EFORT open reviews

FOOT & ANKLE | 7:9 | 628–643

Retrograde tibiotalocalcaneal nailing for the treatment of acute ankle fractures in the elderly: a systematic review and meta-analysis

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- *Introduction:* Fragility ankle fractures are traditionally managed conservatively or with open reduction internal fixation. Tibiotalocalcaneal (TTC) nailing is an alternative option for the geriatric patient. This meta-analysis provides the most detailed analysis of TTC nailing for fragility ankle fractures.
- *Methods:* A systematic search was performed on MEDLINE, EMBASE, Cochrane Library, and Web of Science, identifying 14 studies for inclusion. Studies including patients with a fragility ankle fracture, defined according to NICE guidelines as a low-energy fracture obtained following a fall from standing height or less, that were treated with TTC nail were included. Patients with a previous fracture of the ipsilateral limb, fibular nails, and pathological fractures were excluded. This review was registered in PROSPERO (ID: CRD42021258893).
- *Results:* A total of 312 ankle fractures were included. The mean age was 77.3 years old. In this study, 26.9% were male, and 41.9% were diabetics. The pooled proportion of superficial infection was 10% (95% CI: 0.06–0.16), deep infection 8% (95% CI: 0.06–0.11), implant failure 11% (95% CI: 0.07–0.15), malunion 11% (95% CI: 0.06–0.18), and all-cause mortality 27% (95% CI: 0.20–0.34). The pooled mean post-operative Olerud–Molander ankle score was 54.07 (95% CI: 48.98–59.16). Egger's test (P=0.56) showed no significant publication bias.
- *Conclusion:* TTC nailing is an adequate alternative option for fragility ankle fractures. However, current evidence includes mainly case series with inconsistent post-operative rehabilitation protocols. Prospective randomised control trials with long follow-up times and large cohort sizes are needed to guide the use of TTC nailing for ankle fractures.

Keywords
- ankle fracture
- tibiotalocalcaneal nailing
- fragility fracture
- ORIF
- meta-analysis

EFORT Open Reviews (2022) **7**, 628–643

Introduction

After the hip and distal radius, ankle fragility fractures (FFs) are the third most common type of fracture in the geriatric population, with an incidence of 184 cases per 100,000 population in the elderly per year (1). Despite occurring following low-energy injuries, ankle FFs lead to disproportionately high morbidity levels (2).

The management of ankle FFs poses specific challenges in the geriatric patient. In addition to being inherently unstable, ankle FFs occur in osteopenic bone, and the fracture-dislocation leads to significant soft tissue stripping (3). Conservative and surgical management options have both been utilised. Compared to surgery, closed contact casting has a reduced risk of infection and wound dehiscence; however, there is a higher risk of radiological malunion (4). The incidence of chronic pain 1 year following non-operative treatment can be as high as 79% (5). Despite a study by Makwana *et al.* reporting an anatomical fixation rate of 86% in patients over 55 (6), open reduction internal fixation (ORIF) have not produced satisfactory outcomes in some studies. Litchfield reported a 22.6% non-union rate (7/31) (7), whilst Beauchamp *et al.* reported a total complication rate of 50.1% and an anatomical fixation rate of 53.5% in patients over the age of 50 (8), which is a rather low cut-off age, especially for patients without comorbidities. Litchfield *et al.* suggested that inactivity is a risk factor for treatment failure, since those who were physically active pre-injury had the best chance of ORIF success (7). Nevertheless, the poor purchase in osteopenic bone and the need to add further soft tissue insult to a traumatised region make ORIF an unattractive option in the comorbid patient.

Tibiotalocalcaneal (TTC) nailing is a viable alternative to ORIF. This involves the insertion of an intramedullary nail through the plantar surface of the calcaneus, subtalar, and tibiotalar joints into the tibial canal. Advantages include its greater mechanical stability and decreased surgical trauma, allowing immediate weight-bearing. This is especially beneficial for the elderly, for whom prolonged periods of non-weight-bearing (NWB) can be challenging, often leading to pressure sores, vascular complications such as deep vein thrombosis, and lengthier hospital stays. Furthermore, the decreased soft tissue disruption with TTC lowers the chance of post-operative complications like surgical site infections, especially in those who are at risk of wound dehiscence or infection (9).

This study aims to provide a comprehensive review with a detailed meta-analysis of the current evidence for using a TTC nail as the primary surgical option to treat fragility ankle fractures in the elderly.

Methods

Search algorithm

This review was carried out according to the 2020 Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) statement protocol (10). A systematic search was performed on Ovid EMBASE, PubMed MEDLINE, Web of Science, and Cochrane Library from inception to 1 December 2021. The search contained variations of the terms 'ankle fragility fracture', 'tibiotalocalcaneal nail', 'elderly', 'outcome'; a detailed search strategy is shown in Supplementary Table 1 (see section on supplementary materials given at the end of this article). A 'snowball' search was performed, whereby references of included studies, and studies that cited any included studies were independently searched, using Google Scholar to identify studies. All studies found by our search were imported into Mendeley and deduplicated. VL and MT independently completed title and abstract screening. A third reviewer (MK) was contacted for unresolvable disagreements.

Full-text screening was performed by VL and MT, based on the inclusion and exclusion criteria shown in Supplementary Table 2. A third reviewer (MK) was consulted for any disagreements. Inclusion and exclusion criteria were determined using the Population, Intervention, Comparison, Outcome, Study type model (11).

Data extraction

Data extraction was independently performed by VL and MT, with a third reviewer (MK) to resolve disagreements. Data were extracted into data tables created in a standardised excel spreadsheet for evidence synthesis and risk of bias analysis. Data from each study were split into six categories:

1. Study characteristics
2. Patient demographics
3. Patient selection
4. Intra-operative details
5. Clinical and functional outcomes
6. Post-operative complications

Missing data were retrieved by contacting the corresponding author of each study.

Data analysis

Quantitative data that were comparable across studies were selected for meta-analysis. This included post-operative complications and clinical outcomes such as percentage returned to pre-injury mobility and all-cause mortality. Extracted numerical data were rounded to three significant figures.

Meta-analyses were carried out using RStudio version 4.0.5 through the 'metafor' package (12). As we anticipated some between-study heterogeneity, a random-effects model was used. To pool effect sizes, the inverse-variance weighting method was used. For continuous data, the Wan *et al.* estimator (13) was used where mean ± s.d. was not given in the manuscript.

Knapp–Hartung adjustments were made when calculating the CI of pooled effect sizes, to reduce the chance of false positives (14). Higgins and Thompson's I^2 statistic (15) and Cochran's Q test (16) were used as measures of heterogeneity. Given the intrinsic limitations with Cochran's Q test and the I^2 statistic (17, 18), prediction intervals were also included to provide a range into which future studies' effect size can be expected to fall into. Subgroup analyses were performed according to (1) use of ankle fusion nail vs use of non-ankle fusion nails adapted for use in the ankle, (2) open vs closed fractures, (3) immediate post-operative full weight-bearing (FWB) vs post-operative NWB, and (4) majority of cohort are diabetics vs minority of cohort are diabetics. The Q test was used to determine if there is a difference in the true effect sizes between subgroups. A meta-regression was carried out using the REML estimator to determine how much of the heterogeneity variance various covariates can explain. Publication bias will be assessed using a funnel plot and Egger's test. For all analyses, a value of $P < 0.05$ was used to determine statistical significance.

Risk-of-bias assessment was carried out independently by VL and MT using Cochrane's RoB 2.0 tool for randomised trials containing five domains (19) and the methodological index for non-randomised studies (MINORS (Methodological Index for Non-Randomized Studies) tool) (20).

This review was prospectively registered in the International Prospective Register of Systematic Reviews PROSPERO (ID: CRD42021258893).

Results

A total of 1282 studies were identified from database searching. After deduplication, 1161 studies were identified for title and abstract screening, from which 125 full-text studies were reviewed. Thirteen studies were eligible for data synthesis. Searching studies that cited any of the included studies as well as references of the included studies yielded one extra study for inclusion, giving a total of 14 for qualitative and quantitative synthesis. To estimate interobserver reliability, a kappa coefficient of 0.84 was obtained, suggesting excellent agreement between reviewers. Twelve studies were retrospective case series (1, 2, 3, 21, 22, 23, 24, 25, 26, 27, 28, 29), one was a prospective case series (30), and one was a randomised control trial (31). Figure 1 presents a PRISMA flowchart.

Patient demographics

Table 1 presents the study characteristics and patient demographics. Seven studies were performed in the UK (2, 3, 22, 23, 24, 25, 28) and the majority were published in the last 5 years (1, 3, 21, 25, 26, 27, 28, 30, 31). Apart from 2 studies (22, 30), all studies collected patient data over a span of at least 3 years. A total of 312 fragility ankle fractures in 311 patients were included. The mean age was 77.3 years. A total of 84 patients (26.9%) were male and 228 (73.1%) were female. One study only included female patients (22). Fragility ankle fractures were defined as fractures that result from mechanical forces that would not ordinarily result in fracture, known as low-level (or 'low energy'), according to the National Institute for Health and Care Excellence (NICE) guidelines (32). NICE defines these fractures as those that occur 'following a fall from standing height or less' (33). Only two studies reported BMI data (27, 28) and two studies reported smoking data (3, 28). The majority of fractures were closed (76.5%), with four studies including only closed fracture patients (2, 22, 29, 31). Despite an average of 23.5% of patients acquiring open fractures, patients sustained low-energy fractures, satisfying the NICE guideline's definition for FFs.

Eight studies reported the number of diabetics (1, 2, 3, 21, 23, 26, 27, 28), with an average of 41.9%. One study included only diabetics in their study group (27). Since this study focused on ankle fractures in the geriatric population, we would assume that all study cohorts had some degree of comorbidity, yet only six studies reported comorbidities (3, 21, 23, 25, 28, 30). Lu *et al.* utilised the CCI, which gives a comorbidity-age combined risk score (28). Follow-up time was provided by all studies apart from 3 (3, 23, 30), giving a mean of 18.5 months.

Intra-operative details

A hindfoot fusion/arthrodesis nail was used in six studies (1, 2, 26, 27, 28, 31), with the remaining utilising other types of nails such as a humeral nail (24), femoral nail (23, 25, 30), Gallagher nail (29), and an expandable nail (22) (Table 2). Joint preparation was only performed in one study (28). Five studies reported the total operative time, with a mean of 86.7 min (1, 21, 26, 27, 28). Seven studies reported the length of hospital stay, with a mean of 9.86 days (3, 21, 26, 27, 28, 30, 31). In the RCT performed by Georgiannos *et al.*, a significantly shorter hospital stay

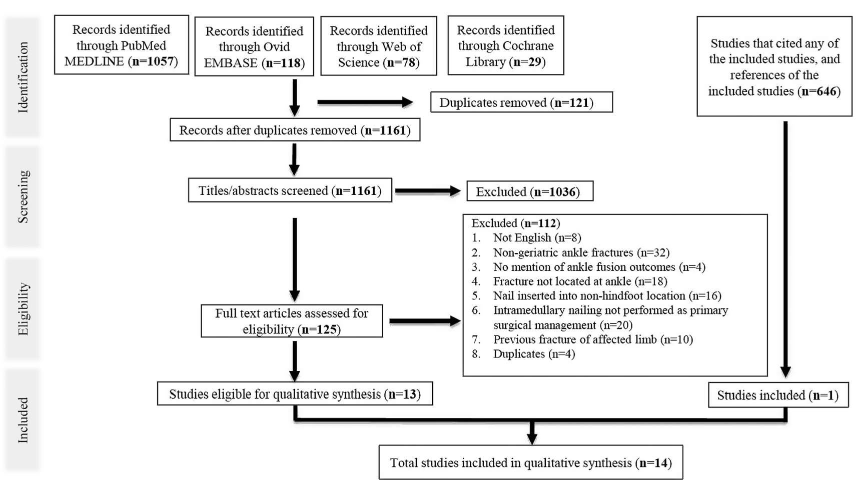

Figure 1
PRISMA flowchart.

Table 1 Study characteristics and patient demographics.

Reference	Study type	Country	Years studied	Ankle number	MeanAge	Male, *n* (%)	BMI	Smoker (%)	Diabetics (%)	Follow-up time (months)	Comorbidities (mean *n*)
Al-Nammari *et al.* (23)	RCS	UK	2010–2013	48	82	7 (14.6)	N/A	N/A	15 (31.3)	N/A	3.3
Amirfeyz *et al.* (24)	RCS	UK	1999–2005	13	78.9	1 (7.7)	N/A	N/A	N/A	11	N/A
Armstrong *et al.* (3)	RCS	UK	2011–2016	21	76	3 (14.3)	N/A	2 (9.5)	5 (23.8)	N/A	2.9
Baker *et al.* (25)	RCS	UK	2014–2017	16	73	4 (25)	N/A	N/A	N/A	21	4
Ebaugh *et al.* (27)	RCS	USA	2010–2017	27	66	20 (74.1)	38 (21–68)	N/A	27 (100)	29	N/A
Georgiannos *et al.* (31)	RCT	Greece	2009–2015	43	78	13 (30.2)	N/A	N/A	N/A	14	N/A
Herrera-Pérez *et al.* (1)	RCS	Spain	2016–2019	17	81.5	1 (5.9)	N/A	N/A	11 (64.7)	20.9	N/A
Jonas *et al.*(2)	RCS	UK	2008–2011	31	77	10 (32.3)	N/A	N/A	8 (25.8)	18	N/A
Kulakli-Inceleme *et al.* (26)	RCS	Switzerland	2015–2019	10	85.2	1 (10)	N/A	N/A	1 (10)	11.2	N/A
Lemon *et al.* (22)	RCS	UK	2002–2003	12	84	0	N/A	N/A	N/A	15.4	N/A
Lu *et al.* (28)	RCS	UK	2015–2020	20	77.8	7 (35)	30.1 (16.7–49.5)	2 (10)	5 (25)	16.4	5.05*
O'Daly *et al.* (29)	RCS	Ireland	1996–2005	9	80.1	1 (11.1)	N/A	N/A	N/A	34	N/A
Persigant *et al.* (30)	PCS	France	2014–2016	14	79.6	2 (14.3)	N/A	N/A	N/A	N/A	2.4
Taylor *et al.* (21)	RCS	USA	2006–2012	31	63	14 (45.2)	N/A	N/A	17 (54.8)	13.4	1.3

*Mean Charlson Comorbidity Index.
N/A, not mentioned in study; PCS, prospective cohort study; RCS, retrospective cohort study; RCT, randomised control trial.

was found in the TTC cohort than ORIF cohort (5.2 vs 8.4 days; $P < 0.001$) (31).

Outcomes and complications

The average time to weight-bearing and union was 22.2 weeks and 15.7 weeks, respectively (Table 3). Only Lu *et al.* provided a formal definition of union, namely the presence of bridging callus on anterior-posterior (AP) and lateral X-ray views, and painless FWB (28). Nine studies allowed immediate post-operative FWB (1, 2, 21, 22, 23, 28, 29, 30, 31), whilst the other five required patients to undergo a period of NWB (3, 24, 25, 26, 27). Pre-operative Olerud–Molander ankle scores (OMAS) were reported in five studies (1, 2, 22, 23, 31), and post-operatively in seven studies (1, 2, 22, 23, 24, 28, 31). OMAS was measured on a 0–100 scale, with lower scores indicating inferior ankle function. The pooled mean post-operative OMAS and standard mean difference between the pre-operative and post-operative OMAS are 54.07 (95% CI: 48.98–59.16; $I^2 = 85\%$) and −0.88 (95% CI: 0.50–1.25; $P = 0.001$), respectively (Fig. 2A and B). Both the Foot and Ankle Outcome Score (26) and Parker score (30) were used in one study each. The former consists of 42 items on a scale of 0–100, with a lower score indicating worse function; the latter assesses mobility prior to fracture on a scale of 0–9, with a lower score indicating worse function. The pooled proportion for return to pre-operative mobility was 71% (95% CI: 0.6–0.8) (Fig. 2C).

Table 4 shows the complication profile. Surgical infection was reported in all 14 studies and had a pooled proportion of 13% (95% CI: 0.09–0.19; $I^2 = 25\%$) (Fig. 3A). Thirteen studies reported on superficial infection, with a pooled proportion of 10% (95% CI: 0.06–0.16; $I^2 = 44\%$) (Fig. 3B), and 12 studies reported on deep infection, with a pooled proportion of 8% (95% CI: 0.06–0.11, $I^2 = 0\%$) (Fig. 3C). Implant failure was reported in 11 and had a pooled proportion of 11% (95% CI: 0.07–0.15, $I^2 = 0\%$) (Fig. 3D). Implant failure was defined as broken/loose screws, nail breakages, or nail protrusions.

Twelve studies reported on malunion/non-union, with a pooled proportion of 11% (95% CI: 0.06–0.18; $I^2 = 51\%$) (Fig. 3E). Only Kulakli-Inceleme *et al.* (26) and Persigant *et al.* (30) provided a detailed definition of non-union and malunion, respectively.

Eleven studies reported patients returning to the operating theatre, with a pooled proportion of 12% (95% CI: 0.07–0.19, $I^2 = 19\%$) (Fig. 3F). This was usually as a consequence of deep infection requiring debridement, implant failure requiring removal, or peri-prosthetic fractures requiring re-fixation and revision nailing. Patients passed away in six studies due to medical complications (22, 23, 24, 25, 27, 31), including pneumonia occurring from 35 days (24) to 6 months post-surgery (23), and

Table 2 Intra-operative details.

Reference	Prosthesis	Nail diameter (mm)	Joint preparation	ASA grade	Fracture classification	Operative time (min)	Hospital stay (days)
Al-Nammari *et al.* (23)	T2 retrograde femoral nailing system	N/A	No	3	Lauge–Hansen classification: 35 (73%) supination–external rotation; 9 (19%) pronation–external rotation; 4 (8%) pronation–abduction	N/A	N/A
Amirfeyz *et al.* (24)	ACE retrograde locked intramedullary humeral nail and VersaNail Humeral Universal Nailing System	N/A	No	N/A	AO/OTA classification: 44B2, 44B3, or 44C	N/A	N/A
Armstrong *et al.* (3)	T2 Ankle Arthrodesis Nail (10 patients); VersaNail Humeral Nail (9 patients); Hindfoot Arthodesis Nail (2 patients)	10–12	No	N/A	N/A	N/A	18
Baker *et al.* (25)	T2 Stryker supracondylar femoral nail	11	No	3	AO/OTA: 43A1 (7 patients); 43A3 (1 patient); 44A1 (2 patients); 44A2 (2 patients); 44B2 (2 patients); 44B3 (1 patient); 44C2 (1 patient)	N/A	N/A
Ebaugh *et al.* (27)	Phoenix Ankle Arthrodesis Nail	N/A	No	N/A	N/A	73 (43–108)	6 (0–22)
Georgiannos *et al.* (31)	Trigen hindfoot fusion nail	N/A	No	N/A	Lauge–Hansen classification: 10 (22.7%) supination–abduction; 33 (76.7%) supination–external rotation	N/A	5.2
Herrera-Pérez *et al.* (1)	Expert Hindfoot Arthrodesis Nail	10	No	2.1	N/A	48 (35–93)	N/A
Jonas *et al.* (2)	Trigen hindfoot fusion nail	N/A	No	N/A	AO/OTA: 43A1 (4 patients); 44A2 (1 patient); 44B2 (17 patients); 44C1 (3 patients); 44B3 (5 patients); 44C1 (1 patient)	N/A	N/A
Kulakli-Inceleme *et al.* (26)	T2 Ankle Arthrodesis Nail (7 patients) Expert Hindfoot Arthrodesis Nail (3 patients)	10 (4 patients); 11 (3 patients); 12 (3 patients)	No	2.7	AO/OTA: 44B2 (1 patient); 44B3 (6 patients); 44C1 (2 patients); 44C3 (1 patient)	104.6 (71–136)	15.4 (9–22)
Lemon *et al.* (22)	Fixion IM expandable intramedullary nail	8.5 (expanded to 13.5)	No	N/A	N/A	N/A	N/A
Lu *et al.* (28)	OxBridge Ankle Fusion Nail	10	Yes (17 patients); No (3 patients)	2.4	AO/OTA: 43C1 (1 patient); 44A2 (4 patients); 44B1 (1 patient); 44B2 (5 patients); 44C1 (9 patients)	131.2 (68–227)	10.8 (2–31)
O'Daly *et al.* (29)	Gallagher nail	4.7 (expanded to 9.5)	No	N/A	N/A	N/A	N/A
Persigant *et al.* (30)	T2 femoral nail	N/A	No	2.6	N/A	N/A	6
Taylor *et al.* (21)	Phoenix Ankle Arthrodesis Nail (29 patients); Retrograde supracondylar femoral nail (2 patients)	N/A	No	N/A	N/A	76.7 (43–140)	7.6 (1–16)

myocardial infarction occurring from 24 days (22) to 5 months (23) post-surgery. The pooled proportion all-cause mortality was 27% (95% CI: 0.20–0.34; I^2 = 11%) (Fig. 3G). The pooled proportion of all surgical complications was 28% (95% CI: 0.20–0.39; I^2 = 60%) (Fig. 3H).

Subgroup analyses

A subgroup analysis of open vs closed fracture studies shows that the rate of infection is lower in the latter (P=0.0002) (Table 5). Studies with a diabetic population of over 50% have a higher rate of infection (P=0.0096) than studies with a diabetic population below 50%.

Studies with diabetics in the majority also had a higher rate of implant failure (P=0.034). Although the proportion of patients returning to their pre-operative mobility was high in all studies, the value was higher in studies with a diabetic population below 50% compared with studies with a diabetic population of over 50% (P=0.039) (Table 6).

A subgroup analysis of studies that used an ankle fusion nail vs studies that adapted other nails for use in the ankle

Table 3 Clinical and functional outcomes.

Reference	Pre-operative OMAS	Post-operative OMAS	All-cause mortality (%)	Time to weight-bearing in weeks (range)	Allowed immediate post-op FWB	Returned to pre-injury mobility (%)	Time to union in weeks (range)
Al-Nammari *et al.* (23)	62 (40–80)	57 (35–70)	17 (35.4)	15 (0–52)	Yes	28 (90%)	9 (6–14)
Amirfeyz *et al.* (24)	N/A	50 (30–65)	5 (38.5)	N/A	No (PWB for 6 weeks then FWB)	9 (69.2)	N/A
Armstrong *et al.* (3)	N/A	N/A	4 (19)	19.3 (7–49)	No (NWB for 2 weeks then FWB)	N/A	N/A
Baker *et al.* (25)	N/A	N/A	4 (25)	N/A	No (NWB for 7–10 days then FWB)	16 (100)	N/A
Ebaugh *et al.* (27)	N/A	N/A	8 (29.6)	46.9 (7–119)	No (NWB until plantar wound healed then FWB)	22 (81.5)	18 (6–60)
Georgiannos *et al.* (31)	63.4 (S.D. 8.3)	56.9 (S.D. 9.8)	6 (14)	N/A	Yes	28 (75.6)	N/A
Herrera-Pérez *et al.* (1)	64.1 (55–75)	55.3 (45–65)	2 (11.8)		Yes	15 (88.2)	N/A
Jonas *et al.* (2)	56.6 (35–80)	44.8 (25–75)	9 (29)	N/A	Yes	29 (93.5)	12 (3–36)
Kulakli-Inceleme *et al.* (26)	N/A	N/A	4 (40)		No (NWB for 6 weeks then FWB)	5 (50)	N/A
Lemon *et al.* (22)	69.6 (55–75)	61.4 (50–75)	4 (33.3)	N/A	Yes	9 (81.8)	N/A
Lu *et al.* (28)	N/A	50.9 (20–85)	3 (15)	7.6 (2–24)	Yes	13 (65)	17.2 (13.2–20.7)
O'Daly *et al.* (29)	N/A	N/A	N/A	N/A	Yes	6 (66.7)	N/A
Persigant *et al.* (30)	N/A	N/A	N/A	N/A	Yes	N/A	N/A
Taylor *et al.* (21)	N/A	N/A	N/A	N/A	Yes	N/A	22.2 (S.D. 6.2)

FWB, full weight-bearing; NWB, non-weight-bearing; N/A, not mentioned in study.; OMAS, Olerud–Molander score.

showed that the rate of malunion was lower in the former. Studies using an ankle fusion nail also had a lower rate of implant failure than those that did not. Subgroup analyses of studies that allowed immediate post-operative FWB vs those that did not fail to reveal any significant results. No significant difference was found between subgroups when comparing the pre-injury and post-operative OMAS differences (Table 6).

Meta-regression

Meta-regression analyses were done to explore sources of heterogeneity. Mean age was the only covariate that fit the regression model for post-operative OMAS (P=0.0423). Furthermore, a regression model using mean age and percentage of male patients as covariates produced an even stronger relationship (P=0.026). This was verified by the ANOVA model test, with an Akaike's information criterion of 36.88 for the full model and 42.2963 for the reduced model (Table 7).

Risk of bias

Publication bias was assessed with the funnel plot (Fig. 4). Egger's test (P=0.56, intercept=0.54; 95% CI=−1.23 to 2.31) showed no statistically significant asymmetry in the funnel plot.

Risk of bias assessment was performed using the MINORS tool for each non-randomised study (Table 8A). The average score was 51.9% (31.3–68.8%). Only Persigant *et al.* performed prospective data collection (30). Although all studies besides one (29) stated some sort of aim, this was only properly done in two recently published studies (26, 28). Risk of bias assessment for the only randomised study in this review (31) was performed using the RoB 2.0 tool, giving an overall low risk of bias (Table 8B).

Discussion

This meta-analysis provides an in-depth analysis regarding the use of TTC nails for the treatment of fragility ankle fractures, evaluating patient selection, intra-operative variables, post-operative complications, patient reported outcome measures (PROMs), and mobility status. The overall complication rate was 28%, with 71% being able to return to their pre-operative mobility status. These results are favourable compared with conservative treatment, which reports a non-union rate of 48–73% (7, 8, 34, 35). Retrospective studies have reported that ORIF resulted in chronic pain in 56% of patients (5) and malunion in 19% (34). Makwana *et al.* performed an RCT between ORIF and conservative treatment of ankle fractures in patients above 55, which showed significantly higher post-operative OMAS (P=0.03) and increased accuracy of reduction

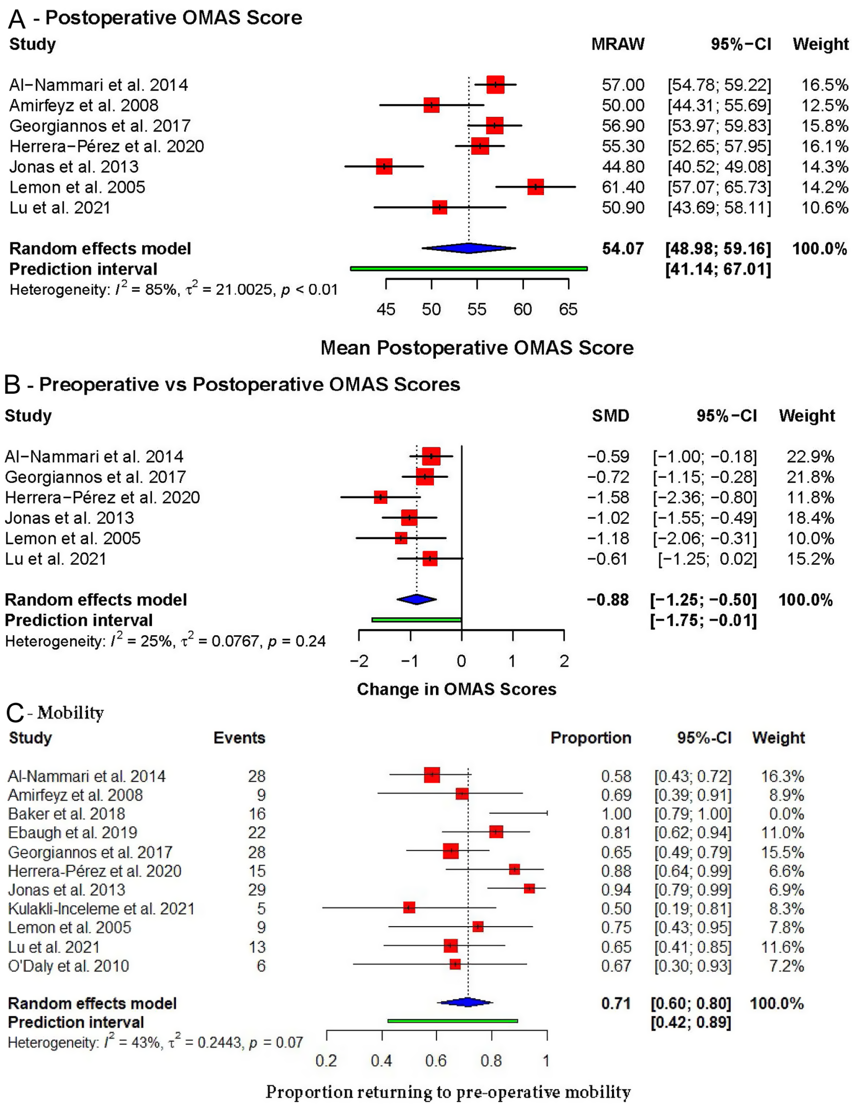

Figure 2

(A) Pooled mean post-operative OMAS. (B) Pooled standard mean difference between pre-injury and post-operative OMAS. (C) Overall proportion of return to pre-injury mobility status.

in the ORIF cohort (*P*=0.03); however, the length of inpatient stay (*P*=0.01) and post-operative complications were greater in the ORIF cohort. Davidovitch *et al.* reported that in the absence of systemic comorbidities, the outcomes after ORIF for patients below and above 60 years old were similar; however, conservative treatment showed significantly inferior outcomes (36).

In addition to conservative treatment and ORIF performed according to the Association for Osteosynthesis/Association for the Study of Internal Fixation (AO/ASIF) manual (37), other joint preserving techniques have been described in a recent review (38). The trans-syndesmotic fixation technique is useful in osteoporotic patients, diabetic patients, and those with syndesmotic instability. It employs a 'tibia pro fibula' technique, which utilises the tibia for increased fibular fixation stabilisation (38). Fixation can be augmented by bone cements such as polymethylmethacrylate or calcium phosphate cement, which can be loaded with antibiotics (39).

With 9 out of 14 included studies published in the last 5 years, this represents a significant increase in interest in the use of TTC nailing for ankle fracture management. In addition to satisfying the NICE guideline's criteria for an FF, namely one that is caused by a low-energy mechanism such as a fall from standing height or less, many studies have outlined further indications for inclusion, namely elderly patients over 60 years (1, 24, 28, 30, 31), poor bone quality verified by radiological evidence of osteopenia or a history of FFs (1, 23, 24, 28, 30), poor pre-operative mobility (2, 23, 25, 30), and unstable fracture pattern defined by a medial clear space ≥ 5 mm on anteroposterior radiographs taken in dorsiflexion (28).

Table 4 Post-operative complications.

Reference	Superficial infection (%)	Deep infection (%)	All infections (%)	Implant failure	Malunion or non-union	Amputation (%)	Periprosthetic fracture (%)	Unplanned secondary surgery (%)	Other post-operative complications
Al-Nammari *et al.* (23)	2 (4.2)	1 (2.1	3	3 (6.3)	2 (4.2)	1 (2.1)	0	3 (6.3)	9 cases of pneumonia; 5 cases of MI
Amirfeyz *et al.* (24)	1 (7.7)	0	1	N/A	1 (7.7)	N/A	N/A	1 (7.7)	1 case of pneumonia
Armstrong *et al.* (3)	6 (28.6)	0	6	0	N/A	0	N/A	1 (4.8)	Failure of SSG graft
Baker *et al.* (25)	0	0	0	0	N/A	N/A	0	N/A	1 case of pneumonia
Ebaugh *et al.* (27)	1 (3.7)	3 (11.1)	4	3 (11.1)	3 (11.1)	2 (7.4)	N/A	4 (14.8)	2 cases of pneumonia
Georgiannos *et al.* (31)	1 (2.3)	N/A	1	1 (2.3)	1 (2.3)	N/A	N/A	1 (2.3)	1 case of DVT
Herrera-Pérez *et al.* (1)	1 (5.9)	0	1	1 (5.9)	1 (5.9)	N/A	0	1 (5.9)	None
Jonas *et al.* (2)	0	0	0	4 (12.9)	8 (19.4)	N/A	3	6 (19.4)	None
Kulakli-Inceleme *et al.* (26)	1 (10)	N/A	1	2 (20)	3 (30)	0	N/A	3 (30)	None
Lemon *et al.* (22)	0	0	0	N/A	0	N/A	N/A	N/A	1 case of myocardial infarction and 1 case of DVT
Lu *et al.* (28)	4 (20)	0	4	4 (20)	0	0	0	4 (20)	None
O'Daly *et al.* (29)	0	0	0	N/A	0	N/A	NA	N/A	None
Persigant *et al.* (30)	N/A	1 (7.1)	1	1 (7.1)	0	N/A	N/A	1 (7.1)	None
Taylor *et al.* (21)	2 (6.5)	3 (9.7)	5	3 (9.7)	3 (9.7)	1 (3.2)	N/A	3 (9.7)	None

DVT, deep vein thrombosis; MI, myocardial infarction; N/A, not mentioned in study; SSG, split thickness skin graft.

Implant failure

The pooled proportion of implant failure was 11% (95% CI: 0.07–0.15) and was commonly caused by locking screw and nail breakage (2, 21, 23, 26, 27, 28, 30, 31). Ruiz *et al.* pointed out three factors that are likely to result in implant failure: open fractures, small diameter nail, and the usage of only one proximal locking screw (40). In their cohort, the median nail diameter that failed and did not fail was 9 mm and 11 mm, respectively. In our included studies, all nails were 10 mm or above, apart from 2 cohorts that received a Gallagher nail (29) and a Fixion intramedullary (IM) expandable intramedullary nail (22). The former is a 4.7-mm diameter nail, whose proximal end can be expanded as a threaded screw to 9.5 mm in diameter. The latter is a 8.5-mm diameter nail expanded to a maximum of 13.5 mm. The Gallagher nail used by O'Daly *et al*. (29) and Fixion IM used by Lemon *et al*. (22) lack proximal or distal interlocking screws. The Fixion IM is marketed as being self-locking; however, later versions of the nail were developed to include proximal and distal locking screws. The small diameter of the Gallagher nail and lack of locking screws with Fixion IM could have contributed to a less stable fixation; however, both studies failed to report whether or not implant failure was observed. Subgroup analysis of implant failure based on studies whose nail diameter was 10 mm or lower vs those with a nail diameter above 10 mm revealed no significant correlation.

The only study that included only open fractures in their cohort (3) reported no cases of implant failure. Furthermore, the study with the highest proportion of implant failure had 90% closed fracture cohort (26). Most papers did not report the number of proximal locking screws used, but some can be inferred from radiographs included in the manuscript (3, 23). Two proximal locking screws were used, apart from the study that utilised an expandable nail (22), which does not rely on interlocking screws, and achieves axial and rotational stability after nail expansion (41). Studies have suggested that a three non-locking screw configuration may have stronger biomechanical performance; however, a case–control study showed that two interlocking screws are biomechanically comparable to three non-locking screws in osteoporotic bone (42).

Subgroup analysis showed that studies that included a majority of diabetics had a significantly higher proportion of implant failure than studies that included a minority of diabetics. Diabetic-induced impaired osseointegration is known in the literature; however, the underlying mechanisms are more obscure. Studies show that there could be an unfavourable microenvironment in the diabetic host at the implant–tissue interface (43). Especially with nails made from a titanium alloy (Ti-6Al-4V) such as the OxBridge Ankle Fusion Nail

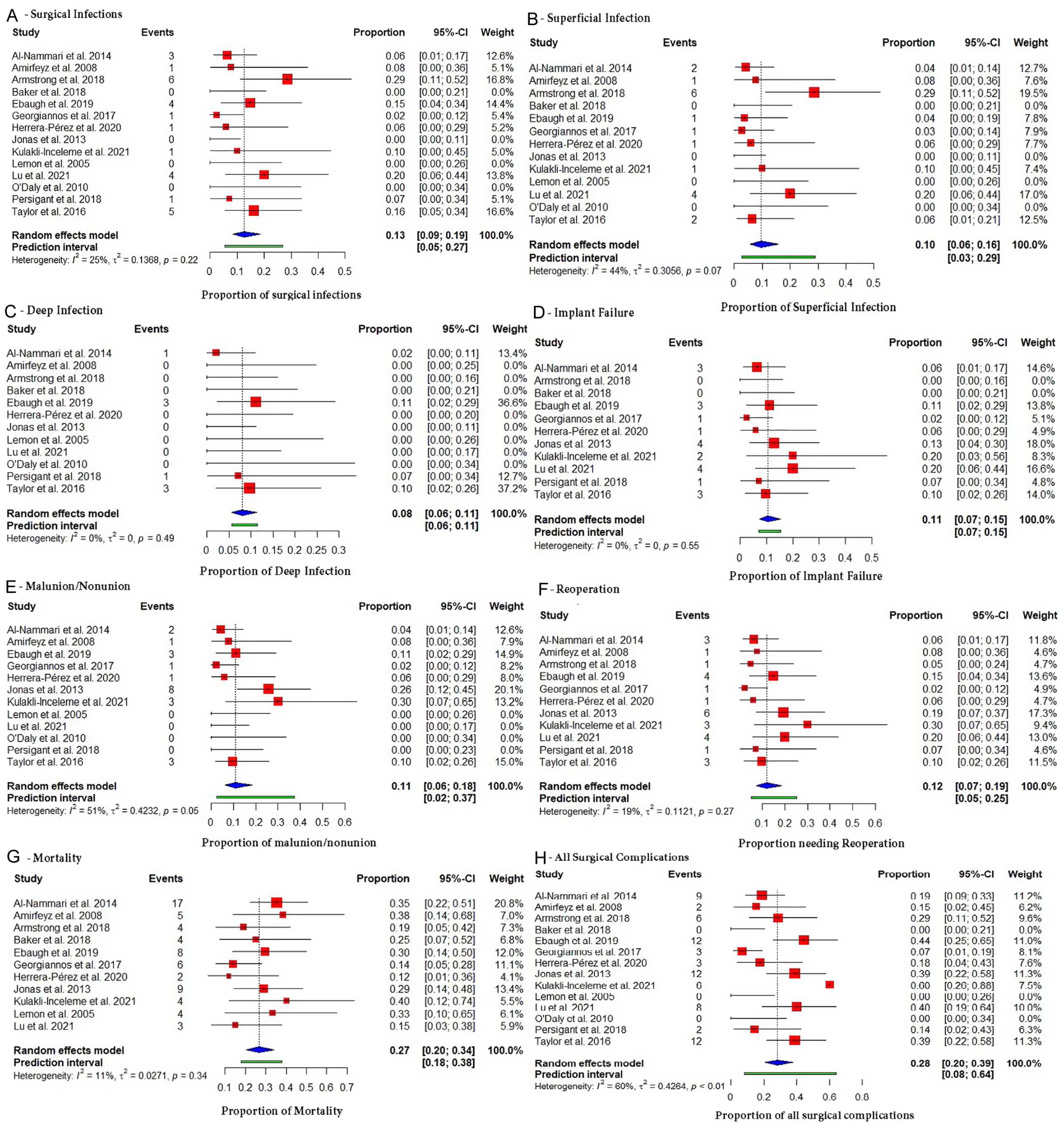

Figure 3

(A) Overall proportion of surgical infection. (B) Overall proportion of superficial infection. (C) Overall proportion of deep infection. (D) Overall proportion of implant failure. (E) Overall proportion of malunion/non-union. (F) Overall proportion of reoperation. (G) Overall proportion of mortality. (H) Overall proportion of total surgical complications.

(28), the oxide form, oxidation and corrosion are major concerns in diabetics, due to the acidic microenvironment and increased reactive oxygen species production (44). The resulting corrosion products have a significant bearing on the biocompatibility and long-term stability of implants (45).

A higher proportion of ankles treated with a non-ankle fusion nail used 'off-label' have implant failure than those that used nails specific for hindfoot stabilisation. Furthermore, short nails that do not cross the tibial isthmus were assumed to lead to periprosthetic fractures (9), yet two of the earliest studies (22, 24) that utilised

Table 5 Subgroup meta-analyses of association between TTC nailing and post-operative complications by study variables. Bold values indicate a *P* value <0.05.

	Number of studies	Number of ankles	Proportion (95% CI)	Prediction interval	I^2	$P_{subgroup}$
Infection						
Type of nail						0.1441
Ankle fusion nail	6	148	0.1216 (0.0567; 0.2418)	(0.0533; –0.2542)	0	
Non-ankle fusion nail	6	112	0.0669 (0.0605; 0.0739)	(0.0600; 0.0745)	0.194	
Post-op weight-bearing status						0.0666
FWB	9	225	0.1002 (0.0571; 0.1699)	(0.0342; 0.2592)	0.261	
NWB	5	87	0.1842 (0.0938; 0.3300)	(0.0844; 0.3562)	0.001	
Open/closed fracture						**0.0002**
Open	2	30	0.2465 (0.0168; 0.8626)	N/A	0.066	
Closed	4	95	0.0984 (0.0681; 0.1402)	(0.0678; 0.1408)	0	
Diabetes						**0.0096**
>50% of cohort	3	75	0.3046 (0.0020; 0.9896)	N/A	0.411	
≤50% of cohort	5	130	0.1089 (0.0656; 0.1754)	(0.0362; 0.2848)	0.364	
Malunion						
Type of nail						**0.0265**
Ankle fusion nail	6	148	0.0532 (0.0349; 0.0803)	(0.0054; 0.3692)	0.57	
Non-ankle fusion nail	5	96	0.1383 (0.0485; 0.3356)	(0.0151; 0.6272)	0	
Post-op weight-bearing status						0.2591
FWB	9	225	0.0868 (0.0419; 0.1713)	(0.0126; 0.4150)	0.193	
NWB	3	50	0.1547 (0.0234; 0.5833)	(0.0001; 0.9971)	0.649	
Diabetes						0.1367
>50% of cohort	3	75	0.0955 (0.0497; 0.1754)	(0.0131; 0.4554)	0	
≤50% of cohort	4	109	0.1883 (0.0446; 0.5351)	(0.0036; 0.9363)	0.594	
Implant failure						
Type of nail						**0.0133**
Ankle fusion nail	6	148	0.0646 (0.0635; 0.2295)	(0.0541; 0.0770)	0.063	
Non-ankle fusion nail	3	78	0.1244 (0.0541; 0.0770)	(0.0635; 0.2295)	0	
Post-op weight-bearing status						0.2125
FWB	7	204	0.0981 (0.0550; 0.1687)	(0.0534; 0.1732)	0	
NWB	4	74	0.1395 (0.0805; 0.2310)	(0.0658; 0.2717)	0	
Diabetes						**0.0340**
>50% of cohort	3	75	0.2197 (0.0009; 0.9884)	N/A	0.347	
≤50% of cohort	5	130	0.0897 (0.0575; 0.1371)	(0.0569; 0.1386)	0	

Table 6 Subgroup meta-analyses of association between TTC nailing, mobility, and OMAS scores by study variables. Bold values indicate a *P* value <0.05.

	Number of studies	Number of ankles	Proportion (95% CI)	Prediction interval	I^2	$P_{subgroup}$
Return to pre-injury mobility status						
Type of nail						0.1422
Ankle fusion nail	6	148	0.7571 (0.5369; 0.8934)	(0.2272; 0.9706)	0.6	
Non-ankle fusion nail	5	98	0.6311 (0.5379; 0.7153)	(0.5239; 0.7267)	0	
Post-op weight-bearing status						0.7582
FWB	7	180	0.7244 (0.5575; 0.8458)	(0.3380; 0.9312)	0.511	
NWB	4	66	0.6951 (0.4274; 0.8744)	(0.1164; 0.9753)	0.416	
Diabetes						**0.0385**
>50% of cohort	3	75	0.7110 (0.5682; 0.8213)	N/A	0	
≤50% of cohort	5	130	0.8124 (0.7345; 0.8715)	(0.3454; 0.9198)	0.483	
Difference between pre-injury and post-operative OMAS scores*						
Type of nail						0.4868
Ankle fusion nail	4	111	0.8772 (0.3348; 1.4196)†	(0.1438; 1.6105)	0.308	
Non-ankle fusion nail	2	60	0.6875 (−2.0196 to 3.3946)†	N/A	0.213	

*Only six studies reported pre- and post-injury OMAS scores, from which detailed information about open fracture and diabetic patients can only be obtained from one study, precluding any subgroup analyses. All six studies allowed immediate post-operative FWB, also precluding subgroup analyses; †standard mean difference (95% CI).

Table 7 Meta-regression analyses of select co-variates for post-operative OMAS scores. Bold values indicate a *P* value <0.05.

Co-variate	I^2 (residual heterogeneity)	R^2 (heterogeneity explained)	Test of moderators (*P*-value)	Regression weight (95% CI)	Standard error
Age	0.6747	0.6737	**0.0423**	−1.5983 (−3.1142 to 0.0824)	0.5897
Sample size	0.8505	0.0048	0.9064	0.0202 (−0.4004 to 0.4409)	0.1636
% Male	0.8556	0.0114	0.8246	−0.0228 (−0.2740 to 0.2284)	0.0977
% Closed fracture	0.8629	0.0619	0.5914	0.0391 (−0.1364 to 0.2147)	0.0683
Publication year	0.8641	0.0319	0.7045	−0.01686 (−1.2471 to 0.9100)	0.4196
Age and % male	0.0554	0.9907	**0.0263**		
Age			0.0106	−2.4996 (−4.0326 to 0.9665)	0.5522
% Male			0.0408	−0.1524 (−0.2944 to −0.0103)	0.0512

short nails reported no periprosthetic fractures. However, small sample size and short follow-up time could be confounding factors.

Infection

The pooled proportion of all surgical infections in included studies was 13% (95% CI: 0.09–0.19). This is likely to be confounded by studies that included open fractures since they are associated with an increased infection risk due to wound contamination and significant soft tissue injury (46). Our subgroup analysis shows a significant difference in the proportion of surgical infections between an open fracture cohort (3, 28) and a closed fracture cohort ($P = 0.0002$) (2, 22, 29, 31). There was only one case of infection amongst 95 ankle fractures in the 4 studies that only included closed fractures, which was reported in the RCT performed by Georgiannos *et al.* (31) The percentage of infections in their ORIF cohort was over five-fold greater (13.8% vs 2.7%). Studies utilising ORIF mentioned that the rate of infection is correlated with the ability to comply with post-operative NWB status (7, 8, 47), with Fong *et al.* reporting a deep infection rate of 12% decreasing to 0% after removing non-compliant patients from analysis (47). However, our subgroup analyses did not find a significant difference in the pooled proportion of surgical infection between studies that allowed immediate post-operative FWB and studies that insisted on a period of post-operative NWB.

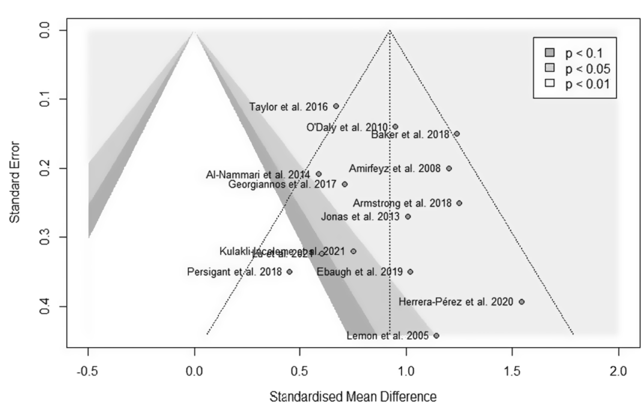

Figure 4
Contour-enhanced funnel plot for publication bias.

Subgroup analysis of studies with a majority of diabetics has a higher pooled proportion of infection than studies with a minority of diabetics ($P = 0.0096$). Apart from the study that included only open fractures (3), the two studies with the highest rate of surgical infections also contained the highest percentage of diabetics (21, 27). The hyperglycaemic environment favours immune dysfunction, and the infection itself can be a precipitating factor for inherent complications, in a vicious cycle that increases morbimortality (48). Nevertheless, the pooled rate of infection in diabetics is still lower than in studies utilising ORIF, which was reported to be as high as 50% (49). This could be because TTC nailing utilises small 1–2 cm incisions and avoids s.c. implants, with the nail being embedded in the medullary canal of the bone and locked proximally and distally. Nevertheless, increased post-operative wound care is still needed for diabetics who undergo TTC nailing to avoid surgical infections.

Malunion/non-union, joint preparation, and arthritis

One disadvantage of hindfoot fusion is the need to disturb the unprepared subtalar joint. Only one study included patients that had undergone formal joint preparation prior to nail insertion, i.e. cartilage was denuded down to the subchondral bone (28). Four studies specifically mentioned that the joints were not prepared (3, 24, 25, 27). Joint preparation is one of the most important modifiable factors influencing non-union rates (50). Yet some surgeons felt that formal joint preparation would devascularise the talar fragments and increase surgical insult, leading to an increased risk of wound healing complications, in exchange for arthrodesis union that is hard to achieve in a comorbid host (28). The low pooled proportion of fracture malunion/non-union (0.11; 95% CI: 0.06–0.18) could suggest that joint preparation may not be necessary for the low-demand geriatric patient. Furthermore, treatment is not indicated for asymptomatic non-union, as the nail will continue to act as a sturdy internal splint (9). Nevertheless, there was insufficient follow-up time in most studies to obtain a robust conclusion, and

Table 8 Risk of bias analysis.

	(23)	(24)	(3)	(25)	(27)	(1)	(2)	(26)	(22)	(28)	(29)	(30)	(21)	(31)
A: Risk of bias analysis for non-randomised studies														
1) A clearly stated aim	1	1	1	1	1	1	1	2	1	2	0	1	1	
2) Inclusion of consecutive patients	0	0	0	0	0	2	2	0	2	0	0	0	0	
3) Prospective collection of data	0	0	0	0	0	0	0	0	0	0	0	2	0	
4) Endpoints appropriate to the aim of the study	2	1	1	1	2	2	2	2	2	2	1	2	1	
5) Unbiased assessment of the study endpoint	2	2	2	1	2	2	1	2	1	2	2	2	2	
6) Follow-up period appropriate to the aim of the study	2	1	2	1	2	2	1	1	2	2	2	2	2	
7) Loss to follow-up less than 5%	2	2	2	1	2	2	1	1	2	2	1	1	1	
8) Prospective calculation of the study size	0	0	0	0	0	0	0	0	0	0	0	0	0	
Total (%)	9/16 (56)	7/16 (44)	8/16 (50)	5/16 (31)	9/16 (56)	11/16 (69)	8/16 (50)	8/16 (50)	10/16 (63)	10/16 (63)	6/16 (38)	10/16 (63)	7/16 (44)	
B: Risk of bias analysis for randomised studies														
Randomisation process														Low
Deviations from the intended interventions														Low
Missing outcome data														Low
Measurement of the outcome														Some concerns
Selection of the reported result														Low
Overall														Low

Additional MINORS criteria were not used since there were no comparative studies assessed.

studies have failed to differentiate between radiographic and clinical union.

The unnecessary fixation of the unprepared subtalar joint is problematic and can increase the rate of symptomatic non-union and ankle arthritis. With the ankle mortise fused, the subtalar joint exerts a compensatory function so as to not concentrate the weight-bearing stress on the medial portion of the ankle and to retain motion and normal gait (51). Removing the compensatory function transfers motion to the midtarsal joints and promotes varus inclination of the subtalar joint, leading to increased medial stress concentration in the midtarsal joints causing arthritic changes (52). Mid-talar joint degeneration was most commonly found (60% of patients), with subtalar joint degeneration observed in 10% of patients (53). None of the studies included in this review reported arthritis, perhaps due to the short follow-up times (average of 18.6 months). Nevertheless, Childress *et al.* followed up 92 patients for 16 years and reported no degenerative changes; however, a narrow Steinman pin was used (54). Furthermore, fractures of the second metatarsal after ankle surgery have been reported in the literature (55), perhaps due to higher von Mises stresses in the second and third metatarsal bones after ankle fusion (56), yet none of the included studies reported such a finding.

Mortality

Our pooled all-cause mortality proportion was 27% (95% CI: 0.20–0.34), with the lowest at 11.8% with 20.9 months of follow-up (1). This is comparable to the mortality rate after hip fractures in the elderly (33%) (57). However, mortality in ORIF cohorts seems to be lower with one study reporting 5.4% with a 15-month follow-up (58). This may however not be a fair comparison since all-cause mortality is determined by many factors unrelated to the ankle fusion process itself, including age, comorbidities, and other injuries. Diabetics accounted for 8.7% of Shivarathre *et al.*'s cohort (58); our figure was 41.9%, which could have contributed to higher mortality. Nevertheless, co-management of geriatric patients by orthopaedic surgeons and geriatricians can lead to a shorter hospital stay and lower mortality and complication rates (59).

Mobility and OMAS

The measurement of pre-operative OMAS in five of the included studies may seem rather pointless since it was measured on the day of admission after an acute fracture. Nevertheless, pre-operative OMAS could provide a snapshot of the patient's extent of disability and allows one to compare with their post-operative status. OMAS was created in 1984 from a cohort of 90 patients treated by Olerud and Molander (60). The overall score is the sum of points obtained by each of the nine parameters. The assignment of points to each parameter is non-linear; frankly, it is not possible to assign each parameter the correct number of points in each situation. The reporting of both pre- and post-operative OMAS presents an intriguing finding. Olerud and Molander acknowledged that the score correlates significantly to the range of motion, rather than with the patient's subjective evaluation of ankle function and mobility (60). It is therefore unsurprising that even though most patients were able to return to their mobility levels prior to injury, the post-operative OMAS was poorer than pre-operative OMAS due to the loss of ankle and subtalar motion. Nevertheless, the average decrease in OMAS post-nailing was 8.06, which is below the value of 10 indicated as the minimal clinicallly significant difference (61).

Despite Georgiannos *et al.* finding a significantly greater post-operative decrease in OMAS compared to pre-operative score in the TTC cohort compared to the ORIF cohort (6.5 vs 4.4; $P=0.01$), it was attributed to the very low rating of stiffness item due to elimination of subtalar and tibiotalar joint movements (31). In a cohort of 43 ankles, after ankle fusion, dorsiflexion decreased from 10.5° to 4.2°, whilst plantarflexion dropped from 24.7° to 14° in the sagittal plane (62). Unfortunately, range of motion was not reported in any of the included studies. Nevertheless, Georgiannos *et al.* reported no significant difference in 1-year post-operative OMAS between the ORIF and TTC cohorts (31). Conservative treatment also does not result in improved post-operative functional outcomes, with an RCT between closed contact casting and surgery reporting no significant difference in OMAS 6 months after randomisation (4).The pooled proportion of patients returning to pre-operative mobility was 71% (95% CI: 0.6–0.8). This high value suggests that TTC nailing is not a life-changing procedure. Furthermore, patients with a low CCI had higher odds of regaining their pre-operative mobility ($P=0.160$; OR = 4.00) (28).

Meta-regression

An I^2 value below 60% suggests low or moderate heterogeneity (63). This was the case for all our pooled data, apart from post-operative OMAS ($I^2 = 85\%$). Hence, a meta-regression was used to determine potential covariates leading to heterogeneity. Age being inversely correlated with higher OMAS was not a surprising finding, given that ageing leads to physical and functional losses (64). What was more intriguing was that older males had a stronger inverse correlation with better OMAS. Some studies report no difference in PROMs between men and women (65, 66). However, studies on hip arthroplasty for osteoarthritic patients report that females achieved better outcomes than males (67), agreeing with our finding. More research is needed regarding the influence of gender on ankle surgery.

Possible benefits of TTC nailing

The results of this meta-analysis show an overall lower complication rate with TTC nailing and improved OMAS when compared to studies utilising conservative treatment and ORIF (4, 7, 8, 34, 35). This could explain why TTC nailing is becoming more popular with the geriatric population, perhaps due to the underlying biomechanics of TTC nailing. They are sturdy internal splints that are biomechanically better than extra-medullary implants, which allows them to mediate fracture union. They have maximum leverage in the distal segment, which promotes a more reliable and rigid fixation system (68). Furthermore, the medullary canal is often reamed to a centimetre above the diameter of the nail. This creates a cancellous autograft, which encourages the formation of a local haematoma that is rich in inflammatory cells and mitogens, which recruits mesenchymal stem cells and promotes neovascularisation, all of which encourage osteoblast activity and bone formation (69). The biggest benefits come from two angles, the first being their load-sharing design makes the fracture site able to tolerate immediate weight-bearing, and the second being the minimal disruption and preservation of fracture biology upon insertion of a TTC nail, which decreases the risk of post-operative wound complications (9), especially in the comorbid host.

Limitations

The main limitation is the small sample size and lack of studies with a control group. Short follow-up times will lead to under-representation of some complications like arthritis. Definitions of outcome measures such as non-union, detailed description of how authors assess whether union has been achieved, or detailed inclusion criteria were lacking in many studies. Outcome measures were heterogeneous, with only five studies reporting pre- and post-injury OMAS. Although this review provides the most detailed analysis of TTC nailing for fragility ankle fractures, prospective multicentre RCTs with longer follow-up times and larger sample sizes are needed to confidently determine the best management option. The results of an RCT are keenly awaited (70).

Conclusion

All included studies present a picture that TTC nailing is an adequate option for managing ankle fractures in the elderly, which allows immediate post-operative weight-bearing and minimises surgical trauma. It has low morbidity, and the majority of patients are able to return to their pre-operative mobility status. There has been a large increase in publications on this topic in the last half-decade; however, the vast majority are case series, with only one RCT available. In order to be able to make strong statements about prefered management strategies, we would need to perform studies which directly compare interventions; ideally, RCTs would be used. There is also poor consistency in post-operative rehabilitation protocols, and no studies evaluated fusion rates of the ankle and subtalar joints, or post-operative hindfoot alignment. Despite initial promising evidence that TTC nailing could be added to the paraphernalia for fragility ankle fracture management, prospective RCTs with long follow-up times and large cohort sizes are needed to create clear guidelines for the use of TTC nailing for ankle fractures.

Supplementary materials

This is linked to the online version of the paper at https://doi.org/10.1530/EOR-22-0017.

ICMJE Conflict of Interest Statement

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Funding Statement

This work did not receive any specific grant from any funding agency in the public, commercial, or not-for-profit sector.

Ethics approval

This is a systematic review. The research ethics committee of Cambridge University Hospitals NHS Foundation Trust has confirmed that no ethical approval is required.

Availability of data and material

The authors confirm that the data supporting the findings of this study are available within the article (and/or) its Supplementary materials.

Author contribution statement

V L, M T, A Z, R P performed full text screening and data collection. V L wrote the manuscript. M F, A T, R P provided guidance on statistics and reviewed previous versions of the manuscript. M K conceptualised the study and edited previous versions of the manuscript. All authors have read and approve of the final version of the manuscript.

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