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Risk factors for nonunion after intramedullary nailing of femoral shaft fractures: Remaining controversies

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ABSTRACT

Introduction: Intramedullary nailing (IMN) is the preferred treatment for femoral shaft fractures in adults. Although previous studies published good outcomes, some controversies remain. The purpose of this retrospective study was to identify factors that influence outcome after IMN for femoral shaft fractures.

Materials and methods: Between July 1998 and July 2013, we treated 230 patients with 248 femoral shaft fractures. Statistical analyses were performed to determine predictors of nonunion. The following set of variables was selected based on the speculation that they would contribute to the outcome: sex (male or female), smoking, obesity, polytrauma, fracture type, open fractures, Gustilo type, primary external fixation (EF) and reaming.

Results: Initial fracture stabilization was performed by IMN in 161 (64.9%) and by EF in 87 (35.1%) fractures. There were no documented cases of deep infection. Nonunion was diagnosed in 27 patients with 28 fractures (11.3%). Factors affecting nonunion in the univariate analysis were Arbeitsgemeinschaft für Osteosynthesefragen/Orthopaedic Trauma Association (AO/OTA) fracture type (odds ratio [OR] 25.0; p < 0.0001), Gustilo type (OR 0.64; p = 0.0358), and EF (OR 0.42; p = 0.0401). Multiple logistic regression analysis only identified AO/OTA fracture type (OR 22.0; p < 0.0001) as a risk factor for nonunion. Fracture reaming did not change the outcome (OR 0.80; p = 0.6073). A separate analysis showed that damage control EF was not a risk factor in polytrauma patients (OR 0.76; p = 0.5825). *Conclusions:* Fracture stabilisation with IMN is a good treatment option for femoral shaft fractures in adults. The purpose of this study was to evaluate risk factors of poor outcome after IMN of femoral shaft fractures was reamed or not. Univariate and unltivariate analysis could only correlate AO/OTA fracture type with the occurrence of nonunion. Therefore, in this study, unreamed nailing and damage control EF were not associated with a negative outcome.

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Introduction

The current standard treatment for femoral shaft fractures in adults is intramedullary nailing (IMN) [1]. Since its description by Kuntscher in 1939 [2], IMN has been reported to have healing rates up to 99% and low complication rates [3,4]. Despite these good outcomes, some controversies remain. One example is the necessity to ream the fracture site. Although previous studies

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http://dx.doi.org/10.1016/j.injury.2015.05.007 0020-1383/© 2015 Elsevier Ltd. All rights reserved. have addressed this issue [3,5-7], a clear consensus is still lacking [1]. The timing of IMN and the safety of reaming in polytrauma patients have also been debated in recent years [1,8]. Several detrimental effects of acute IMN in these patients, especially those with pulmonary compromise, have led to the current practice of damage control orthopaedics (DCO) [9]. Additional trauma due to IMN could push the 'borderline' stable patient towards decompensation [8]. Other open questions are the influence of injury severity and damage control external fixation (EF) on the outcome of femoral shaft fracture treatment [10-12].

The current study addresses these remaining controversies. We performed a retrospective evaluation of a large cohort of patients treated at a single centre. The studied patient population is one of

W.-J. Metsemakers et al. / Injury, Int. J. Care Injured xxx (2015) xxx-xxx

the largest to study the impacts of reaming and damage control EF [6,12,13]. We also critically evaluated our treatment protocol and identified factors influencing outcomes after IMN to treat femoral shaft fractures.

Materials and methods

Study design

The study protocol was conducted following good clinical practice guidelines. The University Hopstals Leuven is a designated trauma referral centre in Belgium. Patients were identified based upon their International Classification of Disease (ICD)-9 coding as having suffered a femoral fracture. Of the identified patients, the injury data were retrieved from the hospital electronic patient file system and included in the study's database.

Between July 1998 and July 2013, the Department of Trauma Surgery treated 5740 patients with femoral fractures, and 420 underwent IMN for femoral shaft fractures. Patients were identified from the operating theatre logbooks, and all case notes were retrieved.

Inclusion criteria included skeletal maturity and femoral shaft fractures treated with IMN. The definition and classification of shaft fractures were based on the Arbeitsgemeinschaft für Osteosynthesefragen/Orthopaedic Trauma Association (AO/OTA) classification [14]. Open fractures were subdivided by the Gustilo-Anderson classification [15], which was determined at the time of initial debridement in the operating room.

Exclusion criteria were skeletal immaturity, amputation within 5 days of the accident, primary treatment with plate osteosynthesis, primary treatment outside the University Hospitals Leuven, or the presence of metaphyseal or pathological fractures.

Patient demographics including age, sex, smoking, obesity (body mass index [BMI]: \geq 30), diabetes, polytrauma (Injury Severity Score [ISS]: >16) [16,17], fracture type, Gustilo type, primary EF, reaming, length of hospital stay, and length of intensive care unit (ICU) stay were recorded.

The minimum follow-up period was 12 months, and follow-up was continued until there was evidence of union. The results were retrospectively reviewed using the patients' hospital and operation charts. The clinical records and radiographs were independently reviewed by three of the authors (WJM, NR, SN).

Treatment protocol

Surgery was undertaken on closed fractures within 24 h after the injury. Open fractures were treated within 6 h with sterile wound irrigation, debridement, and stabilization of the fracture in the operating room. If appropriate, plastic and reconstructive surgeon involvement occurred early in the treatment process. In severe open fracture cases, definitive skeletal stabilization and wound coverage were preferably achieved within 72 h and did not exceed 7 days. Systemic prophylactic antibiotics were administered once before surgery for closed fractures and continued in case of open fractures until wound closure, for a maximum of 5 days. Surgical fixation was performed using four types of nails (DepuySynthes; Johnson & Johnson Co. Inc., New Brunswick, NJ, USA): unreamed femoral nail (UFN), reamed femoral nail (RFN), lateral femoral nail (LFN), and retrograde femoral nail (DFN). These were all Titanium – (6%) Aluminium – (7%) Niobium (TAN) implants. Another surgical treatment option was the external fixator (DepuySynthes; Johnson & Johnson Co., Inc.). The fixation type was selected at the surgeon's discretion. Conversion from EF to IMN was performed between days 5 and 10 after the initial surgery. General indications for DFN placement were: distal femoral shaft fractures, ipsilateral pelvic or tibia fractures, and pregnancy [1]. Fracture dynamizations were not standard and were performed as planned procedures 6–8 weeks after IMN.

Postoperative mobilization started on day 1 under the supervision of a physiotherapist. Full weight bearing within pain limits was allowed in cases of IMN. The first follow-up visits were planned at weeks 6 and 13 for clinical and radiological evaluations. Thereafter, scheduled appointments were made at 3-month intervals until clinical and radiological healing occurred. Nail removal was not planned as a standard procedure.

Outcomes

Outcome measures such as infection and nonunion were retrospectively assessed. Infection was classified into two groups: superficial or deep infections, which were defined according to Dellinger et al. and Centre for Disease Control (CDC) guidelines [18,19]. A superficial wound infection was one located above the fascia, with erythema and tenderness. A deep infection was defined as an infection involving deeper tissues as muscular fascia and bone, which could necessitate removal of the osteosynthetic material.

Fracture healing was clinically defined as no pain or tenderness over the fracture zone and radiographically as three solid bridging callus ridges connecting the fracture fragment on both anteroposterior (AP) and lateral views. We followed the US Food and Drug Administration (FDA) guidelines defining nonunion as a fractured bone that has not completely healed within 9 months of injury and that has not shown progression towards healing over the past 3 consecutive months on serial radiographs [20].

Statistical analysis

Categorical data were described using observed frequencies and percentages, and continuous variables were summarized by their means and standard deviations (or medians and interquartile ranges in case of serious deviations from normality).

The primary outcome was the occurrence of nonunion. The following set of predictive variables was selected based on our speculation that they would contribute: sex (male or female), smoking, obesity (BMI \geq 30), polytrauma (ISS > 16), fracture type, open fractures, Gustilo type, primary EF and reaming. The univariate association of each predictor with outcome was assessed using a generalized estimating equation (GEE) [21] logistic regression using an unstructured variance/covariance matrix to account for multiple fractures per patient. In addition, a multivariable GEE logistic regression was performed that included all of the above variables.

Time to union was assessed using Kaplan–Meier curves. To account for the repeated nature of the data, the robust sandwich estimators of Lin and Wei [21] were used for the variance. Differences between groups were assessed using robust Wald tests.

All analyses were performed with SAS software (version 9.3; SAS Institute, Cary, NC, USA) by L-Biostat University of Leuven. All tests were two-sided and assessed at a significance level of 5%.

Results

Clinical characteristics

During the 15-year study period, 251 patients with 269 fractures met the inclusion criteria. Of these, 9 patients were lost to followup, 4 died from trauma-related causes within the first 30 days after the injury, and 8 died within 5 months from other causes (cardiovascular disease and cancer), leaving 230 patients with 248 fractures for inclusion in this retrospective study (Figure 1). The

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2

W.-J. Metsemakers et al./Injury, Int. J. Care Injured xxx (2015) xxx-xxx



Figure 1. Flow diagram showing patient enrolment.

mean age was 34.6 years (standard deviation [SD] = 19.0, range 16–96).

We identified 171 male patients (74.3%) and 59 female patients (25.7%). Traffic accidents were the most common cause of injury, involving 172 patients (74.8%). Furthermore, 47 (20.4%) patients fell from a height, 8 (3.48%) experienced a crush trauma, and 3 (1.30%) had a sports accident.

The mean ISS was 21.9 (SD = 12.25, range 4–75) with 147 polytrauma patients (63.9%). There were 18 patients with bilateral femoral shaft fractures and 12 patients with bifocal femoral fractures.

Following the AO/OTA classification, the identified fracture types were as follows: 32A, 125 fractures (50.4%); 32B, 78 fractures (31.5%); and 32C, 45 fractures (18.1%). There were 52 (21.0%) open femoral shaft fractures that were classified according to the Gustilo-Anderson criteria. Injuries were classified as type I in 29 cases (11.7%), type II in 15 cases (6.05%) and as type III in 8 cases (3.23%). Type III injuries were further subdivided in type IIIa (3, 1.21%), IIIb (3, 1.21%) and IIIc (2, 0.81%).

Initial stabilization was performed by IMN in 161 (64.9%) and by EF in 87 fractures (35.1%). Of the latter group, 83 (95.4%) were polytrauma patients. In total, 133 fractures (53.6%) were reamed prior to IMN, and 115 fractures (46.4%) were not reamed. Of all the open fractures, 36 (69.2%) were treated with a UFN. In 6 cases,

Table 1

Statistical differences between polytrauma and non-polytrauma patients with respect to hospital and ICU admission times.

Patient characteristic	Statistic	Polytrauma				
		No	Yes	Total	p-Value	
Total number of patients	Ν	83	147	230		
Time in hospital (days)	Ν	83	147	230	<0.0001	
	Mean	10.5	25.6	20.1		
	Median	8.0	21.0	15.0		
	SD	8.72	18.65	17.37		
	Q1, Q3	5.0, 13.0	13.0, 31.0	8.0, 25.0		
Time in ICU (days)	N	83	147	230	<0.0001	
	Mean	0.1	6.4	4.1		
	Median	0.0	3.0	0.0		
	SD	1.10	8.78	7.66		
	Q1, Q3	0.0, 0.0	0.0, 11.0	0.0, 5.0		

Note: Differences between groups were assessed using Wilcoxon rank-sum tests. ICU, intensive care unit; SD, standard deviation; *N*, total number of patients.

Table	2
Patien	t characteristics

Patient characteristics	Statistic, N	No, 27	Yes, 205
Union			
Polytrauma			
No	n/N (%)	5/27 (18.5%)	78/205 (38.1%)
Yes	n/N (%)	22/27 (81.5%)	127/205 (62.0%)
Gender			
Male	n/N (%)	24/27 (88.9%)	149/205 (72.7%)
Female	n/N (%)	3/27 (11.1%)	56/205 (27.3%)
Obesity			
No	n/N (%)	24/27 (88.9%)	184/205 (89.8%)
Yes	n/N (%)	3/27 (11.1%)	21/205 (10.2%)
Diabetes			
No	n/N (%)	25/27 (92.6%)	198/205 (96.6%)
Yes	n/N (%)	2/27 (7.41%)	7/205 (3.41%)

N, total number of patients.

Note that N=232. Two patients with bilateral fractures developed a nonunion at one site and a union on the other site. These patients were included twice.

planned fracture dynamization was performed within 6 to 8 weeks after IMN.

Regarding cardiovascular risk factors, there were 8 patients (3.48%) with diabetes (3 of whom had type 1 diabetes), and 23 patients (10.0%) were obese (BMI \geq 30). The mean BMI was 24.2 (SD = 4.24, range 15.6–41.0). Additionally, 84 patients (36.5%) were active smokers at time of the initial procedure.

The mean hospitalization period was 15 days (range 3–102). The time intervals are summarized in Table 1 for the total population and separately for polytrauma and non-polytrauma patients. A comparison between the two groups revealed that hospital and ICU stay lengths were significantly longer for polytrauma patients (p < 0.0001).

In this study, three superficial wound infections were diagnosed which were all successfully treated with short-term (<10 days) antibiotic treatment. There were no deep infections. Overall, 27 patients with 28 fractures (11.3%) presented with nonunion, including 22 (81.5%) polytrauma patients. Tables 2 and 3

Table 3	
Fracture	characteristics

racture	characteristics.	

Fracture characteristics	Statistic, N	No, 28	Yes, 220
Union			
Type of fracture			
A1	n/N (%)	0/28 (0.00%)	21/220 (9.55%)
A2	n/N (%)	0/28 (0.00%)	32/220 (14.6%)
A3	n/N (%)	2/28 (7.14%)	70/220 (31.8%)
B1	n/N (%)	0/28 (0.00%)	9/220 (4.09%)
B2	n/N (%)	8/28 (28.6%)	47/220 (21.4%)
B3	n/N (%)	5/28 (17.9%)	9/220 (4.09%)
C1	n/N (%)	1/28 (3.6%)	6/220 (2.73%)
C2	n/N (%)	3/28 (10.7%)	9/220 (4.09%)
C3	n/N (%)	9/28 (32.1%)	17/220 (7.73%)
Reaming			
Unreamed	n/N (%)	14/28 (50.0%)	101/220 (45.9%)
Reamed	n/N (%)	14/28 (50.0%)	119/220 (54.1%)
Open fractures			
No	n/N (%)	19/28 (67.9%)	177/220 (80.5%)
Yes	n/N (%)	9/28 (32.1%)	43/220 (19.6%)
External fixation			
No	n/N (%)	13/28 (46.4%)	148/220 (67.3%)
Yes	n/N (%)	15/28 (53.6%)	72/220 (32.7%)
Gustilo type			
Closed	n/N (%)	19/28 (67.9%)	177/220 (80.5%)
Grade I	n/N (%)	3/28 (10.7%)	26/220 (11.8%)
Grade II	n/N (%)	4/28 (14.3%)	11/220 (5.00%)
Grade IIIa	n/N (%)	1/28 (3.57%)	2/220 (0.91%)
Grade IIIb	n/N (%)	1/28 (3.57%)	2/220 (0.91%)
Grade IIIc	n/N (%)	0/28 (0.00%)	2/220 (0.91%)

N, total number of fractures.

4

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W.-J. Metsemakers et al./Injury, Int. J. Care Injured xxx (2015) xxx-xxx



Figure 2. Kaplan-Meier curve for the time to union comparing reamed and unreamed nailing.

summarize the specific characteristics with respect to union rates for each independent variable.

Univariate and multivariable-adjusted predictors of risk for nonunion

The following factors were associated with nonunion in the univariate analysis: AO/OTA fracture type (odds ratio [OR] 25.0; p < 0.0001), Gustilo type (OR 0.64, p = 0.0358), and primary EF (OR 0.42, p = 0.0401). Kaplan–Meier curves for the time to union are given in Figures 2–4, for reaming, polytrauma, and primary EF. Comparisons between the groups did not reveal a difference between reamed and unreamed fractures (p = 0.6027) or between

polytrauma and non-polytrauma patients (p = 0.1046). Healing times for the general study population and for reamed and unreamed fractures are summarized in Table 4. A statistically significant difference in outcome was found between patients with and without primary EF (p = 0.0158), whereby fractures treated without EF tended to have higher union rates. Subgroup analysis including only polytrauma patients did not identify primary or damage control EF as a risk factor for nonunion (OR 0.76, p = 0.5825; Table 5).

Multiple logistic regression analysis showed a statistical correlation between nonunion and AO/OTA fracture type (OR 22.0; p < 0.0001). More specific, higher nonunion rates were



Figure 3. Kaplan-Meier curve for the time to union comparing polytrauma patients (Yes) and non-polytrauma patients (No).

W.-J. Metsemakers et al./Injury, Int. J. Care Injured xxx (2015) xxx-xxx



Figure 4. Kaplan-Meier curve for the time to union comparing patients with (Yes) and without (No) primary EF.

Table 4Healing times for the study population.

	Healing time					
	Ν	Mean	SD	Min.	Median	Max.
Healing						
Nonunion	28	18.46	5.75	10.00	20.00	30.00
Union	220	4.86	1.72	2.00	5.00	13.00
Reaming						
Unreamed	115	6.61	5.58	2.00	5.00	30.00
Reamed	133	6.21	4.42	2.00	5.00	24.00
Total	248	6.40	4.99	2.00	5.00	30.00

N, number of fractures; Min., minimal healing time; Max., maximal healing time.

observed in patients with type C fractures compared to type A fractures. The statistical results are summarized in Table 6.

Discussion

Nonunion remains an important issue for trauma surgeons. As noted by previous authors, it is difficult to treat and has a high financial impact [22,23]. With respect to femoral shaft fractures, IMN is an effective treatment option with nonunion rates less than 10%, regardless of the starting point [1,3], and infection rates in large series ranging from 1% to 3.8% [24]. The advantages of intramedullary fixation include early stable fixation, early

tional intramedullary reaming prior to nail insertion allows appropriate shaping of the medullary canal, facilitating the insertion of larger diameter nails that provide a more stable osteosynthesis, which is necessary for adequate bone healing [27]. Although these effects seem positive, concerns have been raised regarding the local and systemic effects of reaming. The procedure leads to elevated intramedullary pressure and systemic embolization of bone marrow content [28]. Intramedullary instrumentation also stimulates the inflammatory system [29]. These systemic disturbances could contribute to pulmonary morbidity, especially in patients with multiple injuries [8], although there are studies with results that do not support this hypothesis [30]. To address these disadvantages, unreamed solid nails with a smaller diameter were developed. The proponents of unreamed nails state that they are faster to insert and have results comparable to reamed nails [5,7]. Furthermore, preclinical data suggest that unreamed, solid core, nails are less susceptible to infection [31]. Comparative studies of both techniques have yielded conflicting results regarding outcomes [5,7,25,26,32]. In our retrospective study, which is one of the largest on the subject, neither variable correlated with nonunion (Table 6). The Kaplan-Meier curves in Figure 2 show no statistical significant difference

mobilization of hip and knee joints, and less soft tissue damage.

Despite positive results, controversies regarding the treatment and outcome of these fractures remain. For example, several studies have been published on the topic of reaming [3,5,7,25,26]. Addi-

Table 5

Assessment of interaction between polytrauma and external fixation.

Variable	Unadjusted analyses			Adjusted analy	Adjusted analyses ^a		
	OR		p-Value	OR		p-Value	
	Estimate	95% CI		Estimate	95% CI		
Interaction between polytrauma and EF Effect of EF (Yes vs. No)			0.3231			0.8777	
For polytrauma = No For polytrauma = Yes	0.160 0.608	0.01, 1.90 0.24, 1.55	0.1470 0.2957	0.610 0.757	0.04, 8.30 0.28, 2.04	0.7103 0.5825	

Cl, confidence interval; EF, external fixation; OR, odds ratio.

^a Adjusted for fracture type.

W.-J. Metsemakers et al. / Injury, Int. J. Care Injured xxx (2015) xxx-xxx

6

Table 6

Univariate and multivariable ORs of risk factors for the prediction of union.

Variable	Ν	Comparison	Univariate analyses		Multivariate analyses			
			OR		p-Value	OR		p-Value
			Estimate	95% CI		Estimate	95% CI	
Polytrauma	248	Yes vs. No	0.396	0.14, 1.09	0.0730	0.759	0.22, 2.65	0.6659
Fracture type	248	A1, 2, 3 vs. C1, 2, 3	24.984	5.36, 116.39	< 0.0001*	21.993	4.65, 104.03	< 0.0001
		B1, 2, 3 vs. C1, 2, 3	2.031	0.87, 4.73	0.1001	2.106	0.87, 5.11	0.0997
Reaming	248	Reamed vs. Unreamed	1.178	0.52, 2.65	0.6913	0.800	0.34, 1.87	0.6073
Open fracture	248	Yes vs. No	0.513	0.22, 1.18	0.1146	1.612	0.25, 10.49	0.6175
EF	248	Yes vs. No	0.422	0.18, 0.96	0.0401	0.748	0.28, 2.01	0.5650
Gustilo type	248		0.641	0.42, 0.97	0.0358	0.673	0.29, 1.57	0.3596
Sex	248	Female vs. Male	3.197	0.92, 11.07	0.0667	2.801	0.68, 11.49	0.1525
Obesity	248	Yes vs. No	0.926	0.27, 3.20	0.9033	0.751	0.21, 2.63	0.6550
Smoking	248	Yes vs. No	0.609	0.27, 1.39	0.2373	0.826	0.32, 2.16	0.6975

CI, confidence interval; EF, external fixation; OR, odds ratio.

Exploratory analyses indicated that for Gustilo grading, collapsing all III-categories and then including the variable as a continuous variable provided the best fit. p < 0.05.

between reamed and unreamed fractures (p = 0.6027). Indeed, different authors have already confirmed this statement, although in smaller study populations [5,26]. One of the reasons why there was no difference in our study could be that a large portion (69.2%) of open fractures was treated with unreamed nails. Although difficult to compare, recent studies on the outcome after tibia shaft fracture nailing showed that reaming in open fractures was associated with an increased risk of a negative event [33,34].

The timing of IMN and safety of reaming in polytrauma patients have been subjects of debate in the past several decades. The possible detrimental effects of reaming and acute IMN, as already described, have led to the practice of DCO in the acute care of polytrauma patients [9]. The current principles of DCO propagate the temporary use of an EF with early conversion to IMN. Studies by Nowotarski and Scalea stated that it is a safe and effective approach in this group of patients [12,13]. In the univariate regression analysis, primary EF correlated with the occurrence of nonunion, but this was not confirmed by multivariate regression analysis. Furthermore, when performing a subgroup analysis of polytrauma patients, damage control EF was not identified as a risk factor for nonunion in this specific population (Table 5).

Table 6 provides an overview of both the univariate and multivariate regression analyses. The only risk factor that correlated with nonunion in both models was the AO/OTA fracture type. Although polytrauma patients did not seem to have a higher risk for the development of nonunion, hospitalization and ICU stays were significantly longer for these patients (p < 0.0001, Table 1).

We realize that this study has limitations, as it is a retrospective analysis of suspected risk factors. Additionally, the nonunion group was relatively small; therefore, caution is needed before drawing conclusions and generalizing our findings to other subjects. However, the study does suggest that strategies for risk management to avoid these complications can be developed, especially because it is one of the largest patient populations studied on topics such as reaming and damage control EF [6,12,13]. We are aware that not all potential variables were investigated, including alcohol consumption and corticosteroid use. Implant material was also excluded as a variable because only TAN implants were used. Therefore, the results of the current analysis are limited to the variables that were collected as part of this retrospective study. We also realize that omitting patients (e.g. those who died or were lost in follow-up) from the analysis can introduce a selection bias. In addition, the study population was relatively young, and the results may not be generalizable to older patients. This could also explain why smoking and obesity were not identified as statistically significant risk factors, even though they were indicated as possible causes for negative outcome in a previous study [35].

In addition, there is the lack of consensus regarding the assessment of bone union, for which there are no available standard criteria [36]. In 2002, Bhandari et al. performed a large questionnaire study that asked orthopaedic trauma surgeons to give their definition of prolonged fracture healing. Responses varied, with definitions of delayed union ranging from 1 to 8 months, and definitions of nonunion ranging from 2 to 12 months [37]. This variability remains a problem in musculoskeletal trauma research.

Conclusions

In conclusion, musculoskeletal complications place a cost burden on total healthcare expenditure. Better understanding of the epidemiology and pathogenesis of nonunion are essential because this can lead to prevention rather than treatment strategies. The purpose of this study was to evaluate risk factors for the development of nonunion after IMN of femoral shaft fractures. Multivariable regression analysis revealed that only AO/ OTA fracture type correlated with the occurrence of nonunion. Fracture reaming did not change the outcome. Furthermore, damage control EF was not a risk factor in polytrauma patients in our study population.

Conflict of interest

S.N. is consultant for DepuySynthes and has received, apart from consultancy and lecturing fees, food and travel reimbursement. P.R. is a member of the lecture bureau of DepuySynthes and has received, apart from lecturing fees, food and travel reimbursement from DepuySynthes. W.J.M. has received food and travel reimbursement from DepuySynthes. These reimbursements did not correlate with this study. The department of Trauma Surgery receives an unrestricted research grant from DepuySynthes and is a training centre for DepuySynthes. All authors hereby disclose any financial and personal relationships with other people or organisations that could inappropriately influence this work.

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