REVIEW ARTICLE

Induced Membrane Technique for the Management of Segmental Femoral Defects: A Systematic Review and Meta-Analysis of Individual Participant Data

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Several modifications of the induced membrane technique (IMT) have been reported, but there is no consensus regarding their results and prognosis. Moreover, most studies have focused on tibial defects; no meta-analysis of the treatment of femoral defects using the IMT has been reported. This systematic review and meta-analysis aimed to identify the potential risk factors of post-procedural complications following the treatment of segmental femoral defects using the IMT. A comprehensive search was performed on the Cochrane Library, EBSCO, EMBASE, Ovid, PubMed, Scopus, and Web of Science databases, using the keywords "femur," "Masquelet technique," and "induced membrane technique." Original articles composed in English, having accessible individual patient data, and reporting more than two cases of bony defect or nonunion of femur or more than five cases of any body part were included. Post-procedural bone graft infections, final union status, and union time after second-stage operation were analyzed. Fourteen reports, including 90 patients, were used in this study. External fixation in second-stage surgery had an odds ratio of 9.267 for post-procedural bone graft infection ($p = 0.047$). The odds ratio of post-procedural bone graft infection and age >65 years for final non-union status was 51.05 ($p = 0.003$) and 9.18 ($p = 0.042$). Shorter union time was related to impregnated antibiotics in the spacer ($p = 0.005$), transplanting all-autologous grafts ($p = 0.042$), and the application of intramedullary nails as the second-stage fixation method ($p = 0.050$). The IMT appears to be reasonable and reproducible for femoral segmental bone defects. Several preoperative and surgical factors may affect post-procedural complications and union time.

Key words: Induced membrane technique; Masquelet technique; Segmental bone defect

Introduction

A critical segmental bone defect, which could result from trauma, infection, or malignancy, is a bone void that cannot be filled without intervention.[1] Large segmental bone defects, which are defined as segmental defects >6 cm, can be managed using several methods.[2,3] Currently, distraction osteogenesis,[4] a free vascularized fibular bone graft,[5] and the induced membrane technique (IMT) are the preferred treatments for large segmental bone defects.[6] Among these methods, distraction osteogenesis can simultaneously address infection, soft-tissue defects, and correction of deformities. It is the most effective therapeutic strategy for post-traumatic complex nonunion, but, because it requires a long treatment course, patients may be uncooperative due to the inconvenience of external fixators.[7] Conversely, free vascularized bone grafts offer satisfactory results with shorter healing duration, but require microsurgical skills and advanced operation environments, which are technically challenging and may not be accessible at every hospital.[8] As a result, the IMT is now a relatively popular choice for treating large segmental bone defects.

In 2000, Masquelet *et al.* first introduced the IMT in a 35-case series to treat large diaphyseal segmental bone defects.[6] During the first stage, after debridement and utilizing an external fixator to stabilize the bone, an antibiotic-free polymethyl methacrylate (PMMA) cement spacer was placed

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at the defect site to maintain the original length, prevent soft tissue from interposing between fracture ends, and induce a biological membrane. In the second stage, careful incision of the induced membrane was performed, and the spacer was removed. A large volume of cancellous bone graft harvested from the iliac crests was utilized to fill in the area originally occupied by the spacer. It is believed that the self-induced membrane provides osteo-inductive growth factors for bone healing by stockpiling the bone grafts.

Several modifications of this technique have been reported, including bone grafting from different sources, the use of spacers loaded with antibiotics, and different fixation methods in the first and second stages of the procedure.[9–11] Although most studies have presented satisfactory results regarding these modifications, there is no consensus regarding their results and prognosis. Moreover, few studies have analyzed the procedural and non-procedural factors and surgical results, such as union status and post-procedural bone graft infection. As of September 2022, there were only a few systemic reviews concerning the IMT,[12–17] and even fewer of them utilizing the method of meta-analyses focusing on the overall effectiveness of the IMT.[18–20] Furthermore, there were no reviews focusing on the treatment of femoral bone defects using the IMT.

Hence, this systematic review and meta-analysis aimed to identify the factors that were significantly related to surgical outcomes of the IMT and the risk factors for post-procedural bone graft infections, nonunion status, and prolonged union time in patients whose segmental femoral defects were managed with IMT.

Methods

Search Strategy

A systematic review of the medical literature was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement for Individual Patient Data systematic reviews (PRISMA-IPD)[21] (Table S1) and was registered with PROSPERO (ID: CRD42021260968). The researchers searched the following databases: Cochrane Library, EBSCO, EMBASE, Ovid, PubMed, Scopus, and Web of Science. The keywords “femur,” “Masquelet technique,” and “induced membrane technique” were used. The time range for the search was January 2000 to September 2022. The article selection process was performed in two stages: in the first stage, titles and abstracts were screened for relevance by two independent researchers after removing duplicates. In cases of disagreement, a third researcher was consulted, and uncertain articles were scrutinized and further discussed to clinch a consensus. In the second stage, full-text articles were obtained and evaluated to gauge their suitability.

Eligibility Criteria

Original articles were included if they were (1) composed in English, (2) had accessible individual patient data, and (3) reported more than two cases involving patients with a bony defect and septic or aseptic nonunion of the femur treated with the IMT, or reported more than five cases involving patients with a bony defect and septic or aseptic nonunion of any part of the body treated with the IMT. In this study, only cases with affected femurs were included in the analysis. Demographic, union status, defect lengths, and etiology (infected or non-infected) data were acquired. Variations in surgical procedures, such as spacer types (with or without antibiotic administration), definite fixation methods (plate, nail, or external fixator), and bone graft sources (iliac crest, reamer-irrigator-aspirator, or non-autologous graft), were recorded. Post-procedural bone graft infections, final union status, and union time after the second stage operation were analyzed to measure the study outcomes.

Clinical Appraisal

Since most studies related to the IMT were retrospective case series, the Joanna Briggs Institute Critical Appraisal Checklist for Case Series, comprising 10 items, was used to evaluate the risk of bias.[22] Questions were answered as “yes,” “no,” “unclear,” or “not applicable” (Table 1).

Ethical Approval and Informed Consent

Our study did not require ethical approval or informed consent due to its design.

Outcomes

In our analysis, the primary outcomes were post-procedural bone graft infection and final union status, and the secondary outcome was union time after the final operation in patients with final union status.

Statistical Analysis

A meta-analysis was performed using IBM SPSS Statistics for Windows, version 25.0.0 (IBM Corp., Armonk, NY, USA). First, we conducted a series of univariate analyses to evaluate the association between patient demographics, treatment-related factors, and clinical outcomes. The chi-square test or Fisher’s exact test was applied to dichotomous and categorical variables, while nonparametric evaluation using the Mann–Whitney *U* test was performed for continuous variables. In each univariate analysis, $p < 0.05$ was considered statistically significant. After recognizing several factors that met our preset cut-off for significance, a multivariate analysis was conducted using stepwise logistic regression. In addition, a survival analysis was performed using the Kaplan–Meier method on the results with continuous fashion, such as union time. Results are shown as odds ratios (ORs), *p*-values, means, 95% confidence intervals (CIs); the relevant Kaplan–Meier curves were also drawn.

Results

Overview

In total, 588 studies were included in the first stage. After removing duplicates, 143 studies were screened, out of which

TABLE 1 Clinical appraisal using the Joanna Briggs institute critical appraisal checklist for case series for included studies

	Yu 2017	Choufani 2020	Sasaki 2017	Mathieu 2020	Ayouba 2020	El-Alfy 2015	Pesciallo 2021	Stafford 2010	Kombate 2017	Giannoudis 2016	Donegan 2011	Olesen 2015	El-Alfy 2018	Combal 2021
Q1	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Q2	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Q3	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Q4	+	+	-	+	+	+	+	+	+	+	+	+	+	+
Q5	+	+	-	+	+	+	+	+	+	+	+	+	+	+
Q6	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Q7	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Q8	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Q9	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Q10	X	X	X	X	X	X	X	X	X	X	X	X	X	X

+ Low risk of bias / - High risk of bias / X Not applicable
Q1: Were there clear inclusion criteria for the case series?
Q2: Was the condition measured in a standard, reliable way for all participants included in the case series?
Q3: Were valid methods used to identify the condition for all participants included in the case series?
Q4: Did the case series include participants consecutively?
Q5: Did the case series involve complete inclusion of participants?
Q6: Was the reporting of the demographics of the participants in the study clear?
Q7: Was the reporting of the clinical information of the participants clear?
Q8: Were the outcomes or follow-up results of cases clearly reported?
Q9: Was the reporting of demographic information of the presenting site(s)/clinic(s) clear?
Q10: Was the statistical analysis appropriate?

23 studies were assessed for eligibility. Finally, 14 reports of individual patient data (90 patients) were utilized in this study. Additional patient information was not obtained from the authors of any of the studies.[10,23–35] The selection process flowchart is presented in Figure 1.

Most of the included studies were retrospective case series; therefore, the risk of bias was evaluated in each study (Table 1). The included patients had a mean age of 39.8 years (range, 9–80 years), and the majority were male (72; 80%). All patients underwent the IMT because of a bone defect or nonunion of the femur. The cases were categorized by etiology as infected (41; 45.6%) or non-infected (49; 54.4%) nonunion. The mean length of the bone defect was 7.6 cm (range, 1–25 cm) (Table 2).

Primary Outcomes

Evaluation of primary outcomes included two main measurements: post-procedural bone graft infection status after IMT and the final union status. Secondary outcomes were evaluated using union time after the second-stage operation in patients with final union status. Post-procedural bone graft infection occurred in 5/90 (5.6%) patients, who were all treated with the IMT for an infected nonunion. The final union was achieved in 77/90 (85.6%) patients, with a mean union time after the second stage operation of 29.5 weeks (range 16–56 weeks). Other peri-operative factors and post-operative status were also listed (Table 3).

Univariate analyses were first performed based upon individual patient data to determine the possible predictive factors that were associated with the outcomes. The chi-square test and Fisher's exact test were used for categorial variables, while the independent-samples t test was used for continuous variables.

Multivariate analysis with stepwise logistic regression was accordingly performed for variables with significant differences; this revealed that the use of external fixation in the second-stage surgery had an OR of 9.267 for post-procedural bone graft infection ($p = 0.047$, 95% CI: 1.028–83.613) (Table 4). For the final nonunion status, post-procedural bone graft infection had an OR of 51.05 ($p = 0.003$, 95% CI: 3.816–682.919), while >65 years of age had an OR of 9.18 ($p = 0.042$, 95% CI: 1.066–79.135) (Table 4).

Secondary Outcome

Further univariate analyses were performed on the subgroup of cases with final union status and were provided with retrievable union time after the second-stage operation. The result revealed that shorter union time in this particular subgroup was related to the use of antibiotics in the spacer (27.69 ± 10.04 vs. 37 ± 9.63 weeks, $p = 0.005$), the use of an all-autologous graft (26 ± 10.71 vs. 31.66 ± 10.01 weeks, $p = 0.042$), and the use of intramedullary nails as the second stage fixation method (27.86 ± 9.96 vs. 31.92 ± 11.43 weeks, $p = 0.050$) (Table 5). The Kaplan–Meier analysis revealed that the use of antibiotics in the spacer (log rank [Mantel-Cox] = 0.021) (Figure 2) and the use of an all-autologous graft (log rank [Mantel–Cox] = 0.048) (Figure 3) were significantly associated with a shorter union time, but the use of intramedullary nails was not (log rank [Mantel–Cox] = 0.369) (Figure 4).

In addition, in our meta-analysis, sex, different fixation methods in the first-stage operation and different bone graft sources had no significant impact on final union status, post-procedural bone graft infection, or union time with univariate analysis (Tables S1–S3).

Discussion

Main Findings of our Study

Herein, we found that the IMT was a feasible choice of treatment for patients with a critical femoral segmental bone defect. In terms of complications, post-procedural bone graft infections were related to the use of external fixation as definite fixation method, and final non-union status was related to post-procedural bone graft infections and older age (≥65 years).

Current Concepts on the IMT

Management of a critical segmental bone defect—defined as one that requires further surgical intervention because it does not heal spontaneously despite surgical stabilization[36]—is challenging for orthopaedic and plastic surgeons. While there are currently several choices of surgical techniques available for these patients, including distraction osteogenesis,[4] free vascularized fibular bone grafting,[5] and the IMT, high-level evidence to guide management is lacking. Furthermore, these treatments should be individualized because of the diversity of this particular disease.[37] Nevertheless, among these three

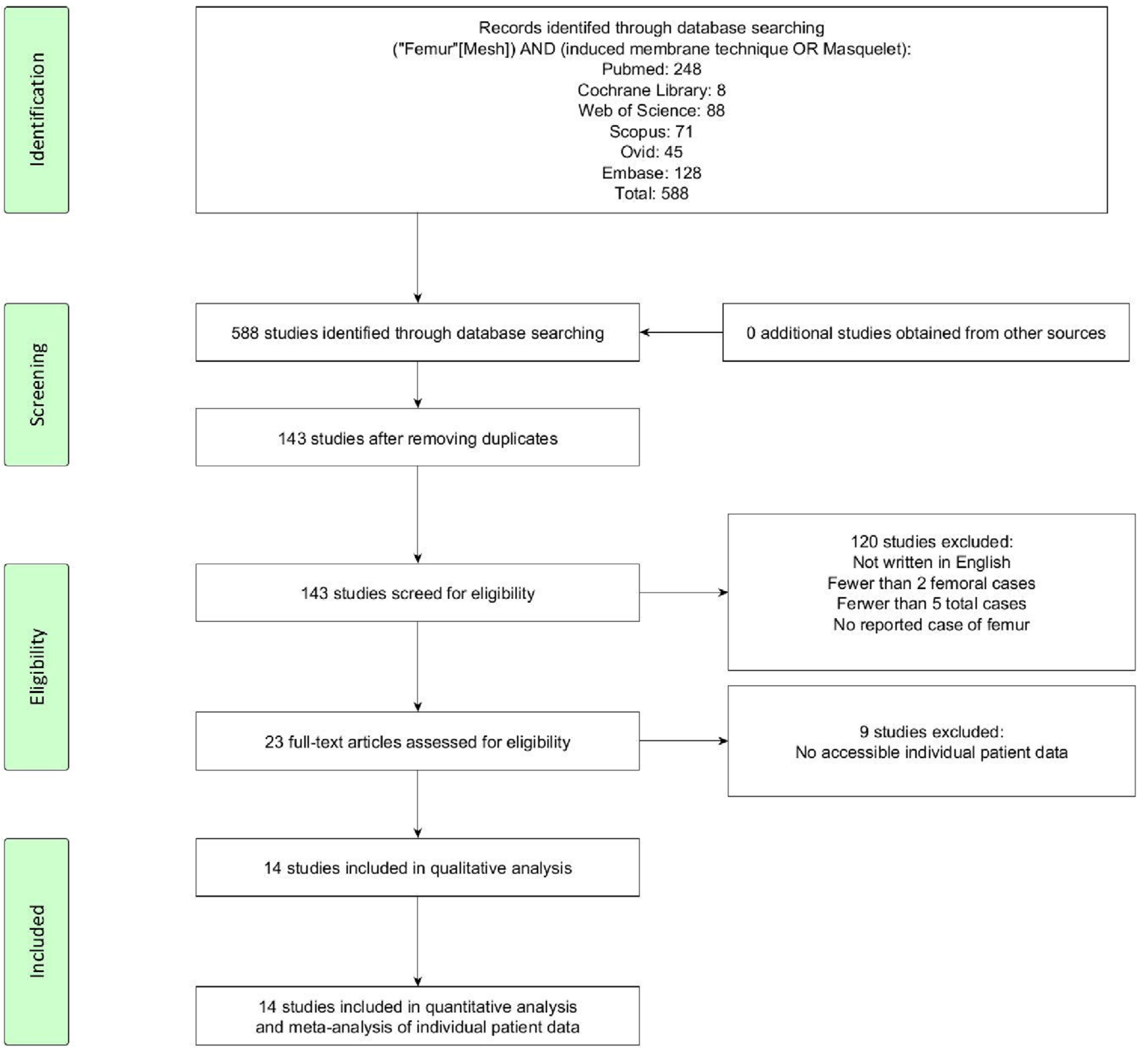

FIGURE 1 Flow chart of article selection. A total of 588 studies were identified by searching various databases. After removing the duplicates, 143 studies were screened, of which 23 studies were assessed for eligibility. Finally, 14 reports of individual patient data (90 patients) were used in this study

TABLE 2 Patient demographics and preoperative characteristics

Study	Design	N of cases femur/total	Age	Sex M	Infection etiology		Defect length (cm)
					Yes	no	
X. Yu 2017	prospective	13/13	39 (16–69)	9/13	0	13	9.8 (5–16)
C. Choufani 2020	prospective	6/16	35 (9–58)	6/6	1	5	5 (3–10)
G. Sasaki 2017	retrospective	2/7	37 (15–69)	1/2	0	2	6.3 (3–12)
L. Mathieu 2020	retrospective	2/8	46 (13–70)	1/2	0	2	6.5 (5–8)
G. Ayouba 2020	retrospective	7/8	31.57 (26–41)	7/7	4	3	8.9 (7–11)
B.S. El-Alfy 2015	retrospective	4/17	41.5 (38–46)	4/4	0	4	6.5 (5–7)
C.A. Pesciallo 2021	retrospective	8/21	46.5 (18–65)	4/8	0	8	7.2 (4.5–14)
P.R. Stafford 2010	retrospective	8/27	35 (20–48)	8/8	6	2	8.44 (1.5–25)
N.K. Kombate 2017	retrospective	6/11	46.5 (41–59)	6/6	6	0	4 (3–5)
P.V. Giannoudis 2016	retrospective	14/43	50.5 (28–80)	10/14	7	7	5.5 (3–12)
D. J. Donegan 2011	retrospective	5/12	39 (15–58)	3/5	4	1	11.2 (6–15)
U.K. Olesen 2015	retrospective	2/8	31 (24–38)	2/8	1	1	43 (35–51)
B.S. El-Alfy 2018	retrospective	9/15	33.5 (24–48)	8/9	9	0	10.2 (7–14)
A. Combal 2021	retrospective	4/4	23.6 (18–44)	3/4	3	1	15 (10–24)
Total		90/210		72/90	41	49	

techniques, IMT is associated with several advantages: it is more convenient for patients and has a shorter treatment course than distraction osteogenesis, and is relatively less technically demanding than vascularized fibular bone grafting.[38]

Several studies on the curative effects, complication rates, and possible risk factors of nonunion and post-procedural bone graft infections in the IMT exist.[16,20,39] The existing literature states that defect lengths, locations, and etiology may affect the surgical results of the IMT.[20] Nonetheless, we did not find a quantitative, systemic, analytic study focusing on femoral segmental bone defects treated with the IMT. To our knowledge, our study is the first systematic review and quantitative analysis focusing on critical bone defects in femurs treated with the IMT.

Post-Procedural Bone Graft Infections

Infection has a great influence on bone healing, especially in the treatment of large bone defects.[40] Our analysis suggests that post-procedural bone graft infections only occurred in patients with infected nonunion. Logically, patients undergoing IMT for infected nonunion were much more likely to sustain post-procedural bone graft infections.[18] Moreover, we found that patients who underwent external fixation in the second-stage operation had higher rates of post-procedural bone graft infection. In another study, external fixation was associated with higher infection rates than internal fixation.[41] In our analysis, external fixation in the second-stage operation had an OR of 9.267 for post-procedural bone graft infection, even in patients who underwent antibiotic-loaded PMMA spacer implantation.

TABLE 3 Peri-operative factors and postoperative status

Study	Union		Post-op infection		Spacer with antibiotics		All autologous bone graft		External fixation as final fixation	
	yes	no	yes	no	yes	no	yes	no	yes	no
X. Yu 2017	12	1	1	12	13	0	13	0	0	13
C. Choufani 2020	2	4	2	4	6	0	6	0	6	0
G. Sasaki 2017	2	0	0	2	2	0	0	2	0	2
L.Mathieu 2020	1	1	1	1	2	0	0	2	0	2
G. Ayouba 2020	7	0	1	6	7	0	7	0	0	7
B.S. El-Alfy 2015	4	0	0	4	0	4	4	0	2	2
C.A. Pesciallo 2021	7	1	0	8	8	0	0	8	0	8
P.R. Stafford 2010	7	1	0	8	8	0	0	8	0	8
N.K. Kombate 2017	6	0	0	6	6	0	6	0	0	6
P.V. Giannoudis 2016	12	2	0	14	14	0	1	13	0	14
D. J. Donegan 2011	5	0	0	5	5	0	3	2	0	5
U.K. Olesen 2015	1	1	0	2	2	0	2	0	0	2
B.S. El-Alfy 2018	8	1	0	9	0	9	0	9	0	9
A. Combal 2021	3	1	0	4	4	0	4	0	0	4
Total	77	13	5	85	77	13	46	44	8	82

TABLE 4 Multivariate analysis of variables associated with final union status and post-procedural bone graft infection

Variable	Infection			Non-union		
	Odds ratios	95% CI	*p* value	Odds ratios	95% CI	*p* value
Patient factors						
Age ≧ 65	N/A[a]	N/A	N/A	9,18	1.066–79.135	0.042*
Operative factors						
External fixation in 2nd surgery	9.267	1.028–83.613	0.047*	4.32	0.893-20.906	0.069
Post-operative status						
Post-procedural infection	N/A[a]	N/A	N/A	51.05	3.816–682.919	0.003*

* $p < 0.05$.; [a] Variable not included in model following variable selection.

TABLE 5 Univariate analysis of variables associated with union time in the subgroup with final union status

Variables	No.	*t* value	Union Time (weeks)	*p* value
No. of cases	61			
		−1.639		0.050
Fixation Method				
With nail	36		27.86 ± 9.960	
Not with nail	25		31.92 ± 11.43	
		−3.001		0.005*
Spacer Type				
With antibiotics	49		27.69 ± 10.042	
Without antibiotics	12		37.00 ± 9.630	
		−2.083		0.042*
Graft				
All autologous	23		26.00 ± 10.719	
Non all autologous	38		31.66 ± 10.012	

* $p < 0.05$.

Final Non-Union

The final union status was the other primary outcome. Our meta-analysis demonstrated that there was a close relationship between post-procedural bone graft infection and the final nonunion status. According to the current literature, residual infection is one of the causative factors of

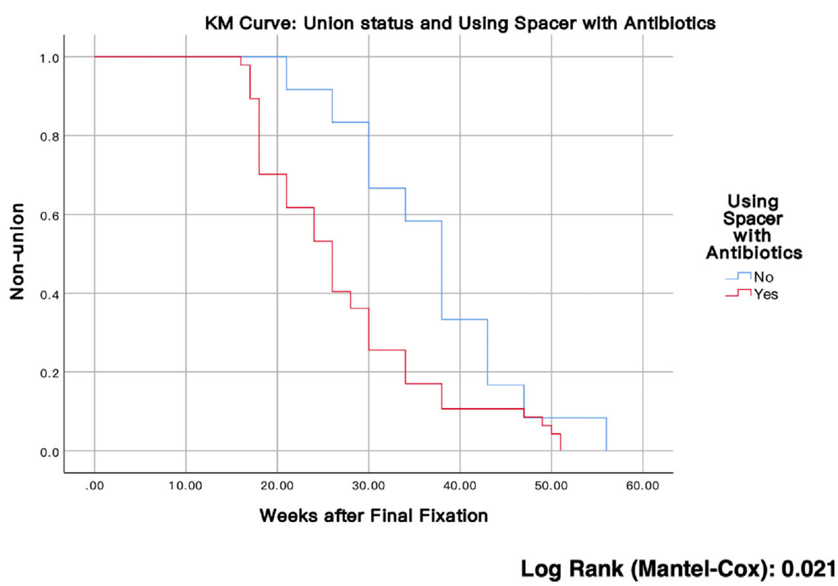

FIGURE 2 Kaplan–Meier survival curve showing a statistically significant difference in union time in patients with final union status managed with the use of antibiotics in the spacer

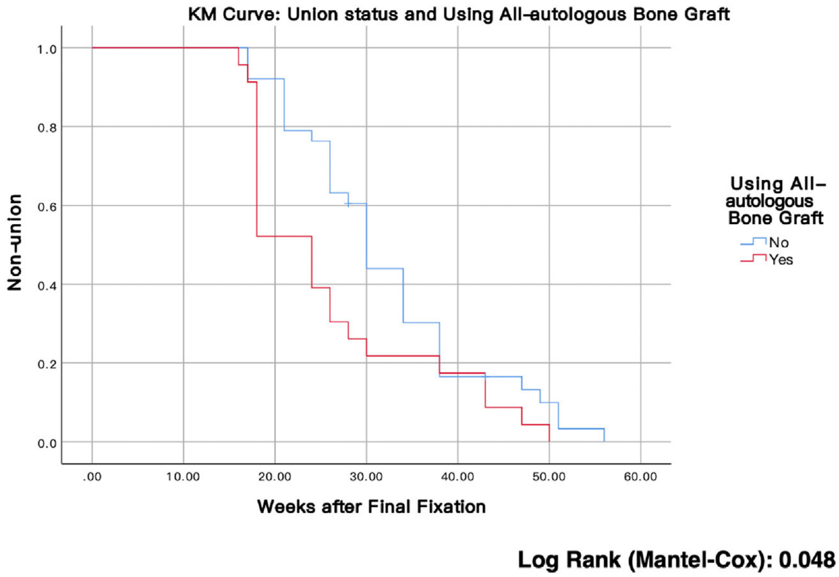

FIGURE 3 Kaplan–Meier survival curve showing a statistically significant difference in union time in patients with final union status managed with the use of all-autologous graft

IMT failure, and it may induce insidious septic recurrence and, thus, result in nonunion.[23] Based on our results, we drew the same conclusion, with post-procedural bone graft infection possessing an OR of 51.05 for final nonunion status in the multivariate analysis. Masquelet *et al.* stressed that IMT can only be conducted after infection is definitively eradicated.[6,42] Thus, devoted and discreet management of infection prior to the IMT is very important for surgeons to prevent complications of post-procedural bone graft infection and nonunion, especially in patients with pre-existing site infection or osteomyelitis.

Age was the other factor that interfered with the final union status. Given the current evidence, it is controversial whether age is a risk factor for nonunion. According to Zura *et al.*, age might pose a strong negative factor for nonunion in some bones (e.g., the clavicle) but not for others (e.g., the humerus).[43] Additionally, in their report, age was reportedly a potential surrogate measure of the prevalence of other comorbidities that increase with age and contribute to nonunion, such as diabetes, obesity, and osteoporosis. Without controlling for potential confounders, it is unclear whether age is a risk factor for nonunion. Recent studies concerning nonunion of the lower limbs revealed that age did not influence the outcomes of lower limb nonunion.[44,45] Some researchers even postulated that the nonunion rate decreased with increasing age.[46] Our study results demonstrated that old age (age ≥ 65) might be a risk factor for final nonunion status. However, due to the lack of complete records from the included studies, we were not able to recognize and further control for potential confounders in our analyses.

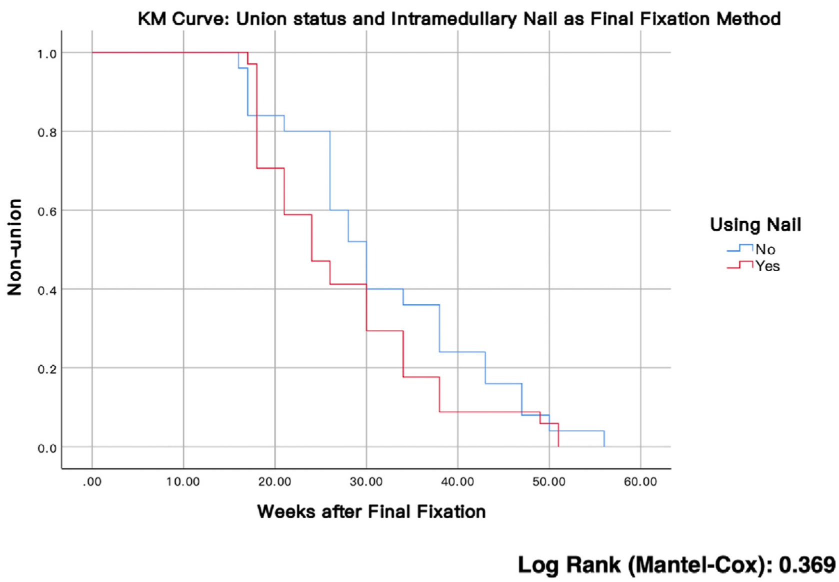

FIGURE 4 Kaplan–Meier survival curve showing no statistically significant difference in union time in patients with final union status managed with the use of intramedullary nail as final fixation method

Union Time

Considering that a shorter union time was one of the benefits of the IMT compared with other techniques,[1] reducing union time was an emphatic objective for surgeons. We further conducted analyses of union time in the subgroup of union cases with accessible data of union time. The results demonstrated that surgical factors, including the use of an antibiotic-loaded spacer, all-autologous bone graft, and intramedullary nails as the final fixation method, were significantly related to union time in this subgroup.

In our study, the use of antibiotic-loaded spacers did not have a significant effect on post-procedural bone graft infection or final union status, which reflects the results of previous studies.[19,20] However, the union time after the final operation was significantly shorter. Lovati *et al.* developed a rat model in a pilot study to mimic complicated femoral fractures in humans, concluding that subclinical low-grade infections may be related to the decreased capability of bone repair and delayed union due to bacterial biofilm formation.[39] Although Masquelet *et al.* did not recommend the routine use of an antibiotic-loaded PMMA spacer to eradicate infections,[37] it might reduce the union time for patients with femoral critical bone defects managed with the IMT.

Bone graft supplementation is a critical step in treating nonunion, especially in procedures involving the IMT.[40,47] Recently, non-autologous bone grafts, such as allografts, xenografts, and synthetic and bone substitutes, as well as bone morphogenetic protein, have been widely utilized in the IMT.[40,48] According to Pesciallo *et al.*, a proportion of allograft usage does not affect the final union and failure rates of the IMT.[28] However, autografts are believed to possess superior mechanical and biological properties compared with allogeneic or synthetic bone substitutes—owing to the osteogenic properties of osteoinduction and osteoconduction.[49] In a cohort study of 182 patients, the autograft cohort had a significantly shorter time to the union than both the allograft and allograft/autograft combined cohorts.[47] In our study, there was no significant difference in final union status between the different sources or the proportion of autologous grafts. However, procedures involving non-autologous grafts did demonstrate a longer union time in patients reaching the final union, while applying the IMT in femoral nonunion.

Implant choices were another factor that interfered with union or union time in the IMT.[50] In our analysis, using an intramedullary nail for definite fixation in the second-stage fixation method provided shorter union time, which was consistent with the results of previous studies.[48,51] Intramedullary nailing is an effective method of treating fractures of the femoral shaft for both fresh fractures and revision cases because of its high union and low complication rates.[52,53] Lai *et al.* conducted a cohort study of patients with atrophic nonunion of femoral shaft fractures, which resulted in an overall union rate of 70.8% in 68 cases, after revision surgeries with either intramedullary nails plus either augmentative anti-rotational plating or exchanging reamed nailing.[54] In our study, although there was no difference in the final union status between intramedullary nailing and other fixation methods, the union time was shorter when an intramedullary nail was used as a definite treatment in the second stage.

The length of the bone defect is generally considered a factor that causes failure in the IMT, especially when applied to tibial defects.[18,20] Additionally, previous systemic reviews suggested that a larger defect size significantly increased the post-procedural infection rates of the IMT.[19,20] Nevertheless, most studies have focused on tibial defects.[19,20] In our study, the bone defect length was not an independent predictor of post-procedural bone graft infection, final nonunion status, or prolonged union time in femoral defects. In a systemic review conducted by Fung *et al.*, they concluded that the tibia had an OR of 7.75, compared to the femur, for post-procedural bone graft infection.[19] Open fractures and decreased soft-tissue coverage were more frequent in tibia defects than in femoral defects, which might influence the different results of defect length.[54]

Strengths and Limitations

The strength of this study lies in that it is, to date, the first study focusing on the treatment effects and post-procedural complications of IMT as a management option for patients with femoral segmental bone defects. We believe that our findings may provide surgeons with several considerations and a treatment solution for such complicated cases.

However, our systematic review and meta-analysis have several limitations. First, the evidence levels of all studies in this review were either level III or level IV, among which most were retrospective case series involving less than 10 cases. This limited the analysis of possible confounding factors and selection bias among these studies, which leads to the strength of our conclusions being limited. Additionally, differences in data reporting made the extraction process and subsequent analyses strenuous. There were variations in the definitions of post-procedural bone graft infection (culture-confirmed, clinical presentations, or elevated C-reactive protein data), final union status (functional, clinical, or radiological), and union time among the selected studies. While we deferred to the authors' definitions of these outcomes, this may have given rise to biased estimates of the true rate of union status, post-procedural bone graft infection, and union time after the final operation. Finally, some of the included studies might have reported results of different study phases in the same patient cohort; however, unless it was specially stated, we assumed that these were independent studies.

Conclusion

When managing a critical femoral segmental bone defect, the IMT appears to be a reliable and reproducible solution. Using external fixation as a definite fixation method in second-stage operation was a risk factor for post-procedural bone graft infection. Additionally, post-procedural bone graft infection and increasing age had negative impacts on the final union status. The use of antibiotic spacers, all-autologous grafts, and intramedullary nails as a definite fixation method could shorten the union time in achieving final union. Nevertheless, given that autologous grafts or different fixation methods did not influence the post-procedural bone graft infection rate and final union status in our analysis, surgeons should consider these surgical factors only when patients' conditions and surgical environments permit it. Considering the relatively low incidence of this disease, rather than large randomized multicenter clinical trials, future studies should report outright, standardized individual patient data and clinical outcomes in a prospective fashion to facilitate the evaluation of the possible influence of surgery-related and patient-related factors, along with other parameters, on postoperative outcomes.

Acknowledgment

N/A.

Authors' Contributions

All authors had full access to the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. *Conceptualization*, Y.L. and Y.H.Y.; *Methodology*, Y.L. and Y.H.Y.; *Investigation*, Y.L., C.Y.L., P.J.L., and Y.H.Y.; *Formal Analysis*, Y.L. and C.Y.L.; *Resources*, Y.H.Y; *Writing - Original Draft*, Y.L., C.Y.L., and P.J.L.; *Writing—Review & Editing*, C.Y.L., and Y.H.Y.; *Visualization*, Y.L.; *Supervision*, Y.H.Y.

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Authorship Declaration

All authors listed meet the authorship criteria according to the latest guidelines of the International Committee of Medical Journal Editors. All authors agree with the manuscript.

Data Availability Statement

All data generated or analyzed in this study are included in this published article. The datasets used and/or analyzed during the current study are available from the corresponding author.

Supporting Information

Additional Supporting Information may be found in the online version of this article on the publisher's web-site:

Table S1. Multivariate analysis of variables associated with post-procedural bone graft infection

Table S2. Multivariate analysis of variables associated with union status

Table S3. Univariate analysis of variables associated with union time in the subgroup with final union status

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