderate to severe symptom burden: 21.6%), regarding depression (n = 12, 32.4%), anxiety (n = 7, 18.9%), obsessive/compulsive disorders (n = 8, 21.6%), somatization (n = 10, 27.0%), and eating disorders (n = 17, 46.0%) (Figure 5).

None of the reported scores of the ISR, SF-36, and EQ-5D was statistically significantly correlated with revision rate, age, or sex.

Discussion

In this study, the quality of life of 37 patients with successfully treated FRIs was assessed with the EQ-5D and SF-36 questionnaires. An outstanding characteristic is the long-term follow-up (mean 4.2 years) and the explicit investigation of the psychological impact using the ICD-10-based symptom rating in FRI patients. After a mean follow-up time of 4.2 years, patients who suffered from a FRI scored significantly lower on quality of life than a German reference population.

In general, studies assessing patient-related outcome measures after FRI treatment are scarce. In 1996, Bowen et al evaluated the quality of life of nine patients with infected tibia nonunion at a mean follow-up time of three years. In accordance with our findings, results were significantly lower compared to an age-matched reference norm. Brinker et al evaluated the quality of life of 237 patients with tibial shaft fracture nonunions and 187 patients with femoral nonunion. Results emphasize the substantial detrimental effect on physical and mental health. An infection was present in 18% of the tibial shaft fracture nonunion cohort and in 5.3% of the femoral nonunion patients; however, a subgroup analysis was not calculated. In addition, Bezstarosti et al included 93 studies on FRI treatment and outcome in a systematic review, out of which only one used the EQ-5D questionnaire, one the SF-36, and another one the SF-12 health survey.

The assessed mean EQ-5D VAS score of 65.7 was even lower than in patients with myocardial infarction (70.3) evaluated at admission. The mean EQ-5D index value of 0.76 reveals that the burden of FRI is comparable to the impact of multiple trauma, for which a score of 0.75 has been calculated after 4.2 years, as well as to the quality of life after one year of arthroplasty, for which an analysis of a large cohort with more than 350 patients resulted in a mean score of 0.8 regarding the hip and 0.73 for the knee. Healed FRI patients scored even lower in the SF-36 summary components than patients two years after a primary total hip arthroplasty (PCS: 45.2, MCS: 53.2). These comparisons highlight the persistent impact a FRI has on the quality of life.

While mental health, assessed with SF-36 and EQ-5D, did not show considerable lower values, reaching 95.7% and 98.1% of a normative reference population, the use of the ISR, which is highly correlated with the Beck-Depression-Inventory-II (BDI-II), revealed that individuals...
are still affected psychologically, with 21.6% of the patients showing moderate to severe impairments according to the total ISR score.11 Mental health sequela is common following injury, which can be reflected in diverse depressive symptoms including appetite changes.12 As it has been shown that psychological morbidity predicts functional outcomes after injury, such as return to work and pain, and has been associated with postoperative infections after arthroplasty as well as substantially higher healthcare costs, it might be enriching to consider the use of additional questionnaires when evaluating the patients’ quality of life.33–36 This has also been emphasized by a recent review on quality of life in patients with long bone fracture nonunions, which identified only one study using specific scales capturing anxiety, depression, and symptoms of post-traumatic stress disorder syndrome.23 Hence, shedding light on the psychological wellbeing of orthopaedic clinical populations should be deemed as a future direction of research, since an underestimation of the burden of injury may affect resource allocation and necessary prevention priorities, and may hinder the implementation of counselling as part of the standard care in trauma surgery.

A limitation of the study is that the small cohort does not allow subgroup analysis for the distinct fracture localization and a comparison of treatment strategies. Additionally, a key limitation is that no baseline quality of life scores for the included patients exist. Furthermore, it remains questionable to what extent the lowered quality of life is attributable to the FRI. To address this problem, patients with multiple injuries were excluded from the study. Nevertheless, additional factors cannot completely be ruled out and the SF-36 subdomain social functioning in particular may have been influenced by other external factors, such as the current COVID-19 pandemic.

To conclude, our results emphasize the serious consequences following FRI as well as the potential of restoring patients’ quality of life. Hence, future clinical studies on FRIs should focus on patient-related outcome measures and newly emerging treatment strategies, and prevention methods as well as interdisciplinaty approaches should be implemented to improve the overall quality of life of FRI patients.37–39

References

1. Amin S, Achenbach SJ, Atkinson EJ, Khosla S, Melton LJ. Trends in fracture incidence: a population-based study over 20 years. J Bone Miner Res. 2014;29(3):581–589.
2. Court-Brown CM, McQueen MM. Global Forum: fractures in the elderly. J Bone Joint Surg Am. 2016;98-A(8):e36.
3. Trampuz A, Zimmerli W. Diagnosis and treatment of infections associated with fracture-fixation devices. Injury. 2008;39 Suppl 2:S59–S66.
4. Metsemakers WJ, Kuehl R, Mairioty TF, et al. Infection after fracture fixation: current surgical and microbiological concepts. Injury. 2018;49(3):511–522.
5. Bose D, Kugan R, Stubbs D, McNally M. Management of infected nonunion of the long bones by a multidisciplinary team. Bone Joint J. 2015;97-B(8):814–817.
6. Bezstarosti H, Van Lieshout EMM, Voskamp LW, et al. Insights into treatment and outcome of fracture-related infection: a systematic literature review. Arch Orthop Trauma Surg. 2019;139(1):61–72.
7. Alt V, Giannoudis PV. Musculoskeletal infections - A global burden and a new subsection in Injury. Injury. 2019;50(12):2152–2153.
8. Depypere M, Morgenstern M, Kuehl R, et al. Pathogenesis and management of fracture-related infection. Clin Microbiol Infect. 2020;26(5):572–578.
9. Thakore RV, Greenberg SE, Shi H, et al. Surgical site infection in orthopedic trauma: a case-control study evaluating risk factors and cost. J Clin Orthop Trauma. 2015;6(6):220–226.
10. Metsemakers W-J, Smets B, Nijs S, Hoekstra H. Infection after fracture fixation of the tibia: analysis of healthcare utilization and related costs. Injury. 2017;48(6):1204–1210.
11. Metsemakers WJ, Morgenstern M, McNally MA, et al. Fracture-related infection: a consensus on definition from an international expert group. Injury. 2018;49(3):505–510.
12. No authors listed. International Statistical Classification of diseases and related health problems. www.who.int/standards/classifications/classification-of-diseases (date last accessed 26 April 2021).
13. World Medical Association. World medical association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA. 2013;310(20):2191–2194.
14. Bullinger M, Kirchberger I, Ware J. The German SF-38 health survey translation and psychometric testing of a generic instrument for the assessment of health-related quality of life. Journal of Public Health. 1999;3:21–36.
15. Brooks R. EuroQol: the current state of play. Health Policy. 1996;37(1):53–72.
16. Tritt K, Von Heymann F, Zaudig M, Zacharias I, Söllner W, Loew T. Development of the “ICD-10-Symptom-Rating” (ISR) questionnaire. Z Psychosom Med Psychother. 2018;64(4):409–418.
17. Devlin NJ, Brooks R. EQ-5D and the EuroQol group: past, present and future. App Health Econ Health Policy. 2017;15(2):127–137.
18. Claes C, Greiner W, Uber A, Graf von der Schulenburg JM. An interview-based comparison of the TTO and VAS values given to EuroQol states of health by the general German population. In: Greiner W, J-M. Gvd, Piercy J. EuroQol plenary meeting, 1-2 October 1998. Discussion papers. Centre for Health Economics and Health Systems Research, University of Hannover, Germany: Uni-Verlag Witte, 1999:13.
19. EuroQol Group. EuroQol—A new facility for the measurement of health-related quality of life. Health Policy. 1990;16(3):189–208.
20. Ellert U, Kurth B-M. [Methodological views on the SF-36 summary scores based on the adult German population]. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz. 2004;47(11):1027–1032. (Article in German)
21. Szende A, Janssen B, Cabases J. Self-reported population health: an international perspective based on EQ-5D. Dordrecht: Springer Netherlands, 2014:20–22.
22. Bowen CV, Botsford DJ, Hudak PL, Evans PJ. Microsurgical treatment of septic nonunion of the tibia: quality of life results. Clin Orthop Relat Res. 1996;322:52–61.
23. Brinker MR, Hanus BD, Sen M, O’Connor DP. The devastating effects of tibial nonunion on health-related quality of life. J Bone Joint Surg Am. 2013;95-A(24):2170–2176.
24. Brinker MR, Trivedi A, O’Connor DP. Debilitating effects of femoral nonunion on health-related quality of life. J Orthop Trauma. 2017;31(2):e37–42.
25. Johnson L, Igoe E, Kle forfeuris G, Papachristos IV, Papakostidis C, Giannoudis PV. Physical health and psychological outcomes in adult patients with long-bone fracture non-unions: evidence today. J Clin Med. 2019;8(111):e1998.1998.
26. Złowodzki M, Obremskey WT, Thomson JB, Kregor PJ. Functional outcome after treatment of lower-extremity nonunions. J Trauma. 2005;58(2):312–317.
27. Schweikert B, Hahmann H, Leidl R. Validation of the EuroQol questionnaire in cardiac rehabilitation. Heart. 2006;92(1):62–67.
28. Angerpointner K, Ernstberger A, Bosch K, Zeman F, Koller M, Kerschbaum M. Quality of life after multiple trauma: results from a patient cohort treated in a certified trauma network. Eur J Trauma Emerg Surg. 2021;47(1):121–127.
29. Jansson Karl-Åke, Granath F. Health-Related quality of life (EQ-5D) before and after orthopedic surgery. J Bone Joint Surg Am. 2011;82(1):82–89.
30. Hozack WJ, Rothman RH, Albert TJ, Balderston RA, Eng K. Relationship of total hip arthroplasty outcomes to other orthopaedic procedures. Clin Orthop Relat Res. 1997;344:95–101.
31. Brandt WA, Loew T, von Heymann F, et al. How does the ICD-10 symptom rating (ISR) with four items assess depression compared to the BDI-II? A validation study. J Affect Disord. 2015;173:143–.
32. Kellezi B, Coupland C, Morris R, et al. The impact of psychological factors on recovery from injury: a multicentre cohort study. Soc Psychiatry Psychiatr Epidemiol. 2017;52(7):955–966.
33. Kendrick D, Vinogradova Y, Coupland C, et al. Recovery from injury: the UK burden of injury multicentre longitudinal study. In: Prev; 2013;43(7):370–381.

BONE & JOINT RESEARCH
34. La A, Nadarajah V, Jauregui JJ, et al. Clinical characteristics associated with depression or anxiety among patients presenting for knee surgery. J Clin Orthop Trauma. 2020;11(Suppl 1):S164–S170.

35. Browne JA, Sandberg BF, D’Apuzzo MR, Novicoff WM. Depression is associated with early postoperative outcomes following total joint arthroplasty: a nationwide database study. J Arthroplasty. 2014;29(3):481–483.

36. Rasouli MR, Menendez ME, Sayadipour A, Purtill JJ, Parvizi J. Direct cost and complications associated with total joint arthroplasty in patients with preoperative anxiety and depression. J Arthroplasty. 2018;31(2):533–536.

37. Rupp M, Popp D, Alt V. Prevention of infection in open fractures: Where are the pendulums now? Injury. 2020;51 Suppl 2:S57–S63.

38. Metsenmakers W-J, Onsea J, Neutjens E, et al. Prevention of fracture-related infection: a multidisciplinary care package. Int Orthop. 2017;41(12):2457–2469.

39. Foster AL, Moriarty TF, Trampuz A, et al. Fracture-related infection: current methods for prevention and treatment. Expert Rev Anti Infect Ther. 2020;18(4):307–321.

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The study was approved by the institutional ethics committee of the University Clinic of Regensburg according to the Helsinki Convention (file number 20-1681-104).

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