Frequency of complications in intramedullary nailing of open tibial shaft fractures: a systematic review

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- Background: Open tibial shaft fractures comprise almost 45% of all open fractures and are frequently the result of high-energy trauma. Due to contamination, limited soft tissue coverage of the tibial shaft and poor tibial blood supply, open tibial shaft fractures are associated with high rates of complication including malunion, non-union and infection. Intramedullary nailing (IMN) is a mainstay of treatment. This study aims to determine the frequency of the various complications in this cohort.
- Methods: A systematic review of papers published on Embase, PubMed and Cochrane
 databases pertaining to the use of IMN to fix open tibial shaft fractures were included. The
 available evidence was collated in regard to the incidence of union, malunion, non-union
 and infection seen in this cohort.
- Results: A total of 2767 citations were reviewed, and 17 studies comprising 1850 patients were included in the analysis. There was a delayed union rate of 22.4%, malunion rate of 8.3%, non-union rate of 9.7% and infection rate of 8.1% (95% Cl: 5.7%—10.8%) in this patient cohort. Subgroup analysis showed a 3-fold increase in non-union and a 2-fold increase in deep infection among Gustilo III injuries compared to Gustilo I and II.
- Conclusions: IMN for open tibial shaft fractures results in high rates of union and low rates
 of infection, comparable to figures seen in closed injuries and superior to those seen with
 alternative methods of fixation. There is a substantially increased risk of complication
 associated with Gustilo III injuries, reinforcing the significance of the soft tissue injury in
 these patients.

Keywords

- ▶ trauma
- open fractures
- ▶ intramedullary nailing
- malunion
- ▶ infection
- ▶ complications

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Introduction

Fractures of the tibial shaft represent 2% of all fractures and 37% of all long bone fractures in adults, at an incidence of 17–21 per 100,000 population (1, 2). Due to the limited soft tissue coverage specific to the tibial shaft, over 15% of all tibial shaft fractures are classified as open (1). This makes open tibial diaphyseal fractures the most common, comprising 44.7% of all open long bone fractures (3).

These fractures are most commonly the result of highenergy trauma such as road traffic accidents (RTA) (3). A frequent sequela of RTA's is the contamination of wounds from injuries sustained in the accident. This contamination, in association with the limited blood supply to the tibia (4), means that open tibial shaft fractures are associated with high rates of complications including malunion, nonunion and infection (5, 6).

The severity of the soft tissue injury associated with open fractures has been considered significant for many years. In 1976, Gustilo and Anderson published a classification

to better categorise the degree of soft tissue injury (7). This system has become widely accepted and is now the benchmark in both research and clinical practice. Despite its limitations (8, 9), many publications have highlighted that the strength of the Gustilo–Anderson classification is the association between its grades and the incidence of the complications previously described (10, 11, 12).

For many years, intramedullary nailing (IMN) has been a mainstay in the treatment of tibial shaft fractures. Other fixation methods remain viable options, and a lot of ongoing research focuses on comparing IMN to external fixators in managing these injuries. Several studies have shown IMN to be associated with superior outcomes when compared to other techniques (13, 14, 15). This evidence is typically derived from comparator studies, and there is no cumulative data available relating specifically to the complication rates associated with IMN in open fractures. As a result, a systematic review was performed to collate the available evidence on this topic, providing accurate statistics on the incidence of complication rates



to better inform choice of fixation, future research and patient education.

Methods

This systematic review was carried out in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (16). This review was not registered prior to being performed. The work was carried out by the lead author and senior author at Department of Orthopaedics, Midland Regional Hospital Tullamore, with input from the second author from another site.

Search strategy

The electronic databases of EMBASE, MEDLINE, and Cochrane were searched using a predefined protocol. A boolean search with truncation was performed, using the terms: (tibia* AND fract* AND (open OR compound OR gustilo) AND nail*).

The databases were searched from their inception to September 1, 2021, and these searches were repeated on October 1, 2021, to ensure no studies had been missed. All search results were combined in the Endnote reference manager and duplicates were removed. The bibliographies of all included studies were also handsearched for completion. The online databases of major orthopaedic journals were also examined to avoid missing relevant papers that were recently published.

Data extraction

Two independent reviewers (LT and IB) evaluated the titles of the retrieved publications from the database search. The inclusion criteria were any ambulatory patient(s) sustaining a diaphyseal tibial fracture, either as an isolated injury or in the setting of polytrauma, who underwent antegrade IMN of the tibial shaft and had reported outcome measures of fracture union, non-union, malunion and infection. We excluded any papers dealing with paediatric, periprosthetic, plateau or plafond fracture, polytrauma patients with an Injury Severity Score

of greater than 25, papers with less than 50 patients in the cohort, non-English papers and any opinion pieces, letters to the editor, case reports, protocols, conference proceedings, cadaveric studies and experimental or nonhuman studies (Table 1).

These criteria were applied to the search results, and the abstracts of all potentially eligible publications were reviewed. Following this, the full text was obtained, and the same two reviewers evaluated the publications against the eligibility criteria prior to inclusion. Any disagreements were resolved by discussion.

The primary outcomes measured were the rate of union and the rate of infection. The secondary outcomes were the rate of delayed union, malunion and non-union. In an attempt to maximise the consistency of our results, strict definitions were adopted for our outcomes which can be seen in Appendix 1 (see section on supplementary materials given at the end of this article).

For each study included, demographics and baseline characteristics (author, country, year of publication, study type, study interval and size of patient cohort) were extracted and recorded. These characteristics were not masked at any stage to avoid duplication of data (Table 2).

Quality analysis

The systematic review was conducted in accordance with the PRISMA guidelines (16). There were 17 studies included, 2 were randomised control trials (RCTs), 5 were prospective cohorts and the remaining 10 were retrospective cohort studies. A quality analysis was performed on each of the cohort studies using the Newcastle-Ottawa Scale. The RCTs were assessed using the ROB 2.0 tool.

Statistical analysis

A statistical analysis of the primary outcomes of interest was performed, and these results were expressed as proportions (e.g. union rate, non-union rate, infection rate, etc.). The data available were pooled via the MedCalc software (version 19), and either a fixed or random effects model was used depending on the degree of heterogeneity. Objective, statistical measurement of heterogeneity was tested with both Cochran's Q test and

Table 1 Inclusion and exclusion criteria applied.

Inclusion criteria

Ambulatory patients sustaining a diaphyseal tibial fracture, either as an isolated injury or in the setting of poly trauma

Anterograde intramedullary nail fixation of the tibial shaft fracture Reported outcome measures of fracture union, non-union, mal-union or infection

Exclusion criteria

Reviews, opinions, letters to the editor, case reports, protocols, conference proceedings, cadaveric studies, experimental or non-human studies

Papers dealing exclusively with a paediatric population

Papers dealing exclusively with patients suffering from plateau, plafond or periprosthetic fractures

Papers where the data are unavailable or uninterpretable and the authors are uncontactable

Papers with less than 50 patients included

Patients involved in severe poly trauma with as ISS >15

Papers written in languages other than English

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Table 2 Epidemiology of the studies included in the paper.

Reference	Country	Year of publication	Study type	Period of study	Size of cohort
Akhtar et al. (18)	Pakistan	2018	Cohort	2012–2016	80
Al-Hourani et al. (32)	UK	2019	Cohort	2014-2018	113
Bali et al. (19)	India	2011	RCT	2006–2009	54
Bonatus et al. (20)	USA	1997	Cohort	1989–1993	72
Court-Brown et al. (21)	Scotland	1992	Cohort	1986–1991	110
Duyos et al. (6)	USA	2017	Cohort	1993-2012	151
Gaebler et al. (22)	Austria & Germany	2001	Cohort	1988–1997	202
Haonga et al. (33)	Tanzania	2019	RCT	2015-2017	111
Henley et al. (23)	USA	1998	Cohort	1988–1993	104
Howard et al. (24)	USA	1992	Cohort	1979–1988	61
Jenny et al. (25)	France	1994	Cohort	1974–1999	249
Kakar & Tornetta (26)	USA	2007	Cohort	1992–1997	143
Keating et al. (27)	Scotland & Canada	1997	Cohort	1987-1993	112
Singh et al. (28)	India	2011	Cohort	2002–2008	88
Tabatabaei et al. (29)	Iran	2012	Cohort	2008-2010	119
Whittle et al. (30)	USA	1992	Cohort	1986–1989	50
Wiss (31)	USA	1986	Cohort	1980–1984	56

Higgins I² test. For the purpose of this study, statistical significance was indicated by a Q score of >0.1 due to its low sensitivity for detecting heterogeneity (17). An I² value of greater than 50% represents moderate heterogeneity and greater than 70% represents significant heterogeneity. Where heterogeneity was evident ($I^2 > 50\%$ or P < 0.1), a random-effect meta-analysis was conducted, and where statistical heterogeneity was absent, a fixed-effect model was used.

In order to evaluate the robustness of the results, following the initial pooling of the results, a subsequent analysis was performed on the data separating the studies into those performed prospectively and those performed retrospectively, to ascertain if the results were similar across both cohorts given the variation in study design.

Several subgroup analyses were also performed using the RevMan (5.3) software with data from different comparator groups. The software was used to provide the pooled estimate of effect size for the outcomes of interest using the Mantel-Haenszel method and either a fixed or random effects model. These results were summarised as odds ratios with 95% confidence intervals (95% CI). Forest plots were used to graphically express the pooled results of the subgroup analyses.

Results

Search results

The database search revealed 2462 citations after duplicates were removed. Of these, 301 abstracts were evaluated, and 35 papers were included for full-text review. Ultimately, 17 papers were included in the study, with a total of 1850 patients from all 17 studies (6, 18-33) (Fig. 1). Several of the studies contained information relating to closed fractures or other methods of fixation. Careful consideration has been taken to include only the results relating to open tibial shaft fractures treated with intramedullary nailing in this study.

Quality analysis

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The quality analysis was performed on each of the cohort studies using the Newcastle-Ottawa Scale. The RCTs were assessed using the ROB 2.0 tool.

All studies received a 'Good' grade and were deemed suitable for inclusion (Table 3). For the RCTs included in this study, quality analysis was conducted using the ROB 2.0 tool. One RCT was found to have a 'low' risk of bias,

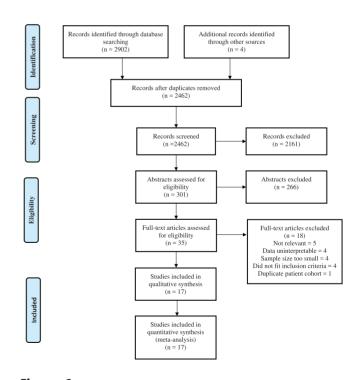


Figure 1 PRISMA flowchart.

		Selec	Selection				Outcome		
Reference	Representativeness	Selection non-exposed	Ascertainment	Demonstration	Comparability	Assessment	Follow-up	Adequacy	Quality
Akhtar et al. (18)	_	-	-	_	_	_	_	_	Good
Al-Hourani et al. (32)	_	-	_	_	_	_	_	_	Good
Bonatus et al. (20)	-	-	_	-	-	_	_	_	Good
Court-Brown et al. (21)	_	_	_	_	-	_	_	0	Good
Duyos <i>et al.</i> (6)	_	_	-	_	_	_	_	0	Good
Gaebler et al. (22)	_	-	_	-	_	-	_	_	Good
Henley <i>et al.</i> (23)	_	_	_	_	_	_	_	_	Good
Howard et al. (24)	_	_	-	_	_	_	_	_	Good
enny <i>et al.</i> (25)	_	_	-	-	_	_	_	0	Cood
Kakar & Tornetta (26)	1	_	-	_	_	_	_	_	Cood
(eating et al. (27)	_	_	-	-	_	_	_	_	Good
Singh <i>et al.</i> (28)	_	_	-	_	_	_	_	_	Cood
Fabatabaei et al. (29)	1	_	-	-	_	_	-	0	Cood
Whittle et al. (30)	_	-	-	-	_	-	-	_	Cood
Wiss (31)	_	_	_	_	_	-	_	_	Good

while there were 'some concerns' regarding the other RCT due to the absence of information regarding the randomisation and concealment of the intervention.

Union rate

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Data for union rates were extracted from 11 studies including 1021 fractures. Pooled estimate of effect size was 91.0% (95% CI: 87.7%–93.8%), using random effects model in the presence of moderate heterogeneity ($I^2=65.6\%$, Q=29, P=0.0012). These results have been depicted in Table 4 along with all of the other results relating to the primary outcomes.

The rate of early union was calculated at 63.6% (95% CI: 50%–76.1%), delayed union at 22.4% (95% CI: 11.1%–36.2%) and malunion at 8.3% (95% CI: 4.6%–13%). All of these were estimated using the random effects model due to heterogeneity (Table 4).

The rate of non-union was extracted from 13 studies combining 1284 fractures. The estimated rate of non-union was 9.7% (95% CI: 6.9%–13.1%) which corresponds to the union rate of 91%. This was also in the setting of moderate heterogeneity using a random effects model ($l^2 = 71.9\%$, Q = 42.7, P < 0.0001) (Table 4).

Infection rate

Data relating to infection were extracted from 14 studies involving 1409 patients. The overall infection rate was 8.1% (95% CI: 5.7%–10.7%), again using random effects model in the presence of significant heterogeneity ($I^2 = 77.4\%$, Q = 53, P < 0.0001). The rate of deep infection was calculated at 7.7% (95% CI: 5.1%–10.7%), as was the superficial infection rate (95% CI: 3.5%–13.4%) (Table 4).

Prospective vs retrospective

All of the results mentioned earlier were also assessed by comparing the prospectively collected data to the retrospectively collected data to compare results for the primary outcomes (Tables 5 and 6).

For union, the rates were 91.0% and 91.4% in the prospective and retrospective groups, respectively. The deep infection rates were also similar at 8.4% and 7.4%, respectively. There was a slight difference in the non-union rates between the two cohorts, with the prospective results showing an 8.5% non-union rate compared to 11.0% in the retrospective group.

Subgroup analysis

Degree of soft tissue injury (Gustilo I & II vs III)

Relevant data regarding the rate of delayed union, malunion, non-union and deep infection specific to each Gustilo class were available from ten studies (6, 20, 21,

Table 4 Primary outcome results.

	Studies, n	Participants, n	Pooled estimate of effect size	95% CI	l² test	Q-test	df	P -value	Statistical model
Union	11	1021	91.0%	87.7%–93.8%	65.6%	29.1	10	0.0012	Random effects
Early union	9	797	63.6%	50%-76.1%	93.4%	120	8	< 0.0001	Random effects
Delayed union	8	797	22.4%	11.1%-36.2%	94.7%	150	8	< 0.0001	Random effects
Non-union	13	1284	9.7%	6.9%-13.1%	71.9%	42.7	12	< 0.0001	Random effects
Malunion	7	627	8.3%	4.6%-13%	73.6%	26.5	7	0.0004	Random effects
Infection	14	1409	8.1%	5.7%-10.8%	77.4%	53	12	< 0.0001	Random effects
Deep infection	12	1185	8.0%	5.7%-10.8%	67.4%	39.8	13	< 0.0001	Random effects
Superficial infection	6	742	7.7%	3.5%–13.4%	84.3%	31.8	5	<0.0001	Random effects

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22, 24, 25, 26, 27, 30, 32, 33). For the purpose of direct comparison, grade I and II injuries were grouped together as these classes are associated with less soft tissue damage and periosteal stripping compared to the severe damage seen in grade III injuries (7).

From the included texts, two studies were available to compare the rate of delayed union (22, 24) and two studies were available to compare the rate of malunion as it relates to the Gustilo classification (24, 27).

There was a statistically significant difference in the rate of delayed union, favouring the Gustilo I and II group (odds ratio: 0.4, 95% CI: 0.19-0.85, P=0.02) (Figs. 2 and **6**).

There was no statistically significant difference between the two groups in relation to the rate of malunion, although the Gustilo I and II group was again heavily favoured (odds ratio: 0.28, 95% CI: 0.08-1.06, P=0.06) (Figs. 3 and 7).

There were three studies comparing the non-union rate in grade of Gustilo injury (22, 24, 27, 32). This analysis showed a lower rate of non-union in the Gustilo I and Il injuries compared to the Gustilo III injuries, and these

findings were statistically significant (odds ratio: 0.26, 95% CI: 0.10–0.69, P = 0.006) (Figs. 4 and 8).

The largest comparator study possible was with regard to deep infection. Nine studies provided data on 1108 patients relating to deep infection in Gustilo I, II and III injuries (6, 20, 21, 22, 24, 25, 26, 27, 30, 32). From these studies, we found a statistically significant increased rate of infection in the Gustilo III group vs the comparator. This analysis was highly powered with nine studies, subject to minimal heterogeneity ($I^2=23\%$), and confirms that Gustilo III injuries carry a significant risk of deep infection (odds ratio: 0.28, 95% CI: 0.15–0.50, P < 0.0001) (Figs. 5 and 9).

After applying the methodology outlined by the GRADE system to the results of this systematic review, our opinion is that the evidence presented here is of 'high' quality (Table 7). All studies included followed their patients until union or a secondary operation to treat their malunion or non-union. As such, the patients have all been followed for long enough for all of the primary endpoints to be reached. Despite the included studies being predominantly cohort and as such low quality by

Table 5 Prospectively collected results.

	Studies, n	Participants, n	Pooled estimate of effect size	95% CI	l² test	Q-test	df	P -value	Statistical model
Union	8	686	91.0%	88.7%-93.1%	47.1%	13.2	7	0.0666	Fixed effects
Early union	6	462	43.8%	27.0%-61.2%	93.1%	72.6	5	< 0.0001	Random effects
Delayed union	6	462	60.0%	32.2%-84.6%	97.3%	186.9	5	< 0.0001	Random effects
Non-union	9	798	8.5%	6.7%-10.7%	34.2%	12.2	8	0.1444	Fixed effects
Malunion	7	574	9.1%	4.2%-15.5%	82.4%	34.0	6	< 0.0001	Random effects
Deep infection	10	917	8.4%	5.2%-12.3%	74.2%	34.8	9	0.0001	Random effects

Table 6 Retrospective results.

	Studies, n	Participants, n	Pooled estimate of effect size	95% CI	l² test	Q-test	df	P -value	Statistical model
Union	3	335	91.4%	81.0%–98.0%	85.4%	13.8	2	0.0010	Random effects
Early union	3	335	75.9%	66.6%-84.1%	67.9%	6.2	2	0.0443	Random effects
Delayed union	3	335	12.2%	6.7%-19.0%	62.2%	5.3	2	0.0708	Random effects
Non-union	4	486	11.0%	3.7%-21.5%	89.7%	29.2	3	< 0.0001	Random effects
Malunion	2	133	10.3%	5.7%-16.7%	0.0%	0.4	1	< 0.0001	Fixed effects
Deep infection	4	492	7.4%	5.3%-10.1%	39.3%	4.9	3	0.1760	Fixed effects

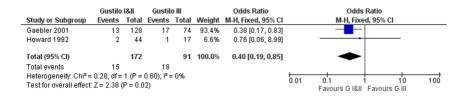


Figure 2 Delayed union rate pooled analysis.

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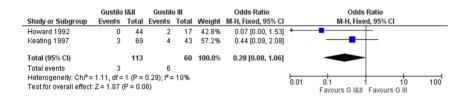


Figure 3 Malunion rate pooled analysis.

GRADE standards, the reliability of the results in this study does not depend on randomisation and is important nonetheless. In addition, this systematic review is not a comparative study between one method of treatment and another, rather it is presenting a numerical value to quantify the risks associated with the injury. The results for each outcome include over a thousand patients, and so our view is that the results are robust enough that the true effect lies close to the estimated effect presented by this study. As such, the results are of high quality and importance in relation to this topic.

Discussion

The results of this systematic review highlight a significant risk of non-union and deep infection associated with IMN of tibial shaft fractures (9.7% and 8%, respectively).

While these results are poorer than those seen in closed fractures (21, 25, 34), it is likely this relates to the complexity of the injury as opposed to the method of fixation used. This study confirms that IMN is a suitable method of fixation for patients with these injuries. Given that this study relates to IMN in isolation, we are not able to infer the superiority of this fixation method over others, such as the application of external fixators or open reduction internal fixation. Further studies would be required to compare these modalities and answer this question directly.

A comparison of results from studies that were both prospectively and retrospectively performed showed very similar results in union and deep infection rates, which were the primary outcomes of this study. In addition, these results were also extremely similar to those results when all of the data is pooled together. Although there was some disparity in the early union and delayed union

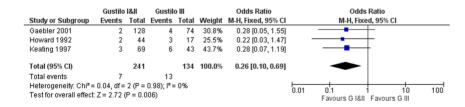


Figure 4 Non-union rate pooled analysis.

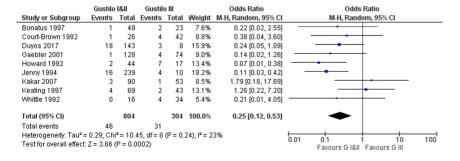


Figure 5Deep infection rate pooled analysis.

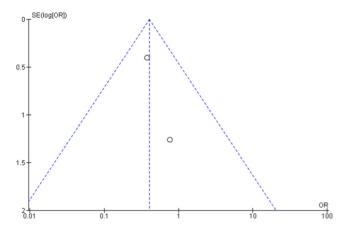


Figure 6Delayed union publication bias.

rates, these were secondary outcomes and were relatively underpowered in the retrospective cohort. This additional analysis adds robustness to the quality of the overall results of the study.

Another success of this review was the findings of the subgroup analyses performed. The evidence shows that there is a statistically significant increase in delayed union, non-union and deep infection in patients with Gustilo III injuries compared to Gustilo I and II patients. Although this is not a new finding (11, 35, 36), it does highlight a greater than 2-fold increase in non-union and delayed union and a 4-fold increase in malunion between the two groups. Although these comparisons are characterised by a lack of power due to sample size, that is not the case in the infection cohort. The analysis of deep infection rates had a large sample size of 1108 patients and illustrated a nearly 2-fold increase in deep infection in the Gustilo III group (31/304 = 10.2% vs 46/804 = 5.7%).

There were many strengths to this study along with the results. By using no date limit and broad search

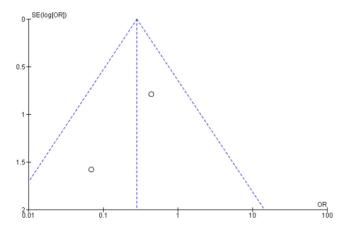


Figure 7 Malunion publication bias.

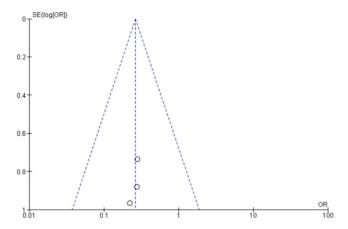


Figure 8Non-union publication bias.

terms, we have allowed the recruitment of all potentially relevant literature and included studies that span over 30 years. Our adherence to all pre-defined methodological principles of conducting a systematic review, along with our strict inclusion and exclusion criteria, has strengthened the validity of the study. By using strict definitions of the outcomes and complications, and including appropriate subgroup analyses, we have, where possible, avoided detection bias and limited potential heterogeneity. Similarly, each study including passed a rigorous quality assessment in the form of the Newcastle-Ottawa Scale or the ROB 2.0 tool, and so in combination with the factors listed earlier, this adds a level of robustness to our results.

Nevertheless, there will always be limitations to the research of this kind. Systematic reviews are generally prone to publication and detection bias despite the best efforts of those involved. Even with our thorough search of the literature, we recognise that limiting our search to only the English language, failing to include unpublished data, and possible errors in the search strategy may have

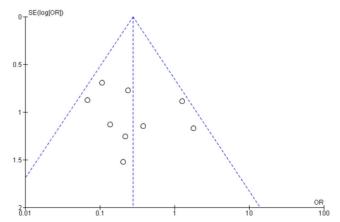


Figure 9 Deep infection publication bias.

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		Studies, n	n								
Outcomes	Total	RCT	Total RCT Cohort	Patients, n	Effect	Limitations	Inconsistency	Indirectness	Imprecision	Publication bias	Importance
Union	1	2	6	1021	91% likelihood	No serious Iimitations	No serious inconsistency	No serious indirectness	Undetected	Undetected	High
Delayed union	6	-	∞	797	22.4% risk	No serious Iimitations	No serious inconsistency	No serious indirectness	Undetected	Undetected	High
Malunion	11	7	6	627	8.3% risk	No serious Iimitations	Inconsistency evident	No serious indirectness	Undetected	Undetected	High
Non-union	13	7	11	1284	8.1% risk	No serious Iimitations	No serious inconsistency	No serious indirectness	Undetected	Undetected	High
Infection (any)	4	7	12	1409	8.1% risk	No serious Iimitations	No serious inconsistency	No serious indirectness	Undetected	Undetected	High
Deep infection	4	2	12	1185	8.0% risk	No serious Iimitations	No serious inconsistency	No serious indirectness	Undetected	Undetected	High

resulted in missing data relevant to the review. However, there was a significant number of papers included, and the results of the subgroup analyses were not affected by significant heterogeneity. As such, we believe it is quite unlikely that we have missed research that would have significantly altered our results for each outcome. With regard to the results, having papers that span over 30 years is both a strength and a weakness. There has been an undoubted improvement in surgical technique and equipment between the 1980s and today, and as such, there is a distinct possibility that the results from older studies are less relevant than those of the modern era.

Conclusion

Using intramedullary nails for the management of open tibial shaft fractures results in satisfactorily high rates of union and low rates of infection and is a suitable method of fixation where appropriate. The purpose of this systematic review was to calculate a summarised estimate of effect size for the most important outcomes in open fractures; namely union, non-union, malunion and infection, based on a thorough review of any relevant existing literature. To the best of the authors' knowledge, there is no literature providing these results in relation to open tibial diaphyseal fractures treated with IMN. This review confirms that on a widespread basis, IMN is associated with acceptable outcomes for open tibial shaft fractures and should be used in their acute management. This systematic review includes results from more than 1800 patients, and as such provides key data that can be used both at a local and regional level for audit purposes. Perhaps most importantly, this data remind us that around 1 in 10 patients with open tibial shaft fractures will suffer from a significant adverse outcome as a result of their injury and should promote vigilance in this patient population.

Supplementary materials

This is linked to the online version of the paper at https://doi.org/10.1530/EOR-22-0076.

ICMJE conflict of interest statement

Each author certifies that there are no funding or commercial associations (consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted article related to the author or any immediate family members.

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Ethical review

As this is a systematic review of already published data, no ethical approval was required.

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