The epidemiology and direct healthcare costs of aseptic nonunions in Germany – a descriptive report

N. Walter, K. Hierl, C. Brochhausen, V. Alt, M. Rupp

From University Hospital Regensburg, Regensburg, Germany

Aims
This observational cross-sectional study aimed to answer the following questions: 1) how has nonunion incidence developed from 2009 to 2019 in a nationwide cohort; 2) what is the age and sex distribution of nonunions for distinct anatomical nonunion localizations; and 3) how high were the costs for surgical nonunion treatment in a level 1 trauma centre in Germany?

Methods
Data consisting of annual International Classification of Diseases (ICD)-10 diagnosis codes from German medical institutions from 2009 to 2019, provided by the Federal Statistical Office of Germany (Destatis), were analyzed. Nonunion incidence was calculated for anatomical localization, sex, and age groups. Incidence rate ratios (IRRs) were determined and compared with a two-sample z-test. Diagnosis-related group (DRG)-reimbursement and length of hospital stay were retrospectively retrieved for each anatomical localization, considering 210 patients.

Results
In 2019, a total of 11,840 nonunion cases (17.4/100,000 inhabitants) were treated. In comparison to 2018, the incidence of nonunion increased by 3% (IRR 1.03, 95% confidence interval (CI) 0.53 to 1.99, p = 0.935). The incidence was higher for male cases (IRR female/male: 0.79, 95% CI 0.76 to 0.82, p = 0.484). Most nonunions occurred at the pelvic and hip region (3.6/100,000 inhabitants, 95% CI 3.5 to 3.8), followed by the ankle and foot as well as the hand (2.9/100,000 inhabitants each). Mean estimated DRG reimbursement for in-hospital treatment of nonunions was highest for nonunions at the pelvic and hip region (€8,319 (SD 2,410), p < 0.001).

Conclusion
Despite attempts to improve fracture treatment in recent years, nonunions remain a problem for orthopaedic and trauma surgery, with a stable incidence throughout the last decade.

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Keywords: Epidemiology, Nonunion, Direct healthcare costs

Article focus
- The epidemiology of nonunion after fracture is unknown, which makes it difficult to estimate healthcare costs and foresee future demands.
- This study investigated how nonunion incidence has developed over the last decade in a nationwide cohort depending on age, sex, and anatomical localization.
- Direct costs for surgical nonunion treatment were analyzed using data from a level 1 trauma centre in Germany.

Key messages
- Nonunion cases remained relatively stable from 2009 to 2019, with an incidence of 17.4/100,000 inhabitants in 2019.
- Most nonunions occurred at the pelvic and hip region, the hand, and the ankle and foot.
- Direct costs were estimated to be relatively low, whereby nonunions at the pelvic and hip region and the lower leg were the most costly.
Strengths and limitations

- An outstanding characteristic is that presented findings are based on nationwide registry data.
- The study is limited by the fact that individual patient data such as comorbidities could not be derived from the International Classification of Diseases-10 codes.

Introduction

Fracture healing can be a tedious process. Complications such as nonunion are still sometimes unavoidable. For the definition of a nonunion, Food and Drug Administration (FDA)1 and National Institute for Health and Care Excellence (NICE)2 guidelines determine a minimum of nine months after injury without visible bone healing progress for three months. Further definitions, such as fractures that do not heal without surgical intervention, are also common in the literature.3,4 The management of nonunion depicts a clinical challenge, as diverse treatment strategies are available to restore bone consolidation.5 Besides having a detrimental effect on patients’ quality of life,6,7 healthcare costs are statistically significantly higher than in uncomplicated fracture cases, mainly driven by indirect costs such as productivity loss.5,8 In addition, depending on different healthcare systems and treatment concepts, direct costs such as surgical and medical treatment for nonunion differ substantially between different countries.8,9 Hence, cost estimations vary widely in the literature, and epidemiological data are required as a keystone to estimate direct and indirect healthcare costs.

Proportions of fractures that result in nonunions between 5% and 10% have been reported.10,11 However, as recently highlighted by the Danish Orthopedic Trauma Society, at least 25 studies refer to a textbook published in 1999, which seems not to be a reliable source for nonunion proportions.4,12 Further, only a few studies used registry data to estimate nonunion incidence. For instance, 12,373 nonunions were included in an inception cohort study of a payer database from 2011 to 2012 in the USA.13 In Scotland, the nonunion incidence was calculated as 18.9 per 100,000 population per annum, based on hospital admission data between 2005 and 2010.14 However, the epidemiology of nonunion in European countries is largely unknown.

We have therefore aimed to answer the following questions using an observational cross-sectional study design: 1) how has nonunion incidence developed from 2009 to 2019 in a nationwide cohort; 2) what is the age and sex distribution of nonunions for distinct anatomical nonunion localizations; and 3) how high were the costs for surgical nonunion treatment in a level 1 trauma centre in Germany?

Methods

Data consisting of annual International Classification of Diseases (ICD)-10 diagnosis codes from German medical institutions, including private ones from 2009 to 2019, were provided by the Federal Statistical Office of Germany (Destatis). These included all inpatient diagnoses, which were reported from medical institutions in all 16 German federal states. The coding is usually performed by physicians. The ICD-10 code “M84.1, nonunion of fracture”15 was used to identify patients aged 20 years or older to ensure that all patients reached skeletal maturity diagnosed with nonunion (Table I). A detailed breakdown of these data by age group in ten-year increments, sex, and anatomical localization (M84.11-M84.17) was performed. First, the incidences for each year were calculated based on Germany’s historical population aged 20 years or older provided by Destatis.16 Here, the number of inhabitants in each of the 16 German federal states was considered by year of birth for each year of the period 2009 to 2019. The deadline of each year was 31 December. Second, age- and sex-standardized incidence rates were estimated for each anatomical localization. Incidence rate ratios (IRRs) with the corresponding 95% confidence intervals (CIs) and percentage changes were calculated by dividing the incidence in 2019 by the incidence of the preceding year for all nonunions. For each anatomical localization, IRRs were determined relative to the year 2009.

To estimate direct total healthcare cost for surgical treatment, diagnosis-related groups (DRGs) reimbursement from nonunion cases treated in our department between 2009 and 2019 were retrospectively retrieved. For the ICD-10 code “M84.13”, only 30 patients were treated. Hence, this sample size was chosen for each anatomical localization to ensure comparability, and for each ICD-10 subcode of nonunion (M84.11-M84.17) 30 patients were considered. In total, 210 cases were reviewed. Patient records were selected in backward chronological order. No patient was excluded. All patients underwent only one inpatient surgical treatment. Further, all cases were solely diagnosed with aseptic nonunion; septic cases, which would have been coded as “T84.6, infection and inflammatory reaction due to internal fixation device” or “M86.-, osteomyelitis” were not considered. Correct coding was ensured by reviewing patients’ medical charts, surgery protocols, and radiographs. For each subgroup, the amount of the DRG-based payment was averaged (mean, standard deviation (SD)). Further, the

### Table I. Descriptions of the used International Classification of Diseases (ICD)-10 codes.

| ICD-10 codes | nonunion Description |
|--------------|----------------------|
| M84.1        | Nonunion of fracture |
| M84.11       | Shoulder region (clavicular, scapula, acromioclavicular, glenohumeral, sternoclavicular joint) |
| M84.12       | Upper arm (humerus) |
| M84.13       | Forearm (radius, ulna, scaphoid) |
| M84.14       | Hand (finger, carpus, metacarpal) |
| M84.15       | Pelvic region and thigh (pelvis, femur) |
| M84.16       | Lower leg (fibula, tibia) |
| M84.17       | Ankle and foot (tarsal, metatarsal, toes, ankle) |

ICD, International Classification of Diseases.
length of hospital stay was determined and averaged for each cohort (mean, SD). The study was approved by the institutional ethics committee of the University Hospital Regensburg according to the Declaration of Helsinki (2013) (file number 20-1681-104).

**Statistical analysis.** Data were analyzed using SPSS statistics version 24.0 (IBM, USA). Descriptive statistics were calculated for all variables. After determining that the distribution was appropriate for parametric testing by Shapiro-Wilk test, homogeneity of variances was asserted using Levene’s test, which showed that equal variances could not be assumed (p < 0.05). Therefore, the Welch test with a Games-Howell post hoc analysis was used to compare DRG reimbursement and length of hospital stay for each M84.1 subcode. Incidence rates were compared using the two-sample z-test. Statistical significance was set at p < 0.01 to reduce the type I error rate.

**Results**

In 2009, a total of 11,653 nonunion cases were listed in Germany, constituting an annual incidence of 17.5 cases per 100,000 inhabitants (95% CI 17.2 to 17.9). In the following years the incidence rose, resulting in a maximum of 19.4 cases per 100,000 inhabitants (95% CI 19.0 to 19.7) in 2011. From this point on, numbers went down to an incidence of 17.0/100,000 inhabitants (95% CI 16.7 to 17.3) in 2018. In 2019, a total number of 11,840 nonunion cases were listed in Germany, constituting an annual incidence of 17.4 cases per 100,000 inhabitants. Compared to 2018, numbers had increased by 3% (IRR 1.03, 95% CI 0.53 to 1.99; p = 0.928, two-sample z-test).

Regarding the age and sex distribution in 2019, highest standardized nonunion incidences at the shoulder were registered for patients aged 50 to 59 years (2.5/100,000 men and 1.5/100,000 women) (Table I). At the upper arm, incidence increased with age for female cases up to 3.6/100,000 women aged older than 90 years, whereas for male cases incidence peaked in the age group of 60 to 69 years (1.8/100,000 inhabitants). Nonunions at the forearm occurred most often in female patients aged 60 to 69 years (1.9/100,000 inhabitants), followed by male patients aged 50 to 59 years (1.8/100,000 inhabitants) (Figure 2c). Nonunions at the hand mainly affected male patients (IRR female/male: 0.20, 95% CI 0.18 to 0.22; p = 0.928, two-sample z-test) with a peak in the age group 20 to 29 years (15.9/100,000 inhabitants) (Figure 2d). The incidence for nonunions at the pelvic and hip region was higher for female patients (IRR female/male: 1.39, 95% CI 1.28 to 1.50; p = 0.334, two-sample z-test) and patients aged older than 70 years (IRR 0.35, 95% CI 0.33 to 0.38; p = 0.003, two-sample z-test). Incidence increased with age for both sexes up to a maximum of 15.3/100,000 women and 13.1/100,000 men aged older than 90 years (Figure 2e). Nonunions at the lower leg reached a maximum for patients aged 50 to 59 years (3.3/100,000 women, 5.4/100,000 men) (Figure 2f). Cases concerning the ankle and foot predominantly comprised female patients aged 50 to 59 years (5.0/100,000 women) and 60 to 69 years (4.4/100,000 women), as well as male patients aged 60 to 69 years (3.4/100,000 men) (Figure 2g).

For overall nonunions in 2019 regardless of anatomical localization, the sex distribution revealed a higher incidence for male cases, although this was not statistically significant (IRR female/male: 0.79, 95% CI 0.76 to 0.82; p = 0.484, two-sample z-test). In 2019, the nonunion incidence was 19.6/100,000 inhabitants (95% CI 19.1 to 20.0) for men and 15.4/100,000 inhabitants (95% CI 15.0 to 15.9) for women. For female patients, the incidence steadily increased with age. For male patients, the incidence was highest in the age group 20 to 29 years.
(26.3/100,000 inhabitants), followed by the age group 50 to 59 years (21.6/100,000 inhabitants) (Figure 2h).

Nonunions at the pelvic and hip region were the most costly, and were associated with the longest stay in hospital (Table IV). The findings presented here are based on nationwide reports from one of the largest countries of the European Union. Additionally, direct healthcare costs for surgical treatment based on DRG reimbursement were estimated. The results demonstrate a fluctuation of nonunion cases in the range of -5% to +7% considering the IRR of the preceding years, respectively. Between 2018 and 2019, the incidence increased by 3%, resulting in an incidence of 17.4/100,000 inhabitants (95% CI 17.1 to 17.8). There was no statistically significant trend in the development of nonunion incidence observable and hence, the variations could be regarded as regularly as, for instance, those also shown for the epidemiology of fracture-related infections.20 Thus, the fluctuations might not be attributed to specific factors such as advances in diagnostics.21–23 In the same stance, the clinical importance of the heightened incidence is questionable.

The overall nonunion incidence is comparable with findings by Mills and Simpson14 analyzing nationwide registry data for the population of Scotland from 2005 to 2010. The authors reported a mean incidence of 18.9/100,000 population per annum, whereby numbers also varied in a range of 18.0 to 20.0 per 100,000 inhabitants between the considered calendar years.14 Further, in accordance with our findings, Mills and Simpson14

### Discussion

In this observational cross-sectional study, the development of nonunion incidence from 2009 to 2019 in Germany was determined, presenting nationwide data from one of the largest countries in Europe. Nonunion cases were analyzed depending on anatomical localization, sex, and age for Germany. Whereas studies relying on data from single hospitals may yield skewed results, the findings presented here are based on nationwide reports from one of the largest countries of the European Union. Additionally, direct healthcare costs for surgical treatment based on DRG reimbursement were estimated.
Table III. Nonunion rates in 2019 divided by anatomical localization.

| Anatomical localization | n   | Incidence per 100,000 inhabitants (95% CI) | Incidence in 2019 relative to 2009, % | IRR relative to 2009 (95% CI), p-value* | Female/ male, % (n) | IRR female/ male (95% CI), p-value* | Aged ≤ 70 years/> 70 years, % (n) | IRR aged ≤ 70 yrs/> 70 yrs (95% CI), p-value* |
|-------------------------|-----|----------------------------------------|-------------------------------------|----------------------------------------|---------------------|--------------------------------------|----------------------------------|--------------------------------------|
| All                     | 11,840 | 17.4 (17.1 to 17.8)                     | -1                                  | 0.99 (0.51 to 1.93), 0.986             | 45/55 (5,365/6,475) | 0.79 (0.76 to 0.82), 0.484          | 78/22 (9,208/2,632) | 0.15 (0.14 to 0.16), 0.178          |
| Shoulder                | 912   | 1.3 (1.3 to 1.4)                        | -16                                 | 0.84 (0.77 to 0.92), 0.539            | 40/60 (362/550)     | 0.63 (0.55 to 0.72), 0.711          | 88/12 (803/109) | 3.37 (2.76 to 4.12), 0.119          |
| Upper arm               | 905   | 1.3 (1.3 to 1.4)                        | -10                                 | 0.90 (0.82 to 0.98), 0.536            | 59/41 (531/374)     | 1.35 (1.18 to 1.54), 0.810          | 63/37 (573/332) | 0.68 (0.60 to 0.78), 0.509          |
| Forearm                 | 859   | 1.3 (1.2 to 1.4)                        | -18                                 | 0.82 (0.75 to 0.89), 0.367            | 48/52 (412/447)     | 0.88 (0.77 to 1.00), 0.540          | 81/19 (692/167) | 1.96 (1.65 to 2.32), 0.330          |
| Hand                    | 1,997 | 2.9 (2.8 to 3.0)                        | -10                                 | 0.90 (0.85 to 0.95), 0.553            | 18/82 (349/1,648)   | 0.20 (0.18 to 0.22), 0.928          | 98/2 (1,961/36) | 29.73 (21.38 to 41.34), 0.008       |
| Pelvis and hip          | 2,454 | 3.6 (3.5 to 3.8)                        | +9                                  | 1.09 (1.03 to 1.15), 0.456            | 59/41 (1,455/999)   | 1.39 (1.28 to 1.50), 0.334          | 51/49 (1,242/1,212) | 0.35 (0.33 to 0.38), 0.003          |
| Lower leg               | 1,927 | 2.8 (2.7 to 3.0)                        | -7                                  | 0.94 (0.88 to 1.00), 0.532            | 40/60(776/1,151)    | 0.64 (0.59 to 0.70), 0.698          | 86/14 (1,656/271) | 3.11 (2.73 to 3.53), 0.032          |
| Ankle and foot          | 1,985 | 2.9 (2.8 to 3.0)                        | +17                                 | 1.17 (1.10 to 1.25), 0.427            | 57/43 (1,127/858)   | 1.25 (1.14 to 1.37), 0.394          | 86/14 (1,714/271) | 3.62 (3.19 to 4.12), 0.019          |
| Other, not specified    | 801   | 1.3 (1.2 to 1.4)                        | +36                                 | 1.51 (1.35 to 1.69), 0.388            | 44/56 (352/449)     | 0.75 (0.65 to 0.86), 0.826          | 71/29 (569/232) | 0.74 (0.63 to 0.86), 0.596          |

Statistical significance set at p < 0.01.
*Two-sample z-test.
CI, confidence interval; IRR, Incidence rate ratio.

Fig. 2

Age-standardized nonunion incidence rates per 100,000 inhabitants in 2019 shown for: a) the shoulder region; b) the upper arm; c) the forearm; d) the hand; e) the pelvic and hip region; f) the lower leg; g) the ankle and foot; and h) all anatomical localizations. Female patients are illustrated in the red curve, male patients in the blue curve, while both male and female cases are shown in the dark green curve.
also observed higher incidence for men than for women (22.4/100,000 men vs 15.7/100,000 women per annum). Similarly to the results shown in Figure 2h, the distribution was bimodal for male cases and unimodal for female cases, whereby the highest peaks were observed for males in the age group 25 to 29 years and for females in the age group 75 to 79 years.14

Here, the peak in the age distribution for male sex aged 20 to 29 years was mainly driven by nonunions occurring in the hand, which might reflect higher fracture incidences of the scaphoid (1.1/100,000 men vs 3.5/100,000 women), as well as carpal and metacarpal bones in the male German population (17.5/100,000 men vs 7.5/100,000 women). Further, it was found that most nonunions occurred at the pelvic and hip region (3.6/100,000 inhabitants, 95% CI 3.5 to 3.8), affecting more women than men (IRR female/male: 1.39, 95% CI 1.28 to 1.50). Incidence heightened with age, which contributed to the steady increase of the overall incidence with age for female sex. This is in line with current data on the epidemiology of fractures in the adult population in Germany, reporting higher incidences in women regarding femoral neck fractures (157.3/100,000 women vs 81.3/100,000 men), pertoctrochanteric femur fractures (148.2/100,000 women vs 67.4/100,000 men), and pelvic ring fractures (94.4/100,000 women vs 23.5/100,000 men), whereby age-standardized incidences increased with longer lifetime for both sexes.24

Costs for surgical treatment. Highest healthcare costs were calculated for nonunion treatment at the pelvic and hip region (mean €8,319 (SD 2,410/patient) followed by the lower leg (mean €6,377 (SD 1,997)/patient). Importantly, these calculated costs should be interpreted with caution. In Germany, each federal state provides different base payment rates, and the presented numbers are only based on one federal state. Furthermore, the base payment rates differed over the last ten years with continuously rising values. Also, the analyzed patients underwent only one inpatient surgical treatment. However, in some cases the management of nonunion requires multiple inpatient treatments. Hence, the findings may be underestimated, and generalizability of the cost analysis is limited.

Cost estimations vary widely in the literature depending on the inclusion of direct or indirect cost, fracture site, as well as treatment procedures. In a review, Kanakis and Giannoudis calculated best-case scenario costs per patient as £15,566 (~ €18,000) for a humeral nonunion and £17,000 (~ €19,650) for a nonunion after femur fracture including indirect costs. Ekegren et al reported median inpatient cost of $14,957 AUD (~ €9,600) per patient, including all complication admissions within two years of index fracture. However, their cohort was mixed, consisting of patients with humeral, femoral, and tibial nonunion. In Germany, cost of therapy for humeral nonunion including surgical interventions was calculated as €6,432 per patient, which was higher than in our findings. Whereas studies on the economics of femoral nonunions are scarce, costs of tibial nonunions have been addressed more frequently. In the USA, total median healthcare costs for tibial shaft nonunions were estimated to be approximately 2.2 times higher with an amount of $25,556 (~ €20,900) compared to tibial shaft fractures, achieving union within one year. However, in contrast to our approach, inpatient, outpatient, and pharmaceutical costs were included in the analysis. In the UK, direct treatment costs of complex tibial nonunion within the Taylor spatial frame of £26,000/case (~€30,000) were revealed, whereas £23,604 (~ €27,000) per patient was calculated using the Ilizarov technique. Dahabreh et al conducted a cost analysis comparing the treatment of tibial nonunions by bone grafting or bone morphogenetic protein-7. Direct costs were higher for the latter with £7,292 (~ €8,400) versus £6,830 (~ €7,800). These results underpin the variance in costs regarding the treatment procedure. Since previously reported healthcare costs were higher in comparison to the estimated DRG reimbursement in our department, further studies differentiating treatment procedure are required. Further, to draw conclusions about the overall economic burden of nonunions, indirect costs such as productivity losses should be considered, as these have been handled as the key driver contributing to 67% to 79% and 82.8% to 93% of the overall treatment costs in the Canadian and European healthcare systems, respectively.

The main limitation of this study is that it represents a purely descriptive report. Furthermore, it is important to note that the analysis is only based on inpatient data. However, surgical treatment is required in the majority of nonunion cases. Although ICD-10 codes divided by
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