

Bone graft versus non-bone graft for treatment of calcaneal fractures

A protocol for meta-analysis

Heng Tian, MD^a, Wenlai Guo, MD^a, Jinlan Zhou, MD^b, Xiaoyue Wang, MD^b, Zhe Zhu, MD, PhD^{a,*}^D

Abstract

Background: Calcaneal fractures are a prevalent form of injury caused by high-energy trauma. This study aimed at investigating whether bone graft and non-bone graft are essential for the internal fixation of calcaneal fractures. A meta-analysis of relevant clinical studies evaluated radiographic parameters, functional outcomes, and complications that offer practical recommendations on the suitability of bone grafts for the management of Calcaneal fractures.

Methods and analysis: This study performed a comprehensive search on PubMed, EMBASE, and Cochrane electronic to retrieve related clinical studies. The studies incorporated in our meta-analysis were identified after doing a preliminarily screening, reading of the full-text articles, and eliminating repeated studies. After quality assessment and data extraction, the standardized mean difference and risk ratio were selected as effect sizes. The data on Böhler angle, Gissane angle, calcaneal height, American Orthopaedic Foot and Ankle Society hindfoot scores, Maryland Foot Evaluation, and rate of wound infection were analyzed using Revman 5.3 software (Cochrane Collaboration).

Results and Conclusions: This study did not reveal any significant differences (P < .05) in both Böhler and Gissane angles, calcaneal height, American Orthopaedic Foot and Ankle Society hindfoot scores, Maryland foot evaluation, and rate of wound infection between the 2 groups. Due to the lack of a large sample of comparative studies, the use of bone grafting for the management of calcaneal fractures requires additional substantiation.

Abbreviations: AOFAS = American Orthopaedic Foot and Ankle Society, CI = confidence interval, NOS = Newcastle–Ottawa scale, RCTs = randomized controlled trials, SBG = small incision bone graft, SMD = standardized mean difference.

Keywords: bone graft, calcaneal fractures, meta-analysis

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No ethical approval and patient safety considerations were required in this study since it was based on previously published studies. The results of this metaanalysis will be published in a peer-reviewed journal and disseminated at scientific conferences.

Patient consent for publication is not required.

Provenance and peer review are not commissioned; externally peer-reviewed.

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The authors have no conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are publicly available.

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1. Background

The treatment goals for a calcaneal fractures include a correction of the height, width, and length of the calcaneus for the accurate anatomic restoration of the displaced joints and robust osteosynthesis. Operative treatment of calcaneal fractures should also achieve anatomical reconstruction of the subtalar and calcaneo-cuboid joints of the foot.^[1,2]

There is currently a controversy over the necessity of performing a bone graft following reduction and internal fixation of calcaneal fractures. The main contention is whether failure to perform a bone graft can predispose the patient to postoperative re-displacement or late articular surface defect and whether it affects postoperative function.^[3–10] This study did a meta-analysis of relevant clinical studies to determine whether bone grafts are needed during the surgery for calcaneal fractures. The parameters evaluated in the present study include Böhler and Gissane angles, calcaneal height, American Orthopaedic Foot and Ankle Society (AOFAS) hindfoot scores, Maryland foot evaluation, and rate of wound infection.

2. Materials and methods

2.1. Search strategy

2.1.1. Retrieval method. The search strategies employed in this meta-analysis were based on the criteria developed by the Cochrane Collaboration. The search included selected keywords and free words, and these retrieval words were combined using Boolean operators. The PubMed, EMBASE, and Cochrane

databases were electronically searched on March 20, 2019, to retrieve journal references on related studies.

2.1.2. Basic PubMed search. The electronic search on PubMed used the strategy: (((Heel Bone[Title/Abstract] OR (("bone and bones" [MeSH Terms] OR ("bone" [All Fields] AND "bones" [All Fields]) OR "bone and bones" [All Fields] OR "bone" [All Fields]) AND Heel[Title/Abstract])) OR "Calcaneus"[MeSH]) AND (((((((((((((((()) Broken Bones[Title/Abstract] OR (("bone and bones"[MeSH Terms] OR ("bone"[All Fields] AND "bones"[All Fields]) OR "bone and bones" [All Fields] OR "bone" [All Fields]) AND Broken[Title/Abstract])) OR (("bone and bones"[MeSH Terms] OR ("bone" [All Fields] AND "bones" [All Fields]) OR "bone and bones" [All Fields] OR "bones" [All Fields]) AND Broken[Title/Abstract])) OR Broken Bone[Title/Abstract]) OR Bone Fractures[Title/Abstract]) OR Bone Fracture[Title/Abstract]) OR Fracture, Bone[Title/Abstract]) OR Spiral Fractures [Title/Abstract]) OR (Fracture, [All Fields] AND Spiral [Title/ Abstract])) OR (Fractures, [All Fields] AND Spiral [Title/Abstract])) OR Spiral Fracture[Title/Abstract]) OR Torsion Fractures[Title/Abstract]) OR (Fracture,[All Fields] AND Torsion [Title/Abstract])) OR (Fractures, [All Fields] AND Torsion [Title/ Abstract])) OR Torsion Fracture[Title/Abstract]) OR "Fractures, Bone" [MeSH])) AND ((((Transplantation, [All Fields] AND Bone [Title/Abstract]) OR (("transplantation"[Subheading] OR "transplantation" [All Fields] OR "grafting" [All Fields] OR "transplantation" [MeSH Terms] OR "grafting" [All Fields]) AND Bone[Title/Abstract])) OR Bone Grafting[Title/Abstract]) OR "Bone Transplantation" [MeSH])

2.2. Inclusion and exclusion criteria

2.2.1. Inclusion criteria. Studies were considered eligible if they satisfied the following inclusion criteria:

- (1) Cohort studies and randomized controlled trials (RCTs) reported in either the Chinese or English languages.
- (2) Intra-articular calcaneal fractures; not limited by sex, age, ethnicity, or nationality, and with a postoperative follow-up of at least 3 months.
- (3) Comparison on efficacy of the presence and absence of bone graft for treatment of intra-articular calcaneal fractures; not limited by internal fixation methods.
- (4) Complete original data including at least 1 of the following parameters: Böhler angle, Gissane angle, calcaneal height, AOFAS hindfoot scores, Maryland foot evaluation, and rate of wound infection.
- (5) True and credible bibliographic data, or one that can be transformed into binary continuous variables to represent each index.

2.2.2. Exclusion criteria. The following criteria were used for exclusion:

- (1) Case reports, reviews, and conference papers lacking full texts.
- (2) Old fractures (over 3 weeks) and pathological fractures (including primary fractures and fractures resulting from metastatic tumors, osteoporosis, or endocrine disorders).

2.3. Measurement of outcomes

2.3.1. Primary outcomes.

(1) Böhler angle: The Böhler angle is an imaging index that serves as an anatomical landmark for the posterior articular surface

of the subtalar joint. The Böhler angle can reflect the heel height and foot arch angle. A Böhler angle of <0 indicates that the outcome will be less successful regardless of whether surgery is performed. However, a Böhler angle of >15 suggests that long-term effects will be more successful. The size of the Böhler angle is a good indicator of the severity of the trauma load on the subtalar joint.^[11] Most manuscripts included in our study did not extensively detail the Böhler angle measurement methods used. However, the same methods and standards were used for each subject in different manuscripts, which brings quality internal consistency. We used the standardized mean difference (SMD) to merge data and to eliminate the interference of the measurement method on the mean outcome.

- (2) Gissane angle: The Gissane angle is a radiographic parameter formed by the posterior facet and the line from the calcaneal sulcus to the tip of the anterior process of the calcaneus. Gissane angle typically ranges from 120° to 145°.^[12]
- (3) Calcaneal height: The Calcaneal height is a radiographic parameter measured on the lateral radiographic view from the most posterior point of the tuberosity to the calcaneo-cuboid joint.^[13]

2.3.2. Secondary outcomes.

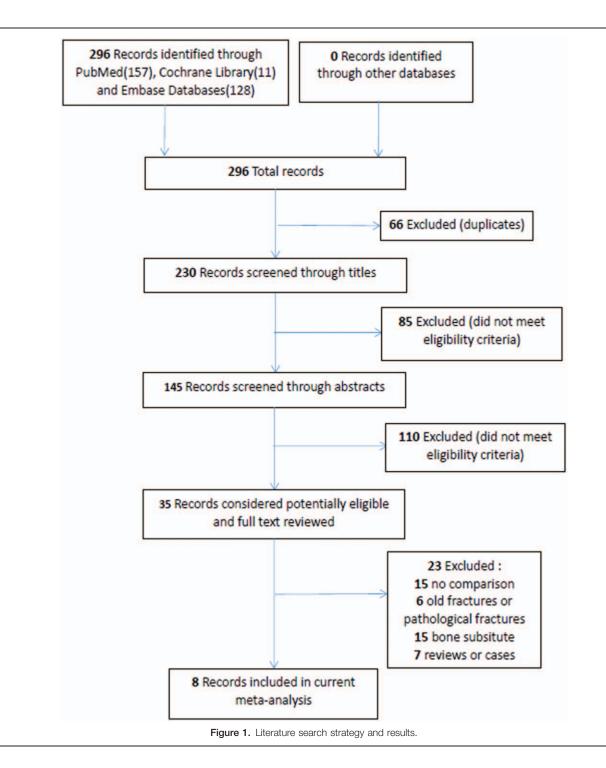
- (1) Functional outcomes: The functional outcomes of walking ability, walking distance, gait, and pain were assessed according to the AOFAS and Maryland Foot Evaluation.
- (2) Rate of wound infections: The incidence of wound infections, including superficial and deep infections following treatment of calcaneal fractures, was used as an indicator of recovery time.^[14,15]

2.3.3. Data extraction. Data extraction indexes included the first author, year of publication, sample size, sex, intervention measures, follow-up time, Böhler angle, Gissane angle, calcaneal height, AOFAS hindfoot scores, Maryland foot evaluation, and rate of wound infection. Two researchers, Heng Tian and Jinlan Zhou, independently extracted the data. Discrepancies between the data obtained by the 2 reviewers were resolved by consensus with the third researcher (Zhe Zhu).

2.3.4. Quality evaluation. Two researchers, Heng Tian and Jinlan Zhou, independently assessed the selection, comparability, and exposure qualities of the 7 included cohort studies according to the Newcastle–Ottawa scale (NOS). Disagreements regarding eligibility were resolved by discussion with a third researcher (Zhe Zhu).

2.4. Statistical analysis

Meta-analysis was done using Revman 5.3 software, and forest plots were drawn for comparison of odds ratios. The Mantel-Haenszel test was used to analyze binary variables, and continuous variables were analyzed using inverse variance. A $P \ge .05$ and $I^2 < 50\%$ indicated low heterogeneity, and a fixed-effects model was selected. On the contrary, a $P \le .05$ and $I^2 > 50\%$ showed high heterogeneity, and a random-effects model was selected. When $I^2 > 50\%$, the included studies were removed one by one to the sensitivity analysis that was conducted to determine the sources of heterogeneity. For result indicators of no less than 10 primary documents, subgroup analysis was performed. The risk ratio was used to measure the effect sizes



of binary variables, while the effect sizes of continuous variables were measured using the SMD. When result indicators of no less than 10 primary documents, publication bias was assessed at a 95% confidence interval (CI) using funnel plots.

2.5. Patient and public involvement

Patients were not involved in any stage of this study, including the development of the research question, design and implementation of the study, and interpretation of the results.

3. Results

3.1. Literature search

The literature search yielded a total of 296 studies, as shown in Figure 1: 157. After excluding duplicates, 230 studies were retained. Then, 145 studies were retained after reading titles, and 35 studies were included after reading abstracts. Among these, 6 studies on old and pathological fractures were excluded. Also excluded were 7 case studies/reviews, 1 study that used a bone substitute, and 15 studies that had no comparisons. The

Table 1

Characteristics of the included trials and participants.

	Cases	Sex	Intervent	ions	Type of bone graft	Follow-up Time
Included Trials	T/C	M/W	т	C	-	-
Longino et al 2001 ^[16]	20/20	38/2	ORIF+BG	ORIF	Autologous	3 mo
Kennedy et al 2003 ^[17]	12/10	16/6	ORIF + BG	ORIF	Allograft	>48 mo
Duymus et al 2017 ^[18]	21/22	35/5	ORIF + BG	ORIF	Allograft	3 mo
Singh et al 2013 ^[19]	202/188	282/108	ORIF + BG	ORIF	Autologous	>24 mo
Gusic et al 2015 ^[20]	20/67	_	ORIF + BG	ORIF	Autologous	12 mo
Nie et al 2009 ^[21]	56/56	74/38	CRPNF + SBG	CRPNF	Autologous or allograft	5–52 mo
Zhang et al 2011 ^[22]	11/11	17/5	IFLTPR + BG	IFLTPR	Autologous	25 mo
Cao H et al 2018 ^[23]	28/29	-	ORIF + BG	ORIF	Autologous	>12 mo

BG=bone graft, C=control group, CRPNF=closed reduction and percutaneous needle fixation, IFLTPR=internal fixation of locking titanium plate after reduction, LCSI=lateral calcaneal skin incision, M=men, ORIF=open reduction and internal fixation, SBG=small incision bone graft, T=treatment group, W=woman.

remaining 8 articles, 6 in English and 2 in Chinese, were included in this meta-analysis.

3.2. Study characteristics

The primary characteristics of sample size, sex, interventions, and follow-up time of the 8 studies are shown in Table 1.

3.3. Literature quality evaluation

The quality of the included 8 cohort studies was assessed by the NOS,^[24] and literature with points ranging from 5 to 9 was regarded as of high quality. According to the NOS analysis, the 8 studies included in this meta-analysis were of high quality: 5 studies had 9 points, 1 study had 8 points, while the other 2 studies had 7 points. The specific results are presented in Table 2.

3.4. Meta-analysis results 3.4.1. Böhler angle

3.4.1.1. Böhler angle in short-term follow-up. Five studies^[16,18–20,22] reported Böhler angle within 1-year post-surgery, including 274 cases in the bone graft group and 308 cases in the non-bone graft group. The $I^2 = 0\%$, and the fixed effects model was, therefore, selected. According to (2.1), SMD=0.03, 95% CI [-0.14, 0.20], and P=.72, suggesting that there were no significant differences (P > .05) between the 2 groups. (Figure 2.1) Figure 3 shows that no publication bias was noted.

3.4.1.2. Böhler angle in long-term follow-up. Four studies^[18,19,22,23] reported Böhler angle in over 1-year post-surgery, including 262 cases in the bone graft group and 250 cases in the

Included trials	Selection	Comparability	Outcome	Overal
	score	score	score	score
Longino et al 2001 ^[16]	4	2	1	7
Kennedy et al 2003 ^[17]	4	2	3	9
Duymus et al 2017 ^[18]	4	2	2	8
Singh et al 2013 ^[19]	4	2	3	9
Gusic et al 2015 ^[20]	4	1	2	7
Nie et al 2009 ^[21]	4	2	3	9
Zhang et al 2011 ^[22]	4	2	3	9
Cao H et al 2018 ^[23]	4	2	3	9

non-bone graft group. The $I^2 = 0\%$, and the fixed effects model was, therefore, selected. According to (2.2), SMD = 0.55, 95% CI [0.37, 0.73], and *P* < .00001, suggesting that the bone graft group was superior to the non-bone graft group (Figure 2.2).

3.4.2. Gissane angle

3.4.2.1. Gissane angle in short-term follow-up. Two studies^[19,22] reported Gissane angle within 1-year post-surgery, including 213 cases in the bone graft group and 199 cases in the non-bone graft group. The $I^2 = 0\%$, and the fixed effects model was, therefore, selected. According to (2.3), SMD = 0.16, 95% CI [-0.03, 0.36], and P=.10, suggesting that no significant differences (P > .05) were recorded between the 2 groups. (Figure 2.3).

3.4.2.2. Gissane angle in long-term follow-up. Three studies^[19,22,23] reported Gissane angle in over 1-year post-surgery, including 241 cases in the bone graft group and 228 cases in the non-bone graft group. The $I^2 = 0\%$, and the fixed effects model was, therefore, selected. As shown in (2.4), SMD = 0.20, 95% CI [0.02, 0.38], and P = .03 indicating that the bone graft group was superior to the non-bone graft group. (Figure 2.4).

3.4.3. Calcaneal height

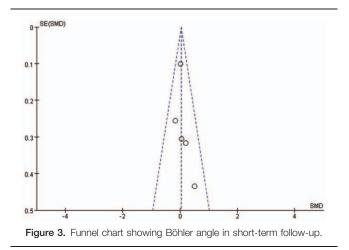
3.4.3.1. Calcaneal height in short-term follow-up. Two studies^[18,19] reported calcaneal height within 1 year after surgery, including 224 cases in the bone graft group and 209 cases in the non-bone graft group. The $I^2 = 0\%$, and the fixed effects model was, therefore, selected. As shown in (2.5), SMD = 0.07, 95% CI [-0.12, 0.26], and P = .47 indicating that no significant differences (P > .05) were noted between the 2 groups. (Figure 2.5).

3.4.3.2. Calcaneal height in long-term follow-up. Three studies^[18,19,23] reported calcaneal height in over 1-year post-surgery, including 252 cases in the bone graft group and 238 cases in the non-bone graft group. The $I^2 = 98\%$, and the random-effects model was, therefore, selected. As shown in (2.6), SMD = 1.73, 95% CI [-0.35, 3.81], and P = .10, suggesting that no significant differences (P > .05) were recorded between the 2 groups. The sensitivity analysis did not find any sources of heterogeneity. (Figure 2.6).

3.4.4. AOFAS hindfoot scores. Three studies^[18,19,23] reported postoperative foot functional scores based on the AOFAS hindfoot scores. The studies included 251 cases in the bone

	Exp	erimen	tal	C	entrol			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD 1		Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Duymus T M et al. 2017 Gusic N et al. 2015	26.7	7.3	21 20	26.2	9.4	22 67	7.7%	0.06 [-0.54, 0.66]	
Longino D et al. 2001	22.7	85	20	21.2	6.6	20	7.2%	0.19 -0.43, 0.81	
Singh A K et al. 2013	28.2	6.2	202	28.1	6.3	188	70.2%	0.02 [-0.18, 0.21]	
Zhang L et al. 2011	35.6	1.4	11	34.7	2	11	3.8%	0.50 [-0.35, 1.35]	- -
						-			
Total (95% CI)			274	-		308	100.0%	0.03 [-0.14, 0.20]	
Heterogeneity: Chi# = 2.0	15, 01 = 4	0 = 0.1	3); P :	0%					-4 -2 0 2 4
Test for overall effect Z =	0.30 (P	- 0.72)							Favours [experimental] Favours [control]
Figure 2.2									
	Expe	riment	al		ontrol			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD		Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Cao H et al. 2018 Duymus T M et al. 2017	28.4	6.1 9.06	28	26.9	7.2	29	11.5%	0.22 [-0.30, 0.74] 0.37 [-0.24, 0.97]	
Singh A K et al. 2013	25.4	6.1	202	21.2	7.2	188	75.5%	0.63 [0.43, 0.83]	
Zhang L et al. 2011	34.64	1.43	11	33.82	2.27	11	4.4%	0.42 [-0.43, 1.26]	
Total (95% CB			262			250	100.0%	0.55 [0.37, 0.73]	
Heterogeneity Chi*= 2.5	7 df = 3 (P=04		0%		250	100.0 %	0.00 [0.01, 0.10]	
Test for overall effect Z =	6.11 (P	0.000	01)						-4 -2 0 2 4 Favours (experimental) Favours (control)
Figure 2.3				-					
Study or Subgroup	Exper	imenta SD	Total	Mean	ontrol SD	Intal	Weight	Std. Mean Difference IV, Fixed, 95% CI	Std. Mean Difference IV, Fixed, 95% CI
Singh A K et al. 2013	120.4	8.4	202	118.8		188		0.18 [-0.02, 0.37]	N. CANU. STATE
Zhang L et al. 2011	125.73	6.42		125.91	5.71	11			Ŧ
Total Inter Co.							-		
Total (95% CI) Heterogeneity: Chi ² = 0.1	22 11	(P - C	213	- 07		199	100.0%	0.16 [-0.03, 0.36]	
Test for overall effect Z:				- 0%					-10 -5 0 5
2500.00									Favours (experimental) Favours (control)
Figure 2.4									
Study or Subgroup	Exper	sp 1		Mean	ntrol SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% Cl	Std. Mean Difference IV. Fixed, 95% CI
Cao H et al. 2018	125.6	5.4	28	124.7	6.2	29	12.2%	0.15[-0.37, 0.67]	-
Singh A K et al. 2013	124.2	7.6	202	122.4	9.2	188	83.1%	0.21 [0.01, 0.41]	
Zhang L et al. 2011	125.55	6.35	11	125.27	4.94	11	4.7%	0.05 [-0.79, 0.88]	+
Total (95% Ch			241			228	100.0%	0.20 [0.02, 0.38]	
Heterogeneity: Chi#= 0.1	18, df= 2	(P = 0.	91); (**	- 0%			-	and functional	-10 -5 0 5
Test for overall effect Z =	= 2.14 (P	= 0.03)							Favours (experimental) Favours (control)
Figure 2.5	12			15				Cod Marco Date	
Study or Subgroup	Exp	erimen SD		Mean	ontrol SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI	Std. Mean Difference IV, Fixed, 95% CI
Duymus T M et al. 2017	42.95	2.06	22	42.54	1.71	21	9.9%	0.21 [-0.39, 0.81]	±
Singh A K et al. 2013	42.8	3.1	202	42.6	4.2	188	90.1%	0.05 [-0.14, 0.25]	-
Total (95% CB			224			209	100.0%	0.07 [-0.12, 0.26]	
Heterogeneity: Chi#= 0.3			62); P	= 0%					10 -5 0 5
Test for overall effect Z =	= 0.73 (P	= 0.47)							Favours (experimental) Favours (control)
Figure 2.6								Sector Colorest and	
		erimer			ontrol SD		Weight	Std. Mean Difference	Std, Mean Difference IV. Random, 95% Cl
Study or Subgroup Cao H et al. 2018	Mean 45.67	2.33	Tota 28	Mean 37.42	SD 1.4	Tota 29	32.2%	M. Random, 95% Cl 4 25 [3 29, 5 21]	N. Random, 95% Cl
Study or Subgroup Cao H et al. 2018 Duymus T M et al. 2017	Mean 45.67 41.62	SD 2.33 1.83	Tota 28 22	Mean 37.42 39.5	SD 1.4 1.92	1ota 29 21	32.2%	V. Random, 95% Cl 4.25 [3.29, 5.21] 1.11 [0.46, 1.76]	N. Random, 95% Cl
Study or Subgroup Cao H et al. 2018	Mean 45.67	SD 2.33 1.83	Tota 28	Mean 37.42 39.5	SD 1.4	Tota 29	32.29	V, Random, 95% Cl 4.25 [3.29, 5.21] 1.11 [0.46, 1.76]	N. Random, 95% Cl
Study or Subgroup Cao H et al. 2018 Duymus T M et al. 2017 Singh A K et al. 2013 Total (95% CI)	Mean 45.67 41.62 40	SD 2.33 1.83 3.6	Tota 28 22 202 252	Mean 37.42 39.5 40.1	SD 1.4 1.92 3.8	10ta 29 21 188 238	32.2% 33.4% 34.4%	W. Random, 95% CI 4 25 [3 29, 5 21] 1 11 [0.46, 1.76] -0.03 [-0.23, 0.17]	N, Random, 95% Cl
Study or Subgroup Cao H et al. 2018 Duymus T M et al. 2017 Singh A K et al. 2013 Total (95% CI) Heterogeneity: Tau ⁴ = 3.	Mean 45.67 41.62 40 26; Chi ^p	SD 2 33 1 83 3 6 = 80.79	Tota 28 20 20 20 252 , df = 1	Mean 37.42 39.5 40.1	SD 1.4 1.92 3.8	10ta 29 21 188 238	32.2% 33.4% 34.4%	W. Random, 95% CI 4 25 [3 29, 5 21] 1 11 [0.46, 1.76] -0.03 [-0.23, 0.17]	N, Random, 95% Cl
Study or Subgroup Cao H et al. 2018 Duymus T M et al. 2017 Singh A K et al. 2013 Total (95% CI)	Mean 45.67 41.62 40 26; Chi ^p	SD 2 33 1 83 3 6 = 80.79	Tota 28 20 20 20 252 , df = 1	Mean 37.42 39.5 40.1	SD 1.4 1.92 3.8	10ta 29 21 188 238	32.2% 33.4% 34.4%	W. Random, 95% CI 4 25 [3 29, 5 21] 1 11 [0.46, 1.76] -0.03 [-0.23, 0.17]	N. Bandom, 95% Cl
Study or Subgroup Cao H et al. 2018 Duymus T M et al. 2017 Singh A K et al. 2013 Total (95% CI) Heterogeneity: Tau ⁴ = 3.	Mean 45.67 41.62 40 26; Chi ^p	SD 2 33 1 83 3 6 = 80.79	Tota 28 20 20 20 252 , df = 1	Mean 37.42 39.5 40.1	SD 1.4 1.92 3.8	10ta 29 21 188 238	32.2% 33.4% 34.4%	W. Random, 95% CI 4 25 [3 29, 5 21] 1 11 [0.46, 1.76] -0.03 [-0.23, 0.17]	M. Random, 95% C1
Study or Subaroup Cao H et al. 2018 Duymus T M et al. 2017 Singh AK et al. 2013 Total (95% CD Heterogeneity: Tau ^e = 3 Test for overall effect. 2: Figure 2.7	Mean 45.67 41.62 40 26, Chi ^p = 1.63 (P Exp	SD 2.33 1.83 3.6 = 80.79 = 0.10	Tota 28 20 202 252 0, df = 1	Mean 37.42 39.5 40.1 2 (P < 0.0	SD 1.4 1.92 3.8 000001)	Tota 29 21 188 238 (P = 9	32 2% 33.4% 34.4% 100.0%	 W. Random, 95% CI 4.25 (3.29, 5.21) 1.11 (0.46, 1.76) -0.03 (-0.23, 0.17) 1.73 (-0.35, 3.81) Std. Mean Difference 	N. Randem. 25% Cl
Study or Subaroup Cao H et al. 2018 Duymus T M et al. 2017 Singh A K et al. 2013 Total (195% C) Heterogeneith Tauf = 3. Test for overall effect Z: Figure 2.7 Study or Subaroup	Mean 45.67 41.62 40 26, ChP = 1.63 (P Exp Mean	SD 2.33 1.83 3.6 = 80.79 = 0.10 erimer	Tota 28 22 202 252 , df = 1) ital Tota	Mean 37.42 39.5 40.1 2 (P < 0.0 C Mean	SD 1.4 1.92 3.8 000001) Control SD	Tota 29 21 188 238 , P = 9	32.2% 33.4% 34.4% 100.0% 8%	K. Random, 95% CI 4 25 [3 29, 5 21] 1 11 [0.46, 1.76] -0.03 ± 0.23, 0.17] 1.73 ± 0.35, 3.81] Stid. Mean Difference K. Random, 95% CI	N. Bandem. 25% Cl
Study or Subaroup Cao H et al. 2018 Duymus T M et al. 2017 Singh AK et al. 2013 Total (95% C) Heterogeneity. Tau*= 3 Test for overall effect 2: Figure 2.7 Study or Subaroup Cao H et al. 2018	Mean 45.67 41.62 40 26; Chi ^p = 1.63 (P Exp Mean 84.6	SD 2.33 1.83 3.6 = 80.79 = 0.10 = 0.10 serimer SD 4.7	Tota 28 20 202 252 , df = 1)) ital <u>Tota</u> 28	Mean 37.42 39.5 40.1 2 (P < 0.0 (D = 0.0 0 Mean 1 82.9	SD 1.4 1.92 3.8 000001) Control SD 5.9	Tota 29 21 188 238 , P = 9 Tota 29	32.2% 33.4% 34.4% 100.0% 8%	K. Random, 95% CI 425 [3 20; 5 21] 1 11 [0.46, 1.76] -0.03 + 0 23, 0.17] 1.73 (-0.35, 3.81] Stid. Mean Difference N. Random, 95% CI 0.31 + 0.21, 0.84]	N. Bandem. 25% Cl
Study or Subaroup Cao H et al. 2018 Duymus T M et al. 2017 Singh A K et al. 2013 Total (195% C) Heterogeneith Tauf = 3. Test for overall effect Z: Figure 2.7 Study or Subaroup	Mean 45.67 41.62 40 26; Chi ^p = 1.63 (P Exp Mean 84.6	SD 2.33 1.83 3.6 = 80.79 = 0.10 = 0.10 science SD 4.7 7.17	Tota 28 20 202 252 0, df = 1)) (tal Tota 28 21 28 21 202 252 252 252 252 252 252 252 252 252	Mean 37.42 39.5 40.1 2 (P < 0.0 0 Mean 82.9 86.09	SD 1.4 1.92 3.8 000001) Control SD 5.9	Tota 29 21 188 238 ; P = 9	32.2% 33.4% 34.4% 100.0% 8% <u>Weight</u> 32.7% 31.7%	M. Random. 95% CI 4 25 [3 29, 5 21] 1 11 [0.46, 1.76] -0.03 [0.23, 0.17] 1.73 [-0.35, 3.81] Std. Mean Difference M. Random. 95% CI 0.31 [-0.21, 0.64] 0.32 [-0.21, 0.64]	M. Randem. 253: C1 H. Randem. 253: C1 Favours [experimental] Favours [control] Stid. Mean Difference M. Randem. 253: C1
Study of Subarous Cao H et al. 2018 Duymus T H et al. 2017 Singh A K et al. 2013 Test 195% CD Heterogeneith: Tauf = 3. Test for overall effect 2: Figure 2.7 Study of Subarous Cao H et al. 2018 Duymus T M et al. 2013 Singh A K et al. 2013	Mean 45.67 41.62 40 26; Chi ^p = 1.63 (P Exp Mean 84.6 86.81	SD 2.33 1.83 3.6 = 80.79 = 0.10 = 0.10 science SD 4.7 7.17	Total 28 202 202 252 , df = 1)) ital <u>Total</u> 28 21 202	Mean 37.42 39.5 40.1 (P < 0.0 Mean 82.09 86.09 81.6	SD 1.4 1.92 3.8 000001) Control SD 5.9 8.99	Tota 29 21 188 238 0, P = 9 Tota 29 21 188	32.2% 33.4% 34.4% 100.0% 8% <u>Weight</u> 32.7% 31.7% 35.6%	IV. Random. 95% CI 4 25 (2 20, 5 21) 1 11 [0 46, 176] -0.03 [0 22, 017] 1.73 [-0.35, 3.81] Std. Mean Difference N. Random, 95% CI 0.31 [-0.21, 0.84] 0.95 [-0.51, 0.68] -1.01 [-1.22, -0.80]	N. Randem. 35% Cl
Study or Subarcoup Cao H et al 2018 Durmus T M et al 2017 Total (95% Ch Heterogeneity: Tauf = 3 Figure 2.7 Study or Subarcoup Cao H et al 2018 Durmus T M et al 2017 Singh A K et al 2013 Total (95% Ch	Mean 45.67 41.62 40 26, Chi ^p = 1.63 (P Exp Mean 84.6 96.81 76.4	SD 2 33 1 83 3 1 83 3 6 = 80.79 = 0.10 = 0.10 = 0.10 5 0 4.7 7.17 5.4	Total 28 22 202 252 , df = 1 252 , df = 1 252 251 202 251	Mean 37.42 39.5 40.1 2 (P < 0.1 (P < 0.1 0 Mean 82.9 86.09 81.6	SD 1.4 1.92 3.8 000001) Control SD 5.9 8.99 4.8	Tota 29 21 188 238 0, P = 9 Tota 239 239 239	 32.2% 33.4% 34.4% 100.0% 100.0% 32.7% 31.7% 35.6% 100.0% 	IV. Random. 95% CI 4 25 (2 20, 5 21) 1 11 [0 46, 176] -0.03 [0 22, 017] 1.73 [-0.35, 3.81] Std. Mean Difference N. Random, 95% CI 0.31 [-0.21, 0.84] 0.95 [-0.51, 0.68] -1.01 [-1.22, -0.80]	N. Random. 253: C1
Study of Subarous Cao H et al. 2018 Duymus T H et al. 2017 Singh A K et al. 2013 Test 195% CD Heterogeneith: Tauf = 3. Test for overall effect 2: Figure 2.7 Study of Subarous Cao H et al. 2018 Duymus T M et al. 2013 Singh A K et al. 2013	Mean 45.67 41.62 40 26, Chi ^p = 1.63 (P Exp Mean 84.6 96.81 76.4	<pre>sb 2 33 1 83 1 83 3 6 = 80.79 = 0.10 50 4.7 7.17 5.4 = 29.41</pre>	Total 28 202 202 252 , df = 2 , df = 2 202 252 , df = 2 202 251 , df = 2	Mean 37.42 39.5 40.1 2 (P < 0.1 (P < 0.1 0 Mean 82.9 86.09 81.6	SD 1.4 1.92 3.8 000001) Control SD 5.9 8.99 4.8	Tota 29 21 188 238 0, P = 9 Tota 239 239 239	 32.2% 33.4% 34.4% 100.0% 100.0% 32.7% 31.7% 35.6% 100.0% 	IV. Random. 95% CI 4 25 (2 20, 5 21) 1 11 [0 46, 176] -0.03 [0 22, 017] 1.73 [-0.35, 3.81] Std. Mean Difference N. Random, 95% CI 0.31 [-0.21, 0.84] 0.95 [-0.51, 0.68] -1.01 [-1.22, -0.80]	M. Randern. 253: C1 H. Randern. 253: C1 Favours [control] Stid. Mean Difference M. Randomference M. Randomference
Subc of Subcroup Cao H et al 2015 Orymou T H et al 2017 Singh A K et al 2013 Tetal (1955) CD Heterogeneity Turf = 3 Test for overall effect 2: Figure 2.7 Study of Subcroup Cao H et al. 2018 Dumnus T H et al. 2017 Singh A K et al. 2013 Total (1951) CD Heterogeneity Turf = 0 Test for overall effect 2:	Mean 45.67 41.62 40 26, Chi ^p = 1.63 (P Exp Mean 84.6 96.81 76.4	<pre>sb 2 33 1 83 1 83 3 6 = 80.79 = 0.10 50 4.7 7.17 5.4 = 29.41</pre>	Total 28 202 202 252 , df = 2 , df = 2 202 252 , df = 2 202 251 , df = 2	Mean 37.42 39.5 40.1 2 (P < 0.1 (P < 0.1 0 Mean 82.9 86.09 81.6	SD 1.4 1.92 3.8 000001) Control SD 5.9 8.99 4.8	Tota 29 21 188 238 0, P = 9 Tota 239 239 239	 32.2% 33.4% 34.4% 100.0% 100.0% 32.7% 31.7% 35.6% 100.0% 	IV. Random. 95% CI 4 25 (2 20, 5 21) 1 11 [0 46, 176] -0.03 [0 22, 017] 1.73 [-0.35, 3.81] Std. Mean Difference N. Random, 95% CI 0.31 [-0.21, 0.84] 0.95 [-0.51, 0.68] -1.01 [-1.22, -0.80]	N. Random. 253: C1
Shihar G Shihar Gup Cao H et al. 2015 Doymus T M et al. 2017 Dight A K et al. 2013 Total (195): CD Heletoopnehl, T auf = 3 Test for overall effect 2: Figure 2.7 Shuhy or Subarcom Cao H et al. 2013 Onymus T M et al. 2013 Test for overall effect 2: Figure 2.7 Shuhy or Subarcom Cao H et al. 2013 Test for overall effect 2: Gan H et al. 2013 Tetal (195): CD Heterogenehl; Tau*e 0	Mean 45.67 41.62 46 26, ChP = 1.63 (P Exp Mean 86.81 86.81 76.4 66, ChP = 0.47 (P	SD 2 233 1 183 1 36 = 80.79 = 0.10 50 1 4.7 7.17 7.17 7.17 5.4 = 29.41 = 0.64	<u>Tota</u> 28 202 252 (, df = 2)) , df = 2 202 251 202 251 , df = 2	Mean 37.42 39.5 40.1 2 (P < 0.0 Mean 82.9 86.09 81.6 2 (P < 0.0	<u>SD</u> 1.4 1.92 3.8 000001) 000001)	Tota 29 21 188 238 0, P = 9 Tota 239 239 239	 32.2% 33.4% 34.4% 100.0% 100.0% 32.7% 31.7% 35.6% 100.0% 	M. Bandom, 355:12 4.25 [2.26, 5.21] 1.11 [0.46, 1.76] -0.03 [2.0, 2.51] 1.73 [-0.05, 3.81] Std. Mean Difference M. Bandom, 355:12 0.31 [0.21, 0.36] 0.31 [0.21, 0.36] 0.10 [1.21, 0.36] 0.31 [0.21, 0.36]	M. Random. 25% Cl 10 5 Favours [experimental Pavours [control] Stid. Mean Difference M. Random. 25% Cl 10 5 Favours [experimental] Favours [control]
Subcar Subarcom Cao He al 2018 Orymus TH et al 2017 Singh A K et al 2013 Tetal (195%) CD Heterogeneity Tarle 3 Test for overall effect 2: Figure 2.7 Study or Subarcom Cao Het al 2017 Singh A K et al 2017 Singh A K et al 2013 Tetal (195%) CD Heterogeneity Tarle 0 Test for overall effect 2: Figure 2.8	Mean 45.67 41.62 40 26, Chi ^a , = 1.63 (P Exp Mean 84.6 96.91 76.4 66, Chi ^a , = 0.47 (P Expeni	SD 1 2.33 1 1.83 1 3.6 = 90.79 = 0.10 i 4.7 7.17 1 i 4.7 7.17 5.4 = 29.41 mental mental	<u>Tota</u> 28 20 252 352 4 1 1 1 1 2 2 2 2 2 2 2 2 2 2 2 2 2 2	Mean 37.42 39.5 40.1 2 (P < 0.1 82.9 86.09 81.6 81.6 2 (P < 0.1 Co	<u>SD</u> 1.4 1.92 3.8 000001) 5.9 8.99 4.8 000001) ntrol	Tota 29 21 186 238 238 238 239 24 22 186 239 239 24 9 24 9 24 9 24 9 24 9 24 25 23 9 24 24 25 24 25 25 25 25 25 25 25 25 25 25 25 25 25	32.2% 33.4% 34.4% 100.0% 8% 100.0% 32.7% 31.7% 35.6% 100.0%	M. Bandom, 255:10 4.25 [22, 5.21] 1.11 [0.61, 176] -0.03 [0.23, 0.71] 1.73 [-0.35, 3.81] Std. Mean Difference M. Bandom, 255: CI 0.03 [0.21, 0.21] 0.03 [0.21, 0.21] 0.03 [0.21, 0.41] 0.03 [0.21, 0.41] 0.03 [0.21, 0.41] 0.03 [0.21, 0.41] 0.02 [1.19, 0.73] Skil. Mean Difference	N. Randem. 253: C1 M. Bandem. 253: C1 Favours [experimental] Favours [control] Std. Mean Difference Favours [control] Std. Mean Difference
Subcar Subarcom Cao Hei al 2018 Dymma T Hei al 2017 Singh A K et al 2013 Tetal (195%) CD Heterogeneity Tarle - 3 Test for overall effect 2: Figure 2.7 Study or Subarcom Cao Hei al 2017 Dymma T Hei al 2017 Singh A K et al 2013 Tetal (195%) CD Heterogeneity Tarle - 0 Test for overall effect 2: Figure 2.8	Mean 45.67 41.62 40 26, Chi ^p = 1.63 (P Exp Mean 84.6 96.81 76.4 66, Chi ^p = 0.47 (P Experii Mean	SD 1 2.33 1 1.83 1 3.6 = 90.79 = 0.10 i 4.7 7.17 1 i 4.7 7.17 5.4 = 29.41 mental mental	<u>Tota</u> 28 20 252 352 4 1 1 1 1 2 2 2 2 2 2 2 2 2 2 2 2 2 2	1 Mean 1 37.42 1 39.5 1 40.1 2 2 (P ≤ 0.1 1 Mean 1 82.9 86.09 81.6 2 2 (P ≤ 0.1 2 (P ≤ 0.1) 2 (P ≤ 0.1) 3 (<u>SD</u> 1.4 1.92 3.8 000001) 5.9 8.99 4.8 000001) ntrol	Total 25 21 186 238 238 238 238 238 238 238 238	 32.2% 33.4% 34.4% 100.0% 3% Weight Weight 	M. Bandom, 355: L1 4.25 [20, 5.21] 1.11 [0.46, 1.76] -0.03 [40.20, 1.71] 1.73 [-0.35, 3.81] Std. Mean Difference M. Bandom, 555: L1 M. Bandom, 555: L1 0.023 [-1.19, 0.73] -0.23 [-1.19, 0.73] Std. Mean Difference M. Read, 95%; C1	M. Random. 25% Cl 10 5 Favours [experimental Pavours [control] Stid. Mean Difference M. Random. 25% Cl 10 5 Favours [experimental] Favours [control]
Cao Hei al 2016 Cao Hei al 2016 Dymma T Hei al 2017 Singh A K et al 2013 Tetal (195%) CD Heterogeneity Taufe al Figure 2.7 Study or Subgroup Cao Hei al 2017 Singh A K et al 2013 Tetal (195%) CD Heterogeneity Taufe al Heterogeneity Taufe al 2017 Figure 2.8 Study or Subgroup	Mean 45.67 41.62 40 26, Chi ^p = 1.63 (P Exp Mean 84.6 96.81 76.4 66, Chi ^p = 0.47 (P Experii Mean	SD 2.33 1.233 1.183 3.6 = 80.79 = 0.10 erimer SD i - 29.41 = 29.41 = 0.64 SD SD 11.7	Total 28 22 202 252 202 2552 1, df = 1 2 20 2 2552 202 2552 202 2551 202 2551 202 2551 202 2551 202 2551 202 2551 202 2551 202 2551 202 202 202 202 202 202 202 202 202 20	1 Mean 1 37.42 1 39.5 1 40.1 2 2 (P ≤ 0.1 2 (P ≤ 0.1 1 82.9 86.09 1 81.6 2 (P ≤ 0.1 2 (P ≤ 0.1 2 (P ≤ 0.1) 2	SD 1.4 1.92 3.8 000001) 59 4.8 000001) 4.8 000001) 1.4 1.92 1.4 1.92 1.4 1.92 1.92	Total 25 21 186 238 238 238 238 238 238 238 238	32.2% 33.4% 34.4% 100.0% 35.6% Weisalit 73.9%	M. Bandom, 255:10 4.25 [22, 5.21] 1.11 [0.61, 176] -0.03 [0.23, 0.71] 1.73 [-0.35, 3.81] Std. Mean Difference M. Bandom, 255: CI 0.03 [0.21, 0.21] 0.03 [0.21, 0.21] 0.03 [0.21, 0.41] 0.03 [0.21, 0.41] 0.03 [0.21, 0.41] 0.03 [0.21, 0.41] 0.02 [1.19, 0.73] Skil. Mean Difference	N. Randem. 253: C1 M. Bandem. 253: C1 Favours [experimental] Favours [control] Std. Mean Difference Favours [control] Std. Mean Difference
Subcor Subcroup Cao Hei al 2016 Orymus T Hei al 2017 Singh A K et al 2013 Telat (8%) CD Helerogeneity Turk* a Test for overall effect 2: Figure 2.7 Study or Subgroup Cao Hei al 2017 Onymos T Hei al 2017 Singh A K et al 2013 Teat for overall effect 2: Singh A K et al 2013 Teat (9%) CD Heiterogeneity Tark* a Teat (9%) CD Heiterogeneity Tark* a Study or Subgroup Guskie N et al 2015 Oussie N et al 2015 Oussie N et al 2015 Oussie N et al 2015	Mean 45.67 41.02 40 26, ChP = 1.63 (P Exp Mean 84.6 96.81 76.4 66, ChP = 0.47 (P Expensi Mean 83.2	SD 2.33 1.233 1.183 3.6 = 80.79 = 0.10 erimer SD i - 29.41 = 29.41 = 0.64 SD SD 11.7	Total 28 20 252 252 252 252 251 202 251 202 251 202 251 202 251 202 201 202 252 252 252 252 252 252 252	I Mean 1 37.42 1 39.57 2 40.1 2 2 (P ≤ 0.1 0 0 0 0 0 0 0 0 0 0 0 0 0	SD 1.4 1.92 3.8 000001) 59 4.8 000001) 4.8 000001) 1.4 1.92 1.4 1.92 1.4 1.92 1.92	Total 22 188 238 238 238 186 238 21 186 21 186 21 186 238 238 238 238 238 238 238 238 238 238 238 186 238	32.2% 33.4% 34.4% 100.0% 8% Weight 32.7% 31.7% 35.6% 100.0% 3% Weight 73.9% 26.1%	M. Bandom, 255: Cl. 4.25 (2.26, 5.21) 1.11 (0.46, 1.76) -0.03 (2.0, 7.7) 1.73 (-0.05, 3.81) Stid. Mean Difference M. Bandom, 255: Cl. 0.03 (-0.05, 0.81) 0.03 (-0.05, 0.81) 0.03 (-0.05, 0.81) 0.03 (-0.05, 0.81) 0.03 (-0.05, 0.81) 0.03 (-0.05, 0.80) -0.23 (-1.19, 0.73) Stid. Mean Difference M. Fined, 955; Cl. 0.11 (0.01, 0.39) 0.21 (-1.19, 0.73) 0.23 (-1.19, 0.73) 0.24 (-0.10, 0.31, 0.31) 0.25 (-0.50, 1.10) 0.26 (-0.50, 1.10)	N. Randem. 253: C1 M. Bandem. 253: C1 Favours [experimental] Favours [control] Std. Mean Difference Favours [control] Std. Mean Difference
Solution Content Can Het al. 2015 Can Het al. 2017 Simph AK et al. 2013 Total (195% Ch. Heterogeneity: Traif* al. Figure 2.7 Simph AK et al. 2017 Coa Het al. 2017 Coa Het al. 2017 Total (195% Ch. Heterogeneity: Their* al. 2017 Total (195% Ch. Total (195% Ch. Test for overall effect 2. Figure 2.8 Souker or Solutions Souker A Solutions Oncirc N et al. 2015 Janang Leit. 2011 Total (195% Ch. Oncirc N et al. 2015 Janang Leit. 2011 Total (195% Ch.	Mean 4567 4166 40 40 28; Chi ^a 40 Exp Mean 764 66; Chi ^a 764 66; Chi ^a 764 66; Chi ^a 76 88 84 83 2 84 63 1	SD 2 233 1 183 3 6 9 2079	Total 28 20 252 252 252 252 252 252 251 202 251 202 251 202 251 202 252 252 252 252 252 252 252	I Mean 1 37.42 1 39.52 40.1 2 (P < 0.1 1 82.9 86.09 1 82.6 1 (P < 0.1 2 (P < 0.1 1 (P < 0.1 1 (P < 0.1) 1 (P	SD 1.4 1.92 3.8 000001) 59 4.8 000001) 4.8 000001) 1.4 1.92 1.4 1.92 1.4 1.92 1.92	Total 22 188 238 238 238 186 238 21 186 21 186 21 186 238 238 238 238 238 238 238 238 238 238 238 186 238	 32.2% 33.4% 34.4% 100.0% 35.6% 35.6% 100.0% 3% Weight 73.9% 	M. Bandom, 255: L1 4.25 [22, 5.21] 1.11 [0.66, 1.76] -0.03 [0.02, 0.07] 1.73 [-0.35, 3.81] Stid, Mean Difference M. Random, 255: C1 0.03 [0.05, 0.08] -0.03 [0.05, 0.08] -0.03 [0.05, 0.08] -0.03 [0.05, 0.08] -0.03 [0.05, 0.08] -0.03 [0.05, 0.08] -0.03 [0.07, 0.08] -0.23 [-1.19, 0.73] Skil, Mean Difference M. Fixed, 955; C1 -0.11 [0.05, 0.38]	M. Randem. 25% Cl
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Subcord Subcord Cao Her al 2016 Cao Her al 2017 Singh AK et al 2013 Tead (8%) CD Helerogeneity Tauf* a Test for overall effect 2: Figure 2.7 Study or Subgroup Cao Het al 2017 Dumos T Met al 2017 Singh AK et al 2013 Test for overall effect 2: Figure 2.8 Study or Subgroup Study as Collection Ousie N et al 2017 Ousie N et al 2017 Test for overall effect 2: Figure 2.8 Study or Subgroup Test al 2015 Oasie N et al 2015 Teal 2015/5 CD Heterogeneity C CH*=0.	Mean 456,7 41,62 40,26, Chi ^a 26, Chi ^a 82,6 96,81 76,4 96,81 76,4 96,81 76,4 96,81 76,4 83,2 84,63 1 1 55, df = 1	SD 2.33 1.833 3.6 = 80.79 = 0.10 i - SD i - SD - SD - SD 11.7 7.44	Total 282 202 252 252 252 252 252 252 202 251 202 251 202 251 202 251 202 252 252 252 252 252 252 255	I Mean 1 37.42 1 39.52 40.1 2 (P < 0.1 1 82.9 86.09 1 82.6 1 (P < 0.1 2 (P < 0.1 1 (P < 0.1 1 (P < 0.1) 1 (P	SD 1.4 1.92 3.8 000001) 59 4.8 000001) 4.8 000001) 1.4 1.92 1.4 1.92 1.4 1.92 1.92	Total 22 188 238 238 238 186 238 21 186 21 186 21 186 238 238 238 238 238 238 238 238 238 238 238 186 238	32.2% 33.4% 34.4% 100.0% 8% Weight 32.7% 31.7% 35.6% 100.0% 3% Weight 73.9% 26.1%	M. Bandom, 255: Cl. 4.25 (2.26, 5.21) 1.11 (0.46, 1.76) -0.03 (2.0, 7.7) 1.73 (-0.05, 3.81) Stid. Mean Difference M. Bandom, 255: Cl. 0.03 (-0.05, 0.81) 0.03 (-0.05, 0.81) 0.03 (-0.05, 0.81) 0.03 (-0.05, 0.81) 0.03 (-0.05, 0.81) 0.03 (-0.05, 0.80) -0.23 (-1.19, 0.73) Stid. Mean Difference M. Fined, 955; Cl. 0.11 (0.01, 0.39) 0.21 (-1.19, 0.73) 0.23 (-1.19, 0.73) 0.24 (-0.10, 0.31, 0.31) 0.25 (-0.50, 1.10) 0.26 (-0.50, 1.10)	M. Randem. 25% Cl
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Subc of Subarcom Cao Hei al 2015 Durmus T Hei al 2017 Singh AV et al 2013 Total (1955 CD) Helerogonetic Tau'e 3 Figure 2.7 Subt of Subarcom Cao Hei al 2015 Durmus T Hei al 2017 Total (1955 CD) Helerogonetic Tau'e 0 Test for overall effect 2 Figure 2.8 Subt of Subarcom Test for overall effect 2 Figure 2.8 Subt of Subarcom Test for overall effect 2 Figure 2.8 Subt of Subarcom Test for overall effect 2 Figure 2.9	Mean 45.671 41.62 41.62 42.67 42.67 43.67 44.62 44.62 46.76.4 66.67 76.4 66.76.4 66.67.47 Expensitive 83.2 55.57.47 = 1 55.57.47 = 1 55.57.47 = 1	SD 2.33 1.83 3.6 = 80.79 = 0.10 setimet SD 1.47 5.4 = 29.41 = 0.64 mental SD SD 1.17 7.44 (P=0.95) perimet	Total 28 22 202 252 252 252 252 252 252	L Mean 1 37.42 1 39.5 1 40.1 2 (P < 0.1 2 (P < 0.1 1 82.9 86.09 1 81.6 1 (P < 0.1 2 (P < 0.1 1 82.9 86.09 1 81.6 1 (P < 0.1 1 (P < 0.1) 1 (P < 0.1) 2 (P < 0.1) 1 (P < 0.1) 2 (P < 0.	SD 1.4 1.92 3.8 000001) SD SD SD 000001) SD 3.8 000001) SD 3.8 000001) SD 2.92 8.38 ntrol	Total 26 21 238 239	1 32.7% 33.4% 1 30.0% 1 34.4% 1 34.4% 1 34.4% 1 34.4% 1 34.4% 1 34.4% 1 34.4% 1 34.4% 1 34.4% 1 34.4% 1 34.4% 1 34.4% 1 34.4% 1 34.	M. Bandom, 355: Cl 4.25 (2.26, 5.21) 1.11 (0.46, 1.76) -0.03 (2.0, 7.7) 1.73 (-0.05, 3.81) Std. Mean Difference M. Bandom, 355: Cl 0.03 (-0.15, 0.86) -0.03 (-0.15, 0.86) -0.03 (-0.15, 0.86) -0.03 (-0.15, 0.86) -0.03 (-1.01, 0.73) Std. Mean Difference M. Fixed, 305: Cl -0.11 (-1.22, -0.80) -0.23 (-1.19, 0.73) Std. Mean Difference M. Fixed, 305: Cl -0.11 (-0.10, 0.76) -0.03 (-0.10, 0.76) -0.04 (0.01, 0.26) -0.01 (-0.44, 0.42) Pissk Fatio	M. Randem. 25% Cl M. Randem. 25% Cl Favours [experimental Favours [cotho] Std. Mean Difference M. Randem. 25% Cl Favours [experimental Favours [cotho] Std. Mean Difference M. Favours [cotho] Std. Mean Difference M. Favours [cotho] Rate Strict Favours [cotho] Rate Strict Favours [cotho] Risk Ratio
Cao Het al. 2015 Cao Het al. 2015 Dormos T Het al. 2017 Singh A K et al. 2013 Tetal 1955 CD Heterogeneity Tar# = 3 Test for overall effect 2: Figure 2.7 Singh A K et al. 2017 Cao Het al. 2017 Cao Het al. 2017 Singh A K et al. 2017 Singh A K et al. 2017 Test for overall effect 2: Figure 2.8 Study or Subjection Heterogeneity Tar# = 3 Test (1995) Heterogeneity Tar# = 3 Study or Subjection Heterogeneity Cao Heterogeneity Heterogeneity Cao Heterogeneity Het	Mean 45,613 45,617 45,617 45,617 45 45,71745,717 45,71745,717 45,717 45,717 45,71745,717 45,717 45,717 45,71745,717 45,717 45,717 45,71745,717 45,717 45,717 45,71745,717 45,717 45,71745,717 45,717 45,71745,717 45,71745,717 45,717 4	SD 2.33 1.83 3.6 9.079 9.079 9.079 9.079 9.079 9.079 9.079 9.079 9.079 9.079 9.079 9.071	Total 28 202 202 252 252 252 252 252 251 31 200 251 201 201 201 201 201 201 201 20	I Mean 1 37.42 39.5 40.1 2 (P < 0.1 2 (P < 0.1 1 82.9 96.09 81.6 2 (P < 0.1 Co Mean 1 82.4 1 79.81 1 79.81 2 (P < 0.1 Co Co Co Co Co Co	SD 1.4 1.92 3.8 3.8 000001) 5.9 4.8 3.8 000001) 5.9 4.8 3.8 000001) 5.9 4.8 3.8 000001) 5.9 4.8 3.8 000001) 5.9 4.8 3.8 000001) 5.9 4.8 3.8 000001) 5.9 4.8 3.8 000001) 5.9 12.92 8.38 13.8 3.8 14.8 5.0 5.9 5.7	Total 26 21 186 238 26 238 24 238 24 238 246 238 246 238 247 186 238 246 238 247 238 247 238 247 238 247 258 259 <t< td=""><td>1 32.9% 33.4% 34.4% 1 100.0% 8% 1 100.0% 1 22.7% 31.7% 1 35.6% 1 100.0% 1 00.0% 1 00.0% 1 00.0% 1 00.0% 1 00.0%</td><td>M. Bandom, 255: Cl. 4 25 [23, 5 21] 111 [0.66, 1.76] -0.03 [0.23, 5.21] 1,73 [-0.35, 3.81] Std. Mean Difference M. Random, 255: Cl. 0.03 [0.23, 0.42] 0.03 [0.23, 0.42] 0.31 [0.23, 0.42] 0.31 [0.23, 0.42] 0.31 [0.43, 0.42] 0.31 [0.43, 0.42] 0.31 [0.43, 0.42] 0.31 [0.43, 0.42] 0.31 [0.43, 0.42] 0.31 [0.44, 0.42] Pisk Ratise Risk Fatise AL, Fixed, 955; Cl.</td><td>N. Bandem. 253: Cl Favours [experimental] Favours [e</td></t<>	1 32.9% 33.4% 34.4% 1 100.0% 8% 1 100.0% 1 22.7% 31.7% 1 35.6% 1 100.0% 1 00.0% 1 00.0% 1 00.0% 1 00.0% 1 00.0%	M. Bandom, 255: Cl. 4 25 [23, 5 21] 111 [0.66, 1.76] -0.03 [0.23, 5.21] 1,73 [-0.35, 3.81] Std. Mean Difference M. Random, 255: Cl. 0.03 [0.23, 0.42] 0.03 [0.23, 0.42] 0.31 [0.23, 0.42] 0.31 [0.23, 0.42] 0.31 [0.43, 0.42] 0.31 [0.43, 0.42] 0.31 [0.43, 0.42] 0.31 [0.43, 0.42] 0.31 [0.43, 0.42] 0.31 [0.44, 0.42] Pisk Ratise Risk Fatise AL, Fixed, 955; Cl.	N. Bandem. 253: Cl Favours [experimental] Favours [e
Subc of Subarcom Cao Hei al 2015 Durmus T Hei al 2017 Singh AV et al 2013 Total (1955 CD) Helerogonetic Tau'e 3 Figure 2.7 Subt of Subarcom Cao Hei al 2015 Durmus T Hei al 2017 Total (1955 CD) Helerogonetic Tau'e 0 Test for overall effect 2 Figure 2.8 Subt of Subarcom Test for overall effect 2 Figure 2.8 Subt of Subarcom Test for overall effect 2 Figure 2.8 Subt of Subarcom Test for overall effect 2 Figure 2.9	Mean 45677 4162	SD 2.33 1.83 3.6 = 80.79 = 0.10 setimet SD 1.47 5.4 = 29.41 = 0.64 mental SD SD 1.17 7.44 (P=0.95) perimet	Total 28 22 202 252 252 252 252 252 252	I Mean 37.42 39.5 40.1 2 (P < 0.1 2 (P < 0.1 (P < 0.1	SD 1.4 1.92 3.8 3.8 000001) 5.9 8.99 4.8 000001) 5.9 8.99 4.8 000001) 5.9 8.99 4.8 000001) 5.9 8.93 4.8 000001) 5.9 12.92 8.38 nttrol 5.9 1 1	Total 26 21 22 186 238 238 238 239 2318 2318 232 186 238 239 2318 238	1 32.7% 33.4% 1 30.0% 1 34.4% 1 34.4% 1 34.4% 1 34.4% 1 34.4% 1 34.4% 1 34.4% 1 34.4% 1 34.4% 1 34.4% 1 34.4% 1 34.4% 1 34.4% 1 34.	M. Bandom, 355: Cl 4.25 (2.26, 5.21) 1.11 (0.46, 1.76) -0.03 (2.0, 7.7) 1.73 (-0.05, 3.81) Std. Moan Difference M. Bandom, 355: Cl 0.03 (-0.15, 0.86) -0.03 (-0.15, 0.86) -0.03 (-0.15, 0.86) -0.03 (-0.15, 0.86) -0.23 (-1.19, 0.73) Std. Mean Difference M. Fined, 955: Cl 0.04 (-0.44, 0.42) Risk Ratio AL Freed, 955: Cl 0.05 (0.01, 0.55; Cl 0.05 (0.55; Cl 0.05 (0.01, 0.55; Cl	M. Randem. 25% Cl M. Randem. 25% Cl Favours [experimental Favours [cotho] Std. Mean Difference M. Randem. 25% Cl Favours [experimental Favours [cotho] Std. Mean Difference M. Favours [cotho] Std. Mean Difference M. Favours [cotho] Rate Strict Favours [cotho] Rate Strict Favours [cotho] Risk Ratio
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Figure 2. (2.1) Graph showing Böhler angle of operative (experimental) versus nonoperative (control) groups (P = .72) in short-term follow-up. The size of each square is proportional to the weight of the study. Z = P-value of weighted test for overall effect. (2.2) Graph showing Böhler angle of operative (experimental) versus nonoperative (control) groups (P < .00001) in long-term follow-up time. The size of each square is proportional to the weight of the study. Z = P-value of weighted test for overall effect. (2.3) Graph showing Gissane angle in operative (experimental) versus nonoperative (control) groups (P = .10) in short-term follow-up. The size of each square is proportional to the weight of the study. Z = P-value of weighted test for overall effect. (2.4) Graph showing Gissane angle of operative (experimental) versus nonoperative (control) groups (P = .03) in long-term follow-up. The size of each square is proportional to the weight of the study. Z = P-value of weighted test for overall effect. (2.4) Graph showing Gissane angle of operative (experimental) versus nonoperative (control) groups (P = .03) in long-term follow-up. The size of each square is proportional to the weight of the study. Z = P-value of weighted test for overall effect. (2.6) Graph showing the calcaneal height of operative (experimental) versus nonoperative (control) groups (P = .47) in short-term follow-up. The size of each square is proportional to the weight of the study. Z = P-value of weighted test for overall effect. (2.6) Graph showing the calcaneal height of operative (experimental) versus nonoperative (control) groups (P = .47) in short-term follow-up. The size of each square is proportional to the weight of the study. Z = P-value of weighted test for overall effect. (2.6) Graph showing the calcaneal height of operative (experimental) versus nonoperative (control) groups (P = .47). The size of each square is proportional to the weight of the study. Z = P-value of weighted test for overall e



graft group and 239 cases in the non-bone graft group. The $I^2 =$ 93%, and the random-effects model was, therefore, selected. As shown in (2.7), SMD = -0.23, 95% CI [-1.19, 0.73], and *P* = .64 indicating that no significant differences (*P* > .05) were observed between the 2 groups. In the sensitivity analysis, Singh A K et al's study^[18] was excluded, and I^2 was reduced to 0.0% (*P* = .571). Using the fixed effect model, the conclusion was unchanged (SMD = 0.22, 95% CI [-0.18, 0.61], *P* = .571). Figure 2.7

3.4.5. *Maryland foot evaluation.* Two studies^[20,22] reported post-surgery foot functional scores based on the Maryland Foot Evaluation, including 31 cases in the bone graft group and 78 cases in the non-bone graft group. The $I^2 = 0\%$, and the fixed effects model was, therefore, used. According to (2.8), SMD=-0.11, 95% CI [-0.44, 0.42], and P=.95, suggesting that no significant differences (P > .05) were noted between the 2 groups. Figure 2.8

3.4.6. Rate of wound infection. Four studies^[16-19] recorded the frequency of post-surgery wound infection, including 255 cases in the bone graft group and 240 cases in the non-bone graft group. The $I^2 = 0\%$, and the fixed effects model was, therefore, used. As shown in (2.9), risk ratio = 1.22, 95% CI [0.71, 2.11], and P = .47 indicating that no significant differences (P > .05) were recorded between the 2 groups. Figure 2.9

4. Discussion

The meta-analysis revealed that the odds of functional scores and rate of wound infection after surgery in the graft group did not significantly differ from those recorded in the non-graft group. In the short-term follow-up, Böhler angle, Gissane angle, and calcaneal height did not significantly differ (P > .05) between the 2 groups. In long-term follow-up, Böhler and Gissane angles were better in the bone graft group than in the non-bone graft group. However, Calcaneal height was not significantly different between the 2 groups. Although radiographic parameters such as Böhler and Gissane angles were better in the long term followup of the bone graft group, no significant differences between the 2 groups were noted in the short-term follow-up. Radiographic parameters provide prognostic information on bone healing. More attention should, however, be on functional scores, which assess walking ability, walking distance, gait, and pain. The findings of this study indicate that bone grafts do not offer any apparent advantages in intra-articular calcaneal surgery.

4.1. Clinical significance

Bone grafts are typically used for defective areas of displaced intra-articular calcaneus to fill significant bone gaps, provide mechanical support, and promote bone healing. The use of bone grafts for the treatment of calcaneal fractures is a widespread clinical practice worldwide and is estimated to be used in 2.2 million cases annually.^[25] Besides, a survey in the Netherlands reported that only 38% of cases do not use bone grafts at all.

Some researchers believe that bone grafts are not generally needed because the calcaneal cancellous bone has a strong regenerative ability.^[26,27] Rammelt^[28] reported that the calcaneal cancellous bone has a strong ability to regenerate. Bone grafts are only necessary in case of a significant bone defect and if the fracture block becomes unstable after reduction (usually 20%–50%). Longino^[16] did not observe any significant differences in postoperative radiological indicators and clinical results between the bone graft group and the non-bone graft group. Letournel^[6] considered that it was difficult to grasp the suitability of a bone graft because the medial wall was also broken. There is currently no clinical evidence that bone grafts contribute to either early functional exercise or weight loss. Bone grafting is, therefore, not recommended.

Furthermore, grafts may pose additional risks to the patient.^[29,30] For instance, previous studies reported that calcaneal transplantation has a high infection rate, can lead to high blood losses, and has a long operation time.^[31,32] Also, calcaneal transplantation increases postoperative pain in patients.^[33–35]

The use of bone grafts in operative treatment of calcaneal fractures remains a debatable subject. The results of our metaanalysis demonstrated that the bone graft group did not exhibit any apparent advantages in radiographic parameters, functional scores, and complications as compared to the non-bone graft group.

Before deciding to perform a bone graft on a calcaneal fracture patient, physicians should consider the patient's expected outcome, postoperative rehabilitation training, and patient's economic situation. It is unnecessary to conduct bone grafting for each patient with a calcaneal fracture.

5. Conclusions

Böhler angle, Gissane angle, calcaneal height, AOFAS hindfoot scores, Maryland foot evaluation, and rate of wound infection in the bone graft group did not significantly differ from those of the non-bone graft group. Since this study did not involve a largesample-size multicenter RCT, the necessity of bone grafting for the treatment of calcaneal fractures remains to be further verified.

6. Strengths and limitations of this study

- (1) This study analyzed the necessity of bone grafting in the treatment of calcaneal fractures. We evaluated radiographic parameters in the short and long terms and assessed 2 different functional outcomes and complications.
- (2) Two reviewers independently conducted study selection, data extraction, and quality assessment.
- (3) The study was limited with regards to RCT since only cohort studies were included. The level of the evidence in the present study is, therefore, limited.
- (4) Although most high-quality articles in the subject of calcaneal fractures have been written in either English or Chinese, the inclusion of only English and Chinese language might have caused a selection bias.

Author contributions

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- Project administration: Zhe Zhu.
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