BJR

INFECTION

Treatment of infected bone defects with the induced membrane technique

A SYSTEMATIC REVIEW

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Aims
This study aimed to evaluate the effectiveness of the induced membrane technique for treating infected bone defects, and to explore the factors that might affect patient outcomes.

Methods
A comprehensive search was performed in PubMed, Embase, and the Cochrane Central Register of Controlled Trials databases between 1 January 2000 and 31 October 2021. Studies with a minimum sample size of five patients with infected bone defects treated with the induced membrane technique were included. Factors associated with nonunion, infection recurrence, and additional procedures were identified using logistic regression analysis on individual patient data.

Results
After the screening, 44 studies were included with 1,079 patients and 1,083 segments of infected bone defects treated with the induced membrane technique. The mean defect size was 6.8 cm (0.5 to 30). After the index second stage procedure, 85% (797/942) of segments achieved union, and 92% (999/1,083) of segments achieved final healing. The multivariate analysis with data from 296 patients suggested that older age was associated with higher nonunion risk. Patients with external fixation in the second stage had a significantly higher risk of developing nonunion, increasing the need for additional procedures. The autografts harvested from the femur reamer-irrigator-aspirator increased nonunion, infection recurrence, and additional procedure rates.

Conclusion
The induced membrane technique is an effective technique for treating infected bone defects. Internal fixation during the second stage might effectively promote bone healing and reduce additional procedures without increasing infection recurrence. Future studies should standardize individual patient data prospectively to facilitate research on the affected patient outcomes.

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Keywords: Infection, Bone defects, Induced membrane technique, Systematic review

Article focus
- The induced membrane technique is an effective method for managing infected bone defects.

Key messages
- Internal fixation during the second stage might effectively promote bone healing and reduce additional procedures without increasing infection recurrence.

Strengths and limitations
- Radical debridement is still an important cornerstone in the treatment of infected bone defects with the induced membrane technique.
- All studies included in this review were low-level evidence except one randomized controlled trial. Thus, the strength of the conclusions drawn from the multivariate analysis is limited.

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Introduction

Managing infected bone defects is complex and challenging, and the surgeon faces two major challenges: infection control and defect reconstruction.[1] In 2000, the French doctor Masquelet first reported the induced membrane technique,[2] also known as the Masquelet technique, to treat infected bone defects. The induced membrane technique is a two-stage surgical procedure, combining the induction of functional biofilms with non-vascularized morcellized cancellous bone grafts to reconstruct segmental bone defects.[2,3] Since the two-stage operation is consistent with first-stage infection control and second-stage bone reconstruction, it is especially advantageous in treating infected bone defects.[4] Antibiotic bone cement can assist in infection control by eliminating dead space, being a local antibiotic carrier, and strengthening bone defect stability to some extent.[5-7] The induced membrane technique has changed with its widespread clinical use.[8,9] For example, antibiotics were added to the bone cement in the first stage,[10,11] internal fixation was established as a stabilization method,[12-14] osteoinductive factors were included, and allograft and osteoconductive scaffold for bone graft expender were added in the second stage.[6,10,11] Although some systematic reviews and meta-analyses have discussed these changes, they included bone defects caused by various factors,[6,10,11,15,16] or other treatment methods.[17] Therefore, we conducted a systematic review to explore the factors affecting the patient outcomes of infected bone defect treated with the induced membrane technique.

Methods

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[18]

Search strategy. Two reviewers (JS, ZW) searched PubMed, Embase, and the Cochrane Central Register of Controlled Trials databases between 1 January 2000 and 31 October 2021, using the terms "induced membrane technique" and "Masquelet technique". Reference lists were also manually searched for relevant studies and reviews.

Inclusion and exclusion criteria. The inclusion criteria were: 1) patients with infected bone defects treated with the induced membrane technique; 2) publications in English; and 3) sample size ≥ five patients. The exclusion criteria were: 1) "review" and "digest", "talk", "letters", "commentary", "Conference article/abstract", and "case report"; 2) animal studies; 3) basic research; 4) aseptic bone defects; and 5) bone transport in an induced membrane.

Study selection. Two authors (JS, ZW) independently performed the initial screening of titles and abstracts. If the study included septic and aseptic bone defects, the number of infected patients was determined based on the description in the Methods and Results sections of the article. A study was included for data extraction and analysis if at least five patients with infected bone defects were included. Studies with fewer than five patients, or unclear descriptions of septic and aseptic bone defects, were excluded. The study included in the qualitative synthesis should provide individual patient data. A third author (GW) independently assessed the full texts for eligibility. Any disagreements were resolved by discussion among the three authors.

Data extraction. The information retrieved included time, study design, number of patients, demographic characteristics, details of the operative technique, and outcomes. When available, the above information was extracted at the individual patient level for further analysis.

The infection diagnosis should be specified in the text. Additional procedures were defined as all surgical procedures performed to achieve bone healing after the second stage, including removing or exchanging the internal fixation, debridement, and duplicate bone grafting. Redebridement before the second stage was excluded from additional procedures. Union was defined as bone healing after the second stage without additional surgery, known as union after the index second stage procedure.[10] Infection recurrence was defined as a deep infection requiring intravenous antibiotics and/or surgical procedures after grafting, excluding pin-track infections unless surgical intervention was required.

Statistical analysis. Statistical analyses were conducted with SPSS v22.0 (IBM, USA). The multivariate logistic regression analysis was conducted using individual patient data. The Hosmer-Lemeshow test determined the fit degree of the model. Statistical significance was set at $p < 0.05$.

Results

Literature search. Initially, we identified 1,092 studies. After removing duplicates, we screened 577 titles and abstracts. Among them, 519 articles did not fit the inclusion criteria, leaving 58 for full-text analysis. Overall, 14 full-text articles did not distinguish between septic and aseptic patients; thus, 44 studies were included for data extraction and analysis.[7,12–14,19–58] Individual patient data were inaccessible in 14 full-text articles. In total, we included 30 studies in the qualitative synthesis (Figure 1).[12,13,29–56]

Demographic characteristics. Of the 44 included studies, 37 were retrospective and seven were prospective, including one randomized controlled trial. Among the 1,079 patients, 1,083 segments of infected bone defects were treated with the induced membrane technique; four patients had two infected bone defects in different locations, and underwent the same treatment.[41,48] Additionally, 83% (851/1,031) of patients were male and 17% (180/1,031) were female, with a mean age of 40.3 years (4 to 88). Among the 1,083 segments, the most frequent location was the tibia (65%, n = 704), followed by the femur (24%, n = 258), forearm (ulna and radius; 8%, n = 86), and humerus (1%, n = 15). Other sites accounted for 2% (n = 20): five segments in the metatarsus, six in the fibula, two in the calcaneus, six in the phalanx, and

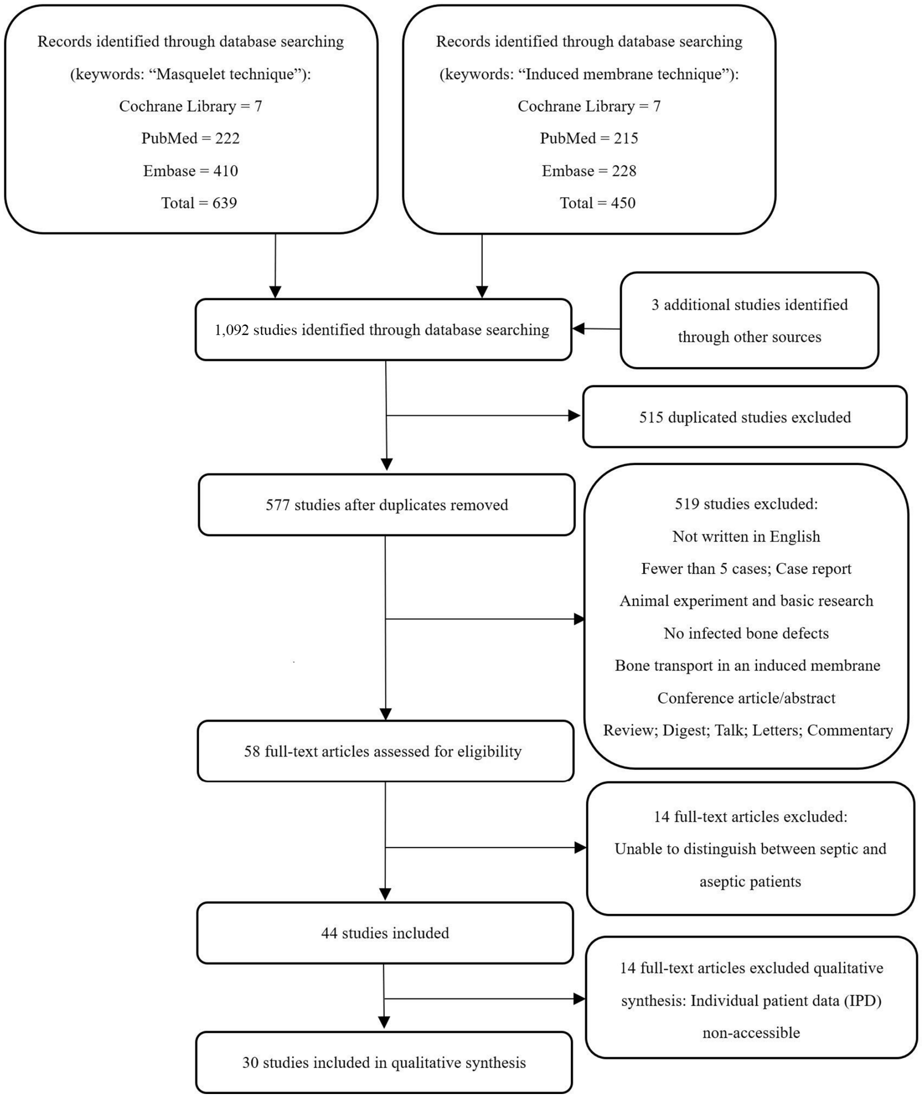

Fig. 1

Study flow diagram.

one in the metacarpal.[19,25,32,38,39,44,55] The mean bone defect length was 6.8 cm (0.5 to 30). Some studies reported the volume of bone defects rather than their length.[21,36,58] Study and patient characteristics are summarized in Table I.

Surgical parameters. The surgical parameters mainly included fixations, antibiotic bone cement, the interval between two stages, different autograft sources, osteoinductive adjunct, allograft, and osteoconductive scaffold (Table II).

The addition of antibiotics to the polymethyl methacrylate spacer was reported in 38 studies, encompassing 94% (1,016/1,083) of segments. Among the patients with known antibiotics, 38% (338/896) used a single antibiotic, while 62% (558/896) used a mixture of two antibiotics in the polymethyl methacrylate spacer. Vancomycin was the most common antibiotic used alone, followed by gentamicin. The most common antibiotic combination was vancomycin and gentamicin, followed by vancomycin and tobramycin. The mean time between the two stages was 10.9 weeks (4.3 to 64).

Overall, 33 studies reported the fixation methods of first-stage surgery. External fixation was the most common (50%, 408/816), followed by internal plate fixation (42%, 347/816). However, intramedullary nails were rarely used as internal fixation (4%, 30/816) compared to plates. Other fixation methods included Kirschner wires (K-wires), braces, and plasters (4%, 31/816). A total of 39 studies reported the fixation methods of second-stage surgery. External fixation remained the most common fixation method (33%, 272/815), followed by intramedullary nail fixation (32%, 258/815) and plate internal fixation (29%, 233/815). Intramedullary nail and plate fixation was rarely used as internal fixation (2%, 18/815). Other fixation methods, including K-wires, plasters, and braces, accounted for 4% (34/815).

Table I. Summary of study and patient characteristics.

Study	Study design	Patients, n	Segments, n	Sex, n		Mean age, yrs (range)	Defect location, n					Mean defect size, cm (range)
				Male	Female		Femur	Tibia	Humerus	Forearm	Other*	
Schöttle 2005[29]	Retrosp	6	6	5	1	49.5 (37 to 61)	0	6	0	0	0	6.5 (5 to 8)
Stafford 2010[30]	Retrosp	7	7	6	1	39.7 (33 to 44)	2	5	0	0	0	6.5 (2 to 17)
El-Alfy 2015[31]	Prosp	17	17	15	2	43.1 (26 to 58)	4	13	0	0	0	7.6 (5 to 11)
Scholz 2015[19]	Retrosp	13	13	12	1	41.4 (16 to 69)	3	5	0	1	4	8.1 (5.5 to 14.5)
Azi 2016[7]	Retrosp	23	23	NR	NR	32.8 (18 to 54)	10	13	0	0	0	7.2 (2.5 to 15.5)
Giannoudis 2016[32]	Prosp	21	21	15	6	45.5 (18 to 80)	7	7	1	5	1	4.7 (2 to 12)
Gupta 2016[33]	Prosp	7	7	6	1	37.6 (22 to 55)	0	7	0	0	0	5.3 (4 to 8.5)
Wang 2016[20]	Retrosp	32	32	22	10	40.0 (19 to 72)	12	20	0	0	0	5.0 (1.5 to 12.5)
Cho 2017[34]	Retrosp	19	19	15	4	51.6 (20 to 80)	6	11	2	0	0	8.7 (3.4 to 16.4)
Luo F 2017[14]	Retrosp	67	67	58	9	37.0 (6 to 61)	0	67	0	0	0	6.8 (2 to 16)
Luo TD 2017[35]	Retrosp	7	10	3	4	47.1 (32 to 74)	0	0	0	10	0	5.6 (4 to 8)
Mühlhäusser 2017[36]	Retrosp	8	8	6	2	NR (34 to 67)	0	8	0	0	0	NR
Qiu 2017[21]	Retrosp	22	22	18	4	36.9 (22 to 68)	0	22	0	0	0	NR
Tong 2017[22]	Retrosp	20	20	15	5	39.9 (NR)	7	13	0	0	0	6.7 (NR)
Wang 2017[37]	Retrosp	15	15	13	2	34 (6 to 51)	0	15	0	0	0	5.1 (2 to 8.4)
Wu 2017[38]	Retrosp	36	36	30	6	41.1 (21 to 68)	16	19	0	0	1	5.5 (2 to 10.9)
Yu 2017[12]	Retrosp	13	13	9	4	39.0 (16 to 69)	13	0	0	0	0	9.8 (5 to 16)
Rousset 2018[39]	Retrosp	8	8	6	2	12.8 (4 to 16)	2	2	2	0	2	12.0 (4 to 30)
Sasaki 2018[40]	Retrosp	7	7	6	1	42.9 (24 to 77)	2	5	0	0	0	3.7 (2.4 to 6.5)
Siboni 2018[41]	Retrosp	18	19	14	4	54.1 (24 to 88)	0	19	0	0	0	5.3 (1.1 to 18)
Dhar 2019[42]	Retrosp	12	12	11	1	37.9 (19 to 56)	0	0	0	12	0	5 (3.5 to 7.0)
Gupta S 2019[23]	Prosp	42	42	40	2	35.0 (18 to 67)	24	16	2	0	0	NR (4 to 12)
Masquelet 2019[43]	Retrosp	14	14	12	2	32.8 (19 to 65)	0	11	1	2	0	11.7 (3 to 25)
Raven 2019[24]	Retrosp	54	54	43	11	48.6 (18 to 83)	14	37	3	0	0	5.0 (0.5 to 26)

Continued

Table I. Continued

Study	Study design	Patients, n	Segments, n	Sex, n		Mean age, yrs (range)	Defect location, n					Mean defect size, cm (range)
				Male	Female		Femur	Tibia	Humerus	Forearm	Other*	
Wang 2019[44]	Retrosp	21	21	15	6	37.9 (16 to 69)	2	12	1	3	3	5.8 (2 to 10)
Choufani 2020[45]	Prosp	13	13	NR	NR	33.7 (9 to 65)	5	6	0	2	0	4.5 (2 to 10)
Gindraux 2020[56]	Retrosp	13	13	9	4	46.8 (21 to 62)	3	7	2	1	0	5.8 (2 to 11)
Inci 2020[46]	Retrosp	24	24	22	2	38.1 (18 to 67)	0	24	0	0	0	6.58 (4 to 10)
Jia 2020[25]	Retrosp	183	183	154	29	42.8 (10 to 68)	81	100	0	0	2	7.7 (1.5 to 22.7)
Mathieu 2020[47]	Retrosp	8	8	7	1	58 (36 to 87)	2	4	0	2	0	8.8 (5 to 20)
Mathieu 2020[48]	Retrosp	11	11	8	3	36 (22 to 71)	0	11	0	0	0	4.4 (2 to 11)
Mathieu 2020[49]	Retrosp	12	12	NR	NR	37.2 (26 to 61)	0	12	0	0	0	6.8 (3 to 12)
Meselhy 2020[26]	Prosp	45	45	40	5	35 (22 to 51)	27	18	0	0	0	8.16 (4 to 12)
Zhao 2020[50]	Retrosp	12	12	9	3	39.5 (18 to 59)	3	8	1	0	0	10 (6.1 to 17.2)
Commeil[51] 2021	Retrosp	6	6	5	1	43.8 (33 to 59)	0	0	0	6	0	4.2 (2 to 8)
Lauthe 2021[52]	Retrosp	6	6	6	0	40.3 (18 to 67)	0	0	0	6	0	3.3 (1 to 9)
Lotzien 2021[53]	Retrosp	31	31	30	1	45.8 (18 to 71)	0	31	0	0	0	8.3 (1.7 to 28)
Ma 2021[27]	Retrosp	32	32	20	12	43.2 (19 to 62)	0	0	0	32	0	6.2 (3.6 to 8)
Pesciallo 2021[54]	Retrosp	21	21	13	8	42.4 (18 to 68)	8	13	0	0	0	5.3 (3.5 to 14)
Rohilla 2021[28]	RCT	12	12	11	1	39.7 (25 to 60)	0	12	0	0	0	3.8 (2 to 6)
Shen 2021[13]	Retrosp	21	21	19	2	44 (19 to 60)	0	21	0	0	0	6.1 (2.5 to 12)
Shen 2021[58]	Retrosp	26	26	19	7	11.8 (4 to 18)	5	17	0	4	0	NR
Toyama 2021[55]	Retrosp	7	7	6	1	56 (29 to 69)	0	0	0	0	7	NR
Xiao 2021[57]	Retrosp	87	87	78	9	40.1 (13 to 65)	0	87	0	0	0	7.2 (3 to 17)
Total	7 Prosp, 37 Retrosp, 1 RCT	1,079	1,083	851 /1,031 (83%)	180 /1,031 (17%)	40.3 (4 to 88)	258 /1,083 (24%)	704 /1,083 (65%)	15 /1,083 (1%)	86/1,083 (8%)	20 /1,083 (2%)	6.8 (0.5 to 30)

*Other: 5 metatarsus, 6 fibula, 2 calcaneus, 6 phalanx, and 1 metacarpal.
NR, not reported; Prosp, prospective study; RCT, randomized controlled trial; Retrosp, retrospective study.

Table II. Summary of surgical parameters.

Study	Segments, n	First-stage fixation				Second-stage fixation					Local antibiotic use, n			Mean time between stages, wks (range)	Autograft origin, n				Osteoinductive adjunct, n (%)*	Allograft, n (%)	Osteoconductive scaffold, n (%)†
		Plate	Nail	EF	Other‡	Plate	Nail	P + N	EF	Other‡	Total (%)	Single	Combination		ICBG	RIA	ICBG + RIA	Other§			
Schöttle 2005[29]	6	0	0	6	0	0	0	0	6	0	6 (100)	6	0	15 (13 to 17)	6	0	0	0	0 (0)	1 (16.7)	0 (0)
Stafford 2010[30]	7	NR	NR	NR	NR	3	2	2	0	0	7 (100)	NR	NR	NR	0	6	1	0	7 (100)	7 (100)	0 (0)
El-Alfy 2015[31]	17	0	0	17	0	0	0	0	17	0	0 (0)	0	0	10.9 (4.3 to 17.4)	17	0	0	0	0 (0)	0 (0)	0 (0)
Scholz 2015[19]	13	0	0	13	0	NR	NR	NR	8	0	13 (100)	NR	NR	9.8 (8 to 14)	13	0	0	0	3 (23.1)	0 (0)	0 (0)
Azi 2016[7]	23	NR	NR	20	0	NR	NR	0	13	0	23 (100)	0	23	12.8 (7 to 25)	23	0	0	0	0 (0)	0 (0)	0 (0)
Giannoudis 2016[32]	21	0	0	21	0	15	5	0	0	1	21 (100)	21	0	7 (6 to 8)	3	18	0	0	19 (90.5)	0 (0)	0 (0)
Gupta G 2016[33]	7	0	0	7	0	0	0	0	7	0	0 (0)	0	0	5.3 (4.3 to 6.4)	7	0	0	0	0 (0)	0 (0)	1 (14.3)
Wang 2016[20]	32	NR	NR	NR	NR	19	0	10	3	0	32 (100)	0	32	8.9 (6 to 14)	32	0	0	0	0 (0)	NR	0 (0)
Cho 2017[34]	19	NR	NR	NR	NR	13	3	3	0	0	19 (100)	0	19	17.1 (6 to 28)	19	0	0	0	0 (0)	0 (0)	19 (100)
Luo F 2017[14]	67	67	0	0	0	0	67	0	0	0	67 (100)	0	67	8 (NR)	67	0	0	0	0 (0)	0 (0)	0 (0)
Luo TD 2017[35]	10	9	0	1	0	10	0	0	0	0	10 (100)	NR	NR	17.9 (NR)	10	0	0	0	0 (0)	0 (0)	1 (10)
Mühlhäusser 2017[36]	8	0	0	8	0	3	5	0	0	0	0 (0)	0	0	13.3 (7 to 26)	NR	NR	NR	NR	3 (37.5)	NR	0 (0)
Qiu 2017[21]	22	0	0	18	4	0	0	0	18	4	22 (100)	0	22	10.3 (NR)	22	0	0	0	0 (0)	11 (50)	0 (0)
Tong 2017[22]	20	NR	NR	NR	NR	9	0	0	11	0	20 (100)	20	0	9.8 (8 to 11.3)	20	0	0	0	20 (100)	0 (0)	0 (0)
Wang 2017[37]	15	5	0	8	2	4	4	0	5	2	15 (100)	15	0	7.1 (6.3 to 15)	9	0	0	0	0 (0)	12 (80)	0 (0)
Wu 2017[38]	36	12	0	24	0	5	22	0	9	0	36 (100)	0	36	12.6 (6 to 36)	36	0	0	0	0 (0)	20 (55.6)	0 (0)
Yu 2017[12]	13	13	0	0	0	0	13	0	0	0	13 (100)	0	13	NR	13	0	0	0	0 (0)	0 (0)	0 (0)
Rousset 2018[39]	8	0	0	0	8	2	2	0	0	4	8 (100)	8	0	NR	2	0	0	0	0 (0)	2 (25)	5 (62.5)
Sasaki 2018[40]	7	4	0	0	3	4	3	0	0	0	7 (100)	7	0	12.7 (6 to 28)	7	0	0	0	0 (0)	0 (0)	7 (100)
Siboni 2018[41]	19	0	0	15	4	8	0	0	6	5	19 (100)	19	0	7.9 (NR)	18	0	0	0	0 (0)	9 (47.4)	0 (0)
Dhar 2019[42]	12	12	0	0	0	12	0	0	0	0	12 (100)	12	0	6 (NR)	12	0	0	0	0 (0)	0 (0)	0 (0)
Gupta S 2019[23]	42	NR	NR	18	0	NR	NR	NR	0	0	42 (100)	0	42	7.7 (5.1 to 12.4)	42	0	0	0	0 (0)	0 (0)	27 (64.3)
Masquelet 2019[43]	14	1	0	13	0	1	1	0	12	0	0 (0)	0	0	NR	14	0	0	0	0 (0)	0 (0)	0 (0)
Raven 2019[24]	54	NR	NR	NR	NR	25	27	0	0	2	54 (100)	NR	NR	NR	4	47	3	0	50 (92.6)	0 (0)	54 (100)
Wang 2019[44]	21	2	0	16	3	NR	NR	0	3	3	21 (100)	21	0	12 (NR)	NR	NR	NR	NR	0 (0)	0 (0)	0 (0)
Choufani 2020	13	0	2	8	3	2	2	0	9	0	13 (100)	13	0	9.1 (6 to 21.4)	13	0	0	0	0 (0)	0 (0)	0 (0)
Gindraux 2020[56]	13	5	6	1	1	NR	NR	NR	NR	NR	9 (69.2)	9	0	30 (5.1 to 64)	NR	NR	NR	NR	0 (0)	0 (0)	0 (0)
Inci 2020[46]	24	0	0	24	0	7	17	0	0	0	24 (100)	NR	NR	9.2 (6 to 16)	NR	NR	NR	NR	0 (0)	NR	NR
Jia 2020[25]	183	183	0	0	0	NR	NR	NR	0	0	183 (100)	0	183	NR	183	0	0	0	0 (0)	NR	0 (0)

Continued

Table II. Continued

Study	Segments, n	First-stage fixation: Plate	Nail	EF	Other‡	Second-stage fixation: Plate	Nail	P + N	EF	Other‡	Local antibiotic use, n: Total (%)	Single	Combination	Mean time between stages, wks (range)	Autograft origin, n: ICBG	RIA	ICBG + RIA	Other§	Osteoinductive adjunct, n (%)*	Allograft, n (%)	Osteoconductive scaffold, n (%)†
Mathieu 2020	8	0	5	0	3	4	4	0	0	0	8 (100)	8	0	12 (8 to 20)	4	1	3	0	0 (0)	0 (0)	0 (0)
Mathieu 2020	11	0	0	11	0	0	0	0	11	0	0 (0)	0	0	11 (6 to 24)	11	0	0	0	0 (0)	0 (0)	0 (0)
Mathieu 2020	12	1	0	11	0	1	2	0	9	0	12 (100)	12	0	21.7 (8 to 49)	NR	NR	0	0	0 (0)	0 (0)	0 (0)
Meselhy 2020[26]	45	0	0	45	0	0	0	0	45	0	45 (100)	0	45	7.1 (6 to 9)	45	0	0	0	0 (0)	0 (0)	0 (0)
Zhao 2020[50]	12	NR	NR	NR	NR	3	3	2	2	2	12 (100)	12	0	NR	12	0	0	0	0 (0)	0 (0)	12 (100)
Commeil 2021[51]	6	3	0	3	0	5	0	1	0	0	6 (100)	6	0	15 (8.6 to 21.4)	6	0	0	0	0 (0)	0 (0)	0 (0)
Lauthe 2021[52]	6	6	0	0	0	6	0	0	0	0	0 (0)	0	0	NR	6	0	0	0	0 (0)	0 (0)	0 (0)
Lotzien 2021[53]	31	NR	NR	NR	NR	0	0	0	31	0	31 (100)	19	12	18.3 (4.5 to 63)	1	13	17	0	20 (64.5)	23 (74.2)	0 (0)
Ma 2021	32	0	0	0	0	32	0	0	0	0	32 (100)	26	6	NR	32	0	0	0	0 (0)	0 (0)	0 (0)
Pesciallo 2021[54]	21	3	17	1	0	3	17	0	1	0	21 (100)	17	4	11 (6 to 28)	21	0	0	0	0 (0)	21 (100)	0 (0)
Rohilla 2021	12	0	0	12	0	0	0	0	12	0	12 (100)	NR	NR	NR	12	0	0	0	0 (0)	0 (0)	0 (0)
Shen 2021	21	21	0	0	0	21	0	0	0	0	21 (100)	0	21	NR (6 to 8)	21	0	0	0	0 (0)	0 (0)	0 (0)
Shen 2021	26	NR	NR	NR	NR	15	2	0	1	8	26 (100)	0	26	NR	0	0	0	0	26 (100)	26 (100)	0 (0)
Toyama 2021[55]	7	NR	NR	NR	NR	1	0	0	3	3	7 (100)	0	7	NR	2	0	0	2	0 (0)	0 (0)	0 (0)
Xiao 2021	87	0	0	87	0	0	57	0	30	0	87 (100)	87	0	NR	87	0	0	0	0 (0)	11 (12.6)	0 (0)
Total	1,083	347 /816 (42%)	30 /816 (4%)	408 /816 (50%)	31 /816 (4%)	233 /815 (29%)	258 /815 (32%)	18 /815 (2%)	272 /815 (33%)	34 /815 (4%)	1,016 /1,083 (94%)	338 /896 (38%)	558 /896 (62%)	10.9 (4.3 to 64)	852 /963 (88%)	85 /963 (9%)	24 /963 (3%)	2 /963 (0%)	148 /1,083 (14%)	143 /1,083 (13%)	126 /1,083 (12%)

*Includes bone morphogenetic proteins, bone marrow aspirate concentrate, platelet-rich plasma, and/or unspecified growth factors.
†Includes calcium sulphate, demineralized bone matrix, gelatin sponge, hydroxyapatite, and/or tricalcium phosphate.
‡Kirschner wire, plaster, and brace.
§Costal cartilage, radius.
EF, external fixation; ICBG, iliac crest bone graft; NR, not reported; P + N, plate + nail; RIA, reamer-irrigator-aspirator.

The autologous bone source was reported in 39 studies, and the most common bone harvest site was the iliac crest. Autologous bone graft was only obtained from the iliac crest bone graft in an estimated 88% (852/963) of segments, followed by the femur using a reamer-irrigator-aspirator system (9%, 85/963). Iliac crest bone graft was also combined with graft obtained using the reamer-irrigator-aspirator system (3%, 24/963). The use of allografts as a bone graft expander was reported in 11 studies, including 143 segments (13%, 143/1,083). In eight studies, including 148 segments (14%, 148/1,083), osteoinductive agents were added to the bone graft, with agents such as bone morphogenetic protein (BMP)-2, BMP-7, bone marrow aspirate concentrate, and platelet-rich plasma. Osteoconductive scaffolds, such as calcium sulphate, calcium phosphate, β-Tricalcium phosphate, and gelatin sponge, were used in eight studies (12%, 126/1,083).

Clinical indices. The clinical indices included final bone union, infection recurrence, union after the index second stage procedure, additional procedure, mean follow-up time, and mean bone healing time (Table III). Final bone union was achieved in 999 segments (92%, 999/1,083), and union after the index second stage procedure was achieved in 797 segments (85%, 797/942) without additional surgery. The infection recurrence rate was 10% (107/1,083). The mean follow-up time was 29.6 months (6 to 262), and the mean bone healing time was 7.5 months (2.3 to 49.9). Additional procedures, such as debridement, implant removal/exchange, and repeat grafting, were required to achieve bone healing in 142 segments (17%, 142/833).

Multivariate analysis. Furthermore, we analyzed the patient and surgical factors, and determined the independent risk factors affecting the prognosis. Individual patient data were reported in 30 studies, encompassing 421 patients (425 segments). However, complete data were unavailable for some patients due to the lack of standardization and unity in individual patient data reporting. Therefore, 296 segments were finally included for multivariate logistic regression analysis. The multivariate analysis suggested that older age was associated with higher nonunion risk (OR 1.032, 95% CI 1.006 to 1.058; p = 0.015). Patients with external fixation in the second stage had a significantly higher risk of developing nonunion (OR 6.740, 95% CI 2.043 to 22.238; p = 0.002; OR 10.188, 95% CI 2.685 to 38.657; p = 0.001), and increasing need of additional procedures (OR 6.399, 95% CI 2.030 to 20.177; p = 0.002; OR 5.784, 95% CI 1.759 to 19.021; p = 0.004). Meanwhile, harvesting autografts from the femur reamer-irrigator-aspirator increased the risk of nonunion (OR 14.057, 95% CI 2.280 to 86.664; p = 0.004), infection recurrence (OR 19.312, 95% CI 3.142 to 118.691; p = 0.001), and additional procedure (OR 8.975, 95% CI 1.509 to 53.388; p = 0.016) (Table IV).

Discussion

Since its first report to treat large segment bone defects by Masquelet in 2000,[2] the induced membrane technique has been widely used in clinical practice because of its remarkable effects. Many changes have occurred to improve patient outcomes.[9,31] In this systematic review, final bone union was achieved in 999 segments (92%, 999/1,083), and the infection recurrence rate was 10% (107/1,083). The mean bone healing time was 7.5 months (2.3 to 49.9), and additional procedures were required to achieve bone healing in 142 segments (17%, 142/833). These results were consistent with other reviews which confirmed that the induced membrane technique is reliable and effective for managing infected bone defects.[6,10] However, patients with tibial defects treated with the induced membrane technique had a high infection rate and a low union rate.[59] Morris et al[59] showed that patients who underwent initial surgery in a smaller unit had an increased rate of complications and required revision surgery more frequently. Therefore, patients transferred from peripheral hospitals should receive a careful assessment of the quality of initial debridement, and the treatment team should be confident that there is no residual infection before proceeding with the induced membrane technique.

Radical debridement is an important cornerstone for the treatment of infected bone defects with the induced membrane technique.[4,5,15,17,43,60] Preoperative evaluation and judgment of lesion boundary, 'pepper sign' in intraoperative bone debridement, repeated flushing, and elimination of dead space have been reported in many studies.[13,50,61] In 2010, Apard et al[62] and Stafford et al[30] added antibiotics to bone cement to improve the efficiency of infection control during the first stage induced membrane technique. A recent systematic review and meta-analysis suggested that adding antibiotics to bone cement can reduce infection recurrence and reoperation rate after the second stage of the induced membrane technique.[10,11] However, we found that the antibiotics used in the bone cement spacer did not reduce the infection recurrence rate, which might be related to our enrolled infected bone defect patients. Therefore, antibiotic bone cement cannot be considered capable of treating bone infection while neglecting the importance of radical debridement.[63]

External fixators are the first choice for local stabilization in Masquelet's clinical patients involving post-traumatic septic nonunions, occasionally requiring iterative excisions.[2] Using an external fixator often impacts the patient's ability to carry out daily activities,[64] and negatively affects their mental health.[65] In contrast, internal fixation might improve the patient's quality of life and avoid potential complications associated with the pin-track.[10] A recent study comparing treatment outcomes with internal and external fixation in the second stage of the induced membrane technique showed no difference in infection

Table III. Summary of clinical indices.

Study	Segments, n	Final union, n (%)	Union after index second stage procedure, n (%)	Mean time to union, mths (range)	Infection recurrence after grafting, n (%)	Mean follow-up time, mths (range)	Additional procedure, n (%)
Schöttle 2005[29]	6	6 (100)	5 (83.3)	7 (6 to 8)	0 (0)	36 (18 to 60)	1 (16.7)
Stafford 2010[30]	7	5 (71.4)	4 (57.1)	NR	1 (14.3)	NR	2 (28.6)
El-Alfy 2015[31]	17	14 (82.4)	8 (47.1)	10 (6 to 19)	2 (11.8)	23 (14 to 38)	10 (58.8)
Scholz 2015[19]	13	13 (100)	8 (61.5)	4.4 (2.8 to 5.5)	0 (0)	13 (9 to 24)	5 (38.5)
Azi 2016[7]	23	20 (87.0)	20 (87.0)	8.6 (4 to 15)	7 (30.4)	30.1 (12 to 61)	7 (30.4)
Giannoudis 2016[32]	21	20 (95.2)	19 (90.5)	5.6 (2 to 11)	1 (4.8)	NR	3 (14.3)
Gupta G 2016[33]	7	6 (85.7)	5 (71.4)	12.0 (8 to 16)	1 (14.3)	NR	2 (28.6)
Wang 2016	32	32 (100)	32 (100)	4.9 (3 to 9)	0 (0)	27.5 (24 to 32)	2 (6.3)
Cho 2017[34]	19	18 (94.7)	16 (84.2)	9.1 (6 to 12)	1 (5.3)	NR	3 (15.8)
Luo F 2017[14]	67	66 (98.5)	66 (98.5)	5.6 (3 to 11)	4 (6.0)	22.5 (18 to 35)	NR
Luo TD 2017[35]	10	10 (100)	9 (90)	NR	0 (0)	86.7 (41 to 150)	2 (20)
Mühlhäusser 2017[36]	8	7 (87.5)	6 (75)	12.7 (6 to 21.4)	0 (0)	NR	2 (25)
Qiu 2017[21]	22	20 (90.9)	20 (90.9)	7.5 (5 to 11)	1 (4.5)	31.2 (18 to 54)	1 (4.5)
Tong 2017[22]	20	20 (100)	19 (95)	NR	1 (5)	23 (NR)	1 (5)
Wang 2017[37]	15	15 (100)	15 (100)	5.3 (3 to 8)	0 (0)	25 (24 to 28)	0 (0)
Wu 2017[38]	36	36 (100)	36 (100)	5.9 (4 to 8)	1 (2.8)	29.5 (24 to 45)	0 (0)
Yu 2017[12]	13	13 (100)	12 (92.3)	4.7 (4.1 to 6.9)	1 (7.7)	17.8 (12 to 24)	1 (7.7)
Rousset 2018[39]	8	8 (100)	8 (100)	4.6 (3 to 12)	0 (0)	28.5 (12 to 60)	1 (12.5)
Sasaki 2018[40]	7	7 (100)	7 (100)	5.7 (4 to 9)	0 (0)	NR (12 to 19)	0 (0)
Siboni 2018[41]	19	17 (89.4)	8 (42.1)	17.1 (4 to 36)	4 (21.1)	34.0 (12 to 82)	11 (57.9)
Dhar 2019[42]	12	12 (100)	12 (100)	7.8 (6 to 12)	0 (0)	NR	0 (0)
Gupta S 2019[23]	42	41 (97.6)	34 (81.0)	9.0 (6 to 15)	4 (9.5)	27.7 (12 to 48)	NR
Masquelet 2019[43]	14	14 (100)	14 (100)	7.6 (3 to 16)	0 (0)	N.R. (120 to 262)	0 (0)
Raven 2019[24]	54	39 (72.2)	NR	10.4 (4.5 to 26.8)	6 (11.1)	NR	NR
Wang 2019[44]	21	21 (100)	20 (95.2)	5.5 (3 to 8)	4 (19.0)	19.5 (12 to 52)	3 (14.3)
Choufani 2020	13	6 (46.1)	5 (38.5)	6.7 (4 to 12)	5 (38.5)	NR	6 (46.2)
Gindraux 2020[56]	13	13 (100)	13 (100)	13.8 (4.6 to 49.9)	0 (0)	NR	0 (0)
Inci 2020[46]	24	22 (91.7)	22 (91.7)	9.2 (5.6 to 14)	2 (8.3)	25.9 (12 to 48)	2 (8.3)
Jia 2020[25]	183	175 (95.6)	159 (86.9)	5.4 (4 to 12)	24 (13.1)	32 (12 to 66)	24 (13.1)
Mathieu 2020	8	7 (87.5)	6 (75)	7 (5 to 10)	2 (25)	21 (12 to 36)	2 (25)
Mathieu 2020	11	9 (81.8)	5 (45.5)	NR	5 (45.5)	64 (52 to 94)	6 (54.5)
Mathieu 2020	12	11 (91.7)	6 (50)	10.2 (8 to 12)	3 (27.3)	NR	6 (50)
Meselhy 2020[26]	45	42 (93.3)	42 (93.3)	6.1 (3.7 to 14)	3 (6.7)	26 (17 to 37)	3 (6.7)
Zhao 2020[50]	12	12 (100)	12 (100)	29 (16 to 48)	0 (0)	69 (30 to 142)	0 (0)
Commeil 2021[51]	6	5 (83.3)	5 (83.3)	9.4 (4 to 13)	0 (0)	62.8 (48 to 74)	1 (16.7)
Lauthe 2021[52]	6	5 (83.3)	5 (83.3)	3.3 (3 to 6)	0 (0)	NR	0 (0)
Lotzien 2021[53]	31	14 (45.2)	5 (16.1)	15.5 (6 to 49)	17 (54.8)	33 (13 to 69)	26 (83.9)
Ma 2021	32	32 (100)	32 (100)	6.6 (4 to 9)	0 (0)	NR	0 (0)
Pesciallo 2021[54]	21	21 (100)	19 (90.5)	8.3 (6 to 12)	2 (9.5)	NR (13 to 54)	4 (19)
Rohilla 2021	12	8 (66.7)	6 (50)	NR	0 (0)	30.4 (24 to 36)	4 (33.3)
Shen 2021	21	21 (100)	21 (100)	4.2 (2.3 to 11.2)	0 (0)	NR	0 (0)
Shen 2021	26	26 (100)	25 (96.2)	5.1 (3 to 10)	0 (0)	23.2 (12 to 60)	1 (3.8)
Toyama 2021[55]	7	7 (100)	7 (100)	NR	0 (0)	9.6 (6 to 16)	0 (0)
Xiao 2021	87	83 (95.4)	NR	6.8 (3 to 16)	5 (5.7)	NR	NR
Total	1,083	999/1,083 (92)	797/942 (85)	7.5 (2.3 to 49.9)	107/1,083 (10)	29.6 (6 to 262)	142/833 (17)

NR, not reported.

control and bone healing. However, higher complication rates were detected in the external fixation group.[57] Lotzien et al[53] reported unsatisfactory results during the reconstruction of septic tibial bone defects with the induced membrane technique and external ring fixation. Siboni et al[41] also believed that a lack of rigid fixation (in the case of an external fixator) after the second stage would lead to nonunion or delayed union. Our results indicated that external fixation in second-stage surgery is an independent risk factor for nonunion and additional procedures, and did not reduce the risk of infection recurrence. These results may be associated with the relative

Table IV. Summary of multivariate logistic regression analysis.

Variable	Nonunion after index second stage procedure, OR (95% CI)	p-value	Infection recurrence after grafting, OR (95% CI)	p-value	Additional procedure, OR (95% CI)	p-value
Sex — male vs female	2.953 (0.862 to 10.117)	0.085	3.964 (0.434 to 36.165)	0.222	2.097 (0.691 to 6.366)	0.191
Age (per year)	1.032 (1.006 to 1.058)	0.015	1.009 (0.977 to 1.043)	0.574	1.019 (0.994 to 1.044)	0.134
Location — tibia vs femur	1.037 (0.356 to 3.020)	0.947	2.471 (0.431 to 14.174)	0.310	1.634 (0.563 to 4.740)	0.366
Size of defect (per cm)	1.033 (0.947 to 1.127)	0.464	1.080 (0.973 to 1.199)	0.150	1.039 (0.955 to 1.131)	0.376
Type of fixation (second stage)						
Nail vs Plate	0.662 (0.178 to 2.453)	0.537	2.674 (0.397 to 18.002)	0.312	1.106 (0.329 to 3.715)	0.870
EF vs Plate	6.740 (2.043 to 22.238)	0.002	4.262 (0.724 to 25.102)	0.109	6.399 (2.030 to 20.177)	0.002
EF vs Nail	10.188 (2.685 to 38.657)	0.001	1.594 (0.333 to 7.636)	0.560	5.784 (1.759 to 19.021)	0.004
Antibiotics used in spacer	0.525 (0.165 to 1.672)	0.276	0.939 (0.147 to 6.003)	0.947	0.777 (0.248 to 2.432)	0.665
Autograft origin — RIA vs ICBG	14.057 (2.280 to 86.664)	0.004	19.312 (3.142 to 118.691)	0.001	8.975 (1.509 to 53.388)	0.016
Osteoinductive adjunct*	0.625 (0.110 to 3.553)	0.596	0.309 (0.059 to 1.606)	0.163	0.663 (0.116 to 3.782)	0.643
Allograft	1.927 (0.779 to 4.770)	0.156	1.458 (0.465 to 4.576)	0.518	1.718 (0.719 to 4.108)	0.223
Osteoconductive scaffold†	1.299 (0.363 to 4.648)	0.687	0.363 (0.032 to 4.156)	0.415	1.075 (0.309 to 3.735)	0.910

*Includes bone morphogenetic proteins, bone marrow aspirate concentrate, platelet-rich plasma, and/or unspecified growth factors.
†Includes calcium sulphate, demineralized bone matrix, gelatin sponge, hydroxyapatite, and/or tricalcium phosphate.
CI, confidence interval; OR, odds ratio; EF, external fixation; ICBG, iliac crest bone graft; RIA, reamer-irrigator-aspirator

stability of the external fixator.[66] Additionally, pin-track infection, the most common complication of external fixation, is correlated with loose pins,[67] which might further reduce external fixation stability. Hence, Azi et al[4] recommend selecting internal fixation for definitive bone stabilization whenever possible. Meanwhile, in contrast to Morwood et al,[68] we did not find any differential effect of the internal fixation method (plate vs intramedullary nail) on outcomes. In their study, acute bone loss after open fracture was the major aetiology of bone defects (67%) rather than infected bone defects. Moreover, there is a lack of comparative studies on second-stage internal fixation (nail vs plate) in the management of infected bone defects with the induced membrane technique.

Morcellized cancellous bone autograft has always been considered to be the ideal bone graft.[69,70] Herein, the most commonly used autografts were harvested from the anterior or posterior iliac crests (88%, 852/963). However, the complication rate of the iliac crest as the donor site can be as high as 10%.[71] Compared to iliac crest bone graft harvesting, reamer-irrigator-aspirator bone graft harvesting produces sufficient graft and has low donor site morbidity.[72,73] Here, 9% (85/963) of patients only obtained autogenous bones using the reamer-irrigator-aspirator. Stafford and Norris[30] reported good results from combining reamer-irrigator-aspirator and the induced membrane technique in treating infected bone defects. However, the multivariate analysis suggested that the reamer-irrigator-aspirator is an independent risk factor for poor outcomes, which might be related to the heterogeneity of the included studies. In Lotzien et al's study,[53] nine different orthopaedic surgeons operated, which might have led to different operating techniques. Therefore, among the patients who obtained bone autograft through reamer-irrigator-aspirator (97%), the initial healing rate was only 17%, the infection recurrence rate was as high as 53%, and the reoperation rate reached 83%. A recent study showed that the success rate of segmental bone defect reconstruction with autogenous bone obtained by reamer-irrigator-aspirator was 54%,[74] far from our expectations. The defect size might be a key factor affecting the final result.[74] Another factor that must be considered is whether preoperative infections are related to the ultimate effect of reamer-irrigator-aspirator bone graft reconstruction on bone defects, which requires further research. Therefore, autogenous iliac bone grafts remain the gold standard for treating bone defects,[75] especially infected ones.

Supplementary allografts and osteoconductive scaffolds are often used when the harvested autograft quantity is insufficient. Our review found that 25% (269/1,083) of segments used these two bone graft expanders. The multivariate analysis did not show a significant negative effect, which might be related to the fact that the bone graft expender to autograft ratio was ≤ 1:3 in some included studies.[20,25,36,38,50,57] Some scholars believe that a percentage of bone graft expander volume between 25%[3,5,9,76] and 40%[70] does not increase the rate of complications (e.g. nonunion, graft resorption). However, good results have also been reported for the complete use of allograft[58] or osteoconductive scaffold,[39] but were limited to immature patients.

Additionally, the use of osteoinductive adjuncts such as BMP, platelet-rich plasma, and/or bone marrow aspirate concentrate concurrently with the induced membrane technique has emerged as a recent trend in an effort to increase union rates.[77] However, our multivariate analysis did not reach that conclusion, which is significantly different from the clinical effects reported in previous studies.[58,78] Masquelet even believed that adding BMP-7 leads to a poor prognosis of infected bone defects.[3]

Age is a recognized factor affecting bone healing.[79,80] However, to treat bone defects, our results regarding age conflicted with other systematic reviews.[6,10,11] Two reasons can be considered: the first might be related to the presence of children (4 to 16 years old) who accounted for a certain proportion of the patients included in this study; the second is the increased comorbidities that come with age.[81] A recent systematic review suggested that old age (age ≥ 65 years) might be a risk factor for final nonunion status for managing femoral bone defects with the induced membrane technique.[16] Therefore, for elderly patients with other risk factors for bone healing, second-stage reconstruction should be performed cautiously, and even second-stage surgery should be delayed indefinitely. Cierny[82] and Shen et al[13] reported a method using permanent spacers, composed of various antibiotic-impregnated bone cement reinforced with a nail, pin, or plate, to treat infected bone defects successfully, which might be effective, but long-term follow-up observations are needed.

Our systematic review has some limitations. First, all studies included had low-level evidence, with only one randomized controlled trial, which limited the capacity to control for confounding variables and selection bias. Moreover, some statistically significant differences have wide confidence intervals, indicating that the effect size estimate is imprecise. Second, the complexity of microbial culture results and the difference in follow-up periods makes it impossible to include them in the multivariate analysis, which is a potential confounder limiting comparability. Third, the studies included in the multivariate analysis lack uniform standards for individual patient data reporting, which makes extraction and follow-up analysis difficult. Missing data included smoking, diabetes, deprivation, and nutrition, which negatively affect bone healing time and union. Thus, the strength of conclusions drawn from the multivariate analysis is limited.

In conclusion, the induced membrane technique is an effective treatment for infected bone defects. Second-stage internal fixation might promote bone healing and reduce additional procedures without increasing infection recurrence. Additionally, reamer-irrigator-aspirator bone grafts might not be suitable for infected bone defects. Nevertheless, future studies should standardize individual patient data reporting – including sex; age; smoking; diabetes; deprivation; nutrition; defect location and size; two-stage fixation methods; local antibiotic use; time between stages; autograft origin; osteoinductive adjunct, allograft, and osteoconductive scaffold use; final union; initial union; union time; infection recurrence; follow-up time; and additional procedure – in a prospective fashion to facilitate research on the influence of relevant factors on patient outcomes.

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