


REVIEW ARTICLE

Comparison of Outcomes After Total Knee Arthroplasty Involving Postoperative Neutral or Residual Mild Varus Alignment: A Systematic Review and Meta-analysis

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Comparing mainly clinical and functional outcomes as well as prosthesis survival with neutral and residual mild varus alignment, we searched PubMed, Embase, Cochrane Library and Web of Science databases from 1 January 1974 to 18 December 2020 to identify studies comparing clinical and functional outcomes as well as prosthesis survival in the presence of different alignments after total knee arthroplasty (TKA) for varus knees. The included studies were assessed by two researchers according to the Newcastle–Ottawa Scale (NOS). Postoperative neutral alignment ($0^\circ \pm 3^\circ$) was compared to residual mild varus ($3^\circ\text{--}6^\circ$) and residual severe varus ($>6^\circ$). Meta-analysis was performed using Review Manager 5.3. The odds ratios (OR) and mean differences (MD) were used to compare dichotomous and continuous variables. The fixed-effect model and random-effect model were used to meta-analyze the data. Nine studies were included in the meta-analysis with 1410 cases of postoperative neutral alignment, 564 of residual mild varus alignment and 175 of residual severe varus alignment following TKA, all of which were published after 2013. Three studies scored 7 points on the NOS, while the remaining studies scored 8 points, suggesting high quality. The pooled mean differences (MDs) of the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score were 1.07 [95% confidence interval (CI) -1.06 to 3.20 ; $P = 0.32$; $I^2 = 79\%$]. The meta-analysis showed that neutral alignment and mild varus alignment were associated with similar the Oxford Knee Score (OKS), Knee Society Knee Score (KS-KS), and Knee Society Function Score (KS-FS), while neutral alignment was associated with lower Forgotten Joint Score (FJS) [mean difference -6.0 , 95% confidence interval (CI) -9.37 to -2.64 , $P = 0.0005$]. Neutral alignment was associated with higher KS-KS than severe alignment (M 2.98, 95% CI 1.42 to 4.55, $P = 0.0002$; $I^2 = 0\%$) as well as higher KS-FS (M 8.20, 95% CI 4.58 to 11.82, $P < 0.00001$; $I^2 = 0\%$). Neutral alignment was associated with similar rate of survival as mild varus alignment (95% CI 0.36 to 9.10; $P = 0.48$; $I^2 = 65\%$) or severe varus alignment (95% CI 0.94 to 37.90; $P = 0.06$; $I^2 = 61\%$). There was no statistical difference in others. Residual mild varus alignment after TKA may lead to similar or superior outcomes than neutral alignment in patients with preoperative varus knees, yet the available evidence appears to be insufficient to replace the current gold standard of neutral alignment. Severe varus alignment should be avoided.

Key words: Meta-analysis; Neutral alignment; Total knee arthroplasty; Varus alignment; Varus knees

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Introduction

Total knee arthroplasty (TKA) is the standard treatment for patients with end-stage knee disease, and the number of procedures annually is expected to grow to 1.26 million by 2030 in the US alone¹. Postoperative function and prosthesis survival are closely related to patient satisfaction remained unsatisfaction around 20%, affecting successful outcomes². Alignment after TKA can strongly influence postoperative function and implant longevity³. The gold standard for the last few decades has been postoperative overall mechanical femorotibial alignment (FTMA) of $0^\circ \pm 3^\circ$, often referred to as “neutral alignment”⁴⁻⁷.

However, a series of studies have called into question whether neutral alignment is necessary for optimal outcomes after TKA⁸⁻¹¹: some evidence suggests that deviations in lower extremity alignment do not compromise postoperative clinical and functional outcomes or prosthesis survival^{12,13}. The improvement of prosthesis, especially the design of polyethylene inserts and materials, greatly reduces the wear of joint surface and the prosthesis failure caused by prosthesis misalignment^{14,15}, which reinforces the belief in the advantages of mild varus alignment. It is reported that in the

15-year survival rate of 398 knee joints, neutral alignment did not increase the survival rate of prosthesis. The researchers believe that neutral alignment has no significant effect on the survival prognosis of modern prosthesis¹⁰.

In addition, it has also been shown that a relevant proportion of the physiologically normal human population has a natural limb alignment of 3° varus or more¹⁶. This natural alignment as constitutional varus was defined by Bellemans *et al.*¹⁷ and its incidence is approximately 32% in men and 17% in women. Therefore, the literature on the possible beneficial effects of under-correction deformity also makes surgeons question the conventional assumption that neutral alignment is the optimal alignment after TKA. If patients have constitutional varus or severe varus deformities, restoring their constitutional alignment may be a more physiological choice, which brings better results than restoring neutral alignment. In fact, several studies have suggested that in patients with varus knees, postoperative varus alignment $>3^\circ$ increases efficacy of TKA without increasing the rate of prosthesis failure¹⁸⁻²². Previous meta-analysis has found that more than 3° post-operative varus alignment should be avoided, including patients with pre-operative severe varus

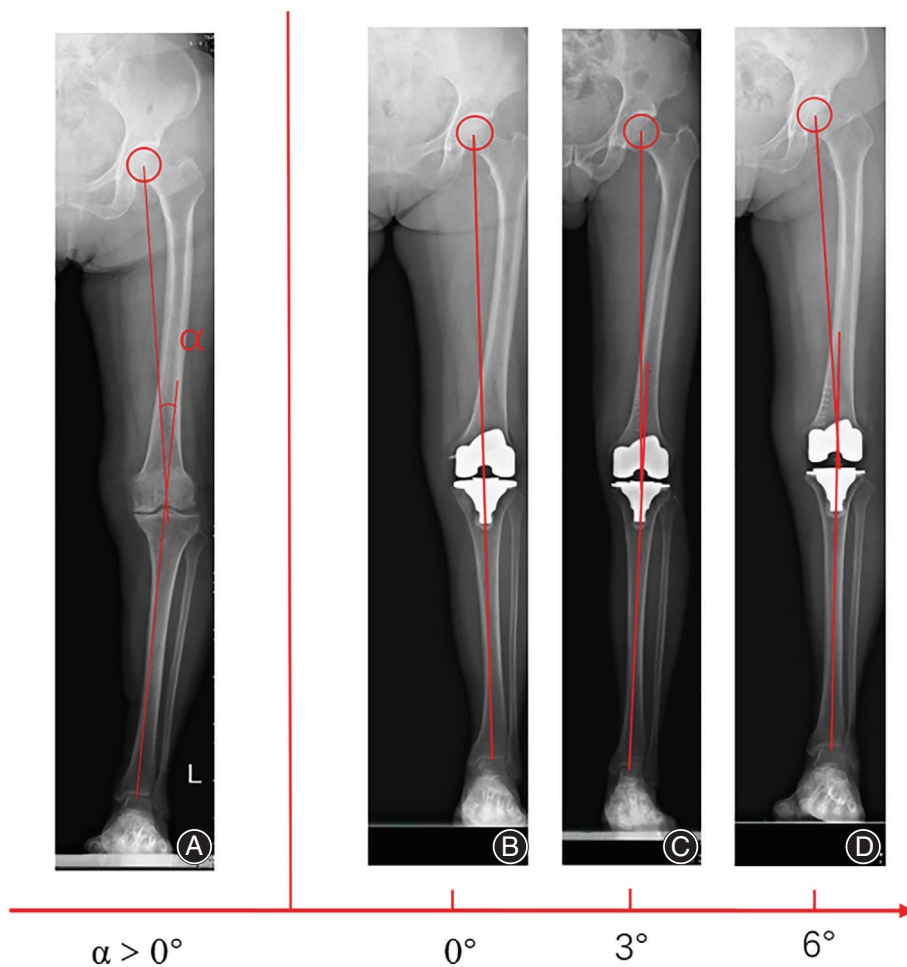


Fig. 1 Method of calculation of preoperative and postoperative alignment and illustration of preoperative alignment and the neutral, mild varus and severe varus alignment after the operation. (A) Preoperative varus alignment; (B-D) postoperative alignments; (B,C) neutral alignment; (C,D) mild varus alignment; ($>D$) severe varus alignment.

deformity or constitutional varus²³. This has led to some studies comparing residual mild varus alignment (3° – 6°) and neutral alignment ($0^{\circ} \pm 3^{\circ}$) after TKA in patients with preoperative varus deformity^{24–26}, but they have not reached consistent conclusions. Some studies have suggested that neutral alignment can have similar or even better outcomes than mild varus alignment^{24,27–29}, Rajasekaran *et al.*²⁷ reported 88 postoperative mild varus knees with preoperative varus alignment and showed that minimal under-correction gave superior functional outcomes at 3 months, but minimal under-correction and neutral alignment achieved equally good outcomes at 1 year. There are no revision cases in the study by Nishida *et al.* during the follow-up period²⁸. However, other studies have reported the opposite^{3,15,30,31}, one study³² concluded with 905 varus knees and found postoperative neutral alignment results in longer TKA survival time than residual varus alignment. Many of the studies mentioned above included small numbers of cases and low levels of evidence, and a study is urgently needed to reach uniform conclusions.

Moreover, many studies have explored the optimal postoperative alignment strategies, such as kinematic alignment (KA), mechanical alignment (MA), anatomic alignment and so

on. For example, kinematic alignment is a strategy that aims to restore the physiological kinematic axes of knee joints and a series of studies explore its functional outcomes and prosthesis survival, the concept of KA could be used in varus deformities as a reference during TKA, and the knee may be left in residual mild varus so as to preserve the original lower extremity alignment and reduce the extent of soft tissue release³³, but the results are inconclusive. Recent years, with the use of digital assistant technology, targeted and personalized alignment can be accomplished, which makes it imperative to explore the optimal postoperative alignment for patients with TKA. The robotic-assisted surgery guarantees a precise implementation of the planning, and the initial experience showed a promising outcome in the short-term follow-up³⁴. Many patients undergoing TKA have varus deformity before surgery, so it is important to find the optimal postoperative alignment strategy³⁵.

Therefore, we carried out the present systematic review and meta-analysis to compare different types of alignments in terms of neutral, mild varus and severe varus alignments after TKA in patients with preoperative varus knees. The meta-analysis aimed to explore whether: (i) mild varus alignment has better clinical and functional efficacy than neutral alignment; (ii) mild varus alignment has similar survival with neutral

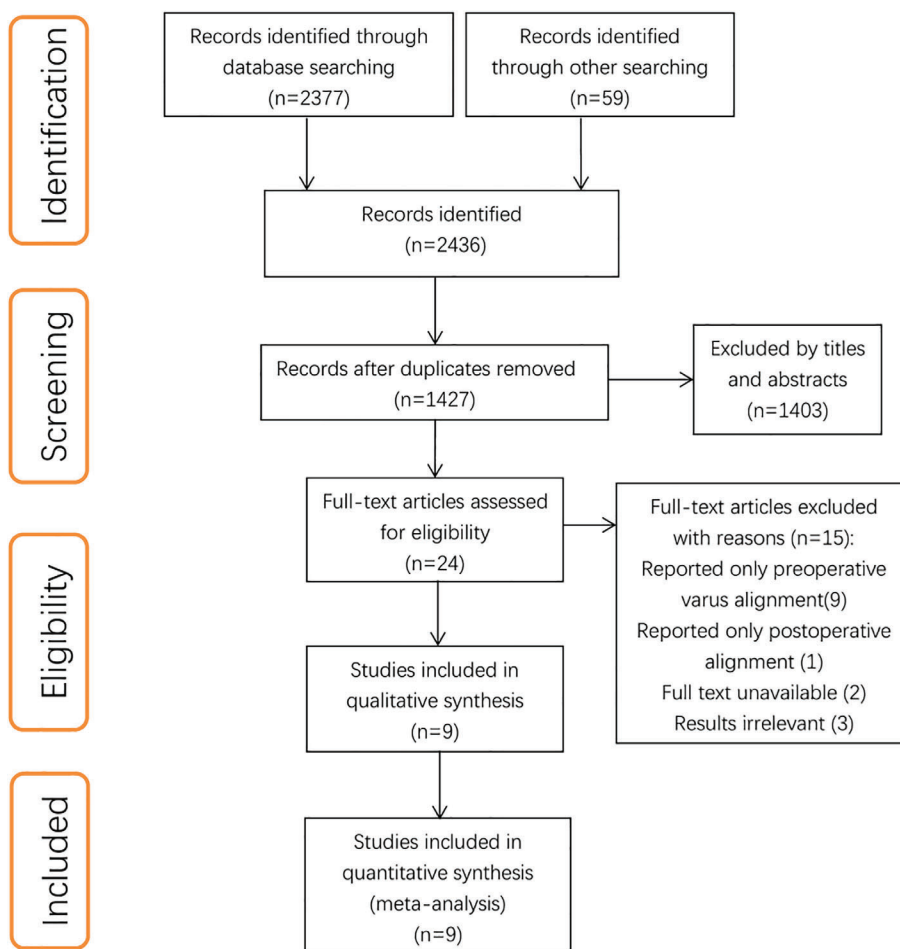


Fig. 2 PRISMA flow diagram.

TABLE 1 Characteristics of patients in the included studies

Study (country)	Knees	Diagnosis	Age (years, M ± SD)	Sex (F/M)	BMI(kg/m ² , M ± SD)	Preoperative alignment (°)	Postoperative alignment (°)	Length of follow-up	Assessments
Zhang ¹⁵ 2020 (China)	N:86 MV:62 SV:27	Varus osteoarthritis	N:68.0 ± 6.7 MV:67.2 ± 7.1 SV:63.9 ± 7.4	N:69/17 MV:50/12 SV:24/3	N: 25.3 ± 3.2 MV: 26.2 ± 3.6 SV: 26.0 ± 3.4	HKA: varus > 3	HKA: N:(-3 to 3) MV: (-6 to -3) SV:<-6	5.2 ± 1.1 years (4-7 years).	KSS WOMAC Survival analysis
Rajasekara ²⁷ 2020 (India)	N:67 MV:88 SV:7	Severe varus osteoarthritis	N:59.1 ± 4.4 MV:64.4 ± 7.0 SV:62.1 ± 2.03	N: 47/20 MV:74/14 SV:6/1	—	FTMA: N:160.99 ± 3.88 MV: 161.35 ± 4.63 SV: 157.29 ± 3.40	FTMA: N: 180 ± 3 MV:173-176 SV: below 172	12 months	OKS WOMAC
Liu ² 2020 (China)	N:50 MV:20 SV:20	Varus osteoarthritis	N:66.3 ± 6.9 MV:65.7 ± 7.1 SV:69.0 ± 6.5	N:35/11 MV:12/6 SV:15/4	N:26.9 ± 4.2 MV:27.5 ± 4.1 SV:26.6 ± 3.5	HKA: Varus 11.1 ± 5.8	HKA: N:0 ± 3 MV:3-6 SV:≥6	18.4 ± 4.0 months	HSS KSS
Schiffner ²⁴ 2019 (Germany)	N:115 MV:33	Varus osteoarthritis	N: 77 ± 8.2 MV: 77 ± 9.2	N:61/54 MV: 23/10	—	HKA: N: varus 8.3 ± 3.5 MV: varus 9.7 ± 2.3	HKA: N:0 ± 3 MV:4.1 ± 1.1	3-5 years	OKS, KOOS
Oh, S. M. ³² 2019 (South Korea)	N:636 MV:176 SV:56	Varus osteoarthritis	N:6.89 ± 6.32 MV:66.93 ± 6.54 SV:66.25 ± 6.70	N:598/38 MV:174/2 SV:52/4	N:27.41 ± 3.52 MV:27.35 ± 3.36 SV:26.38 ± 3.49	Varus	HKA: N:(-3 to 3) MV:(-6 to -3) SV:<-6	8.23 ± 3.47 years	Survival rate Survival time
Rames ³⁰ 2018 (USA)	N:149 MV:60 SV:28	Osteoarthritis or rheumatoid arthritis	N:63.9 ± 8.9 MV: 63.2 ± 9.8 SV: 63.8 ± 9.5	N:79/149 MV:33/3 ± 6.3 SV:36.0 ± 6.1	N:31.9 ± 5.6 MV:33.3 ± 6.3 SV:36.0 ± 6.1	HKA: N: varus 8.7 ± 4.8 MV: varus 9.5 ± 4.7	HKA: N: 0.7 ± 1.5 MV: 4.3 ± 0.9 SV: 7.7 ± 1.7	1.3 ± 0.6 years	SF-12 OKS FJS
Salzmann ³¹ 2017 (Germany)	N:104 MV:18	Osteoarthritis	N:69.5 ± 6.3 MV: 69.6 ± 5.9	N:58/46 MV: 11/7	N:29.8 ± 3.9 MV:29.7 ± 4.3	FTMA: N:7.0 ± 2.3 (4.0-16.0) MV:10.1 ± 3.4 (4.0-15.0)	FTMA: N:1.4 ± 1.0 (-2.0-3.0) MV:4.3 ± 0.8 (3.5-5.5)	2 years	KSS WOMAC FJS
Nishida ²⁸ 2017 (Japan)	N:128 MV:61 SV:15	Varus osteoarthritis	N: 73.6 ± 7.4 MV: 73.5 ± 6.7 SV: 71.3 ± 7.4	N:114/14 MV:50/11 SV:15/0	—	FTMA: N: 168.6 ± 5.4 MV: 166.8 ± 5.2 SV: 166.6 ± 5.1	FTMA: N: 180 ± 3 MV:177-174 SV: <174	3.4 (range 2-5) years	Survival rate KSS ROM Revision
Vanlomme ¹⁶ 2013 (Belgium)	N:75 MV:46 SV:22	—	N: 74.0 ± 8.3 MV: 74.1 ± 8.4 SV: 77.1 ± 6.5	N:58/17 MV:27/19 SV:12/10	N:29.3 ± 4.6 MV:31.2 ± 4.5 SV:31.7 ± 5.5	FTMA: N: 170.7 ± 3.7 SV: 167.7 ± 1.3	FTMA: N: 180 ± 3 MV: 177-174 SV: <174	7.2 years	KSS WOMAC Revision

FJS, Forgotten Joint Score; FTMA, femorotibial mechanical alignment; HKA, hip-knee-ankle angle; HSS, Hospital For Special Surgery Score; KOOS, Knee Injury and Osteoarthritis Outcome Score; KSS, Knee Society Score; M, mean; MV, mild varus alignment; N, neutral alignment; OKS, Oxford Knee Score; ROM, range of motion; SD, standard deviation; SV, severe alignment; WOMAC, the Western Ontario and McMaster Universities Osteoarthritis Index

alignment; and (iii) mild varus alignment and neutral alignment have better postoperative outcomes than severe varus alignment. Our hypothesis was that clinical and functional outcomes as well as prosthesis survival would be better with residual mild varus alignment than with neutral alignment, and that residual severe varus alignment (>6°) would lead to inferior outcomes.

Materials and Methods

Search Strategy

This systematic review, which was registered on the Prospero database (CRD42020221089), was implemented following the

guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement³⁶ and was based on the methods of the Cochrane Collaboration. We searched the PubMed, Embase, Cochrane Library and Web of Science databases on 18 December 2020. Clinical studies were searched with the combination of Medical Subject Headings and keywords as follow: (“arthroplasty, replacement, knee”[MeSH Terms] OR “knee arthroplasty”[Title/Abstract] OR “knee replacement”[Title/Abstract]) AND “alignment”[Title/Abstract] AND (“genu varum”[MeSH Terms] OR “varus”[Title/Abstract]). No limitations were imposed on language. Reference lists of potentially eligible studies and review articles were also searched to identify additional literature.

TABLE 2 Quality assessment of included studies based on the Newcastle–Ottawa scale^[52]

Study*	Newcastle–Ottawa score			Total score
	Selection	Comparability	Exposure/outcome	
Zhang ¹⁵ 2020	4	2	2	8
Rajasekaran ²⁷ 2020	4	1	2	7
Liu ³ 2020	4	2	2	8
Schiffner ²⁴ 2019	3	1	3	7
Oh, S. M. ³² 2019	4	2	2	8
Rames ³⁰ 2018	4	2	2	8
Salzmann ³¹ 2017	4	2	2	8
Nishida ²⁸ 2017	4	1	2	7
Vanlommel ^{16,54} 2013	4	2	3	8

* All studies had a cohort design.

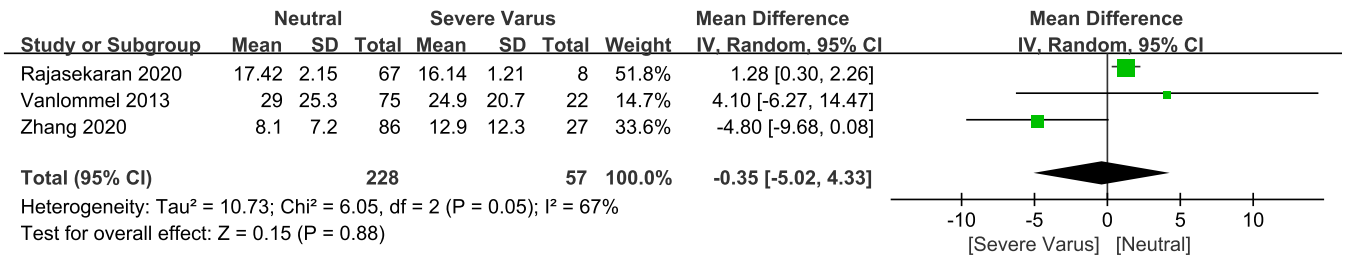
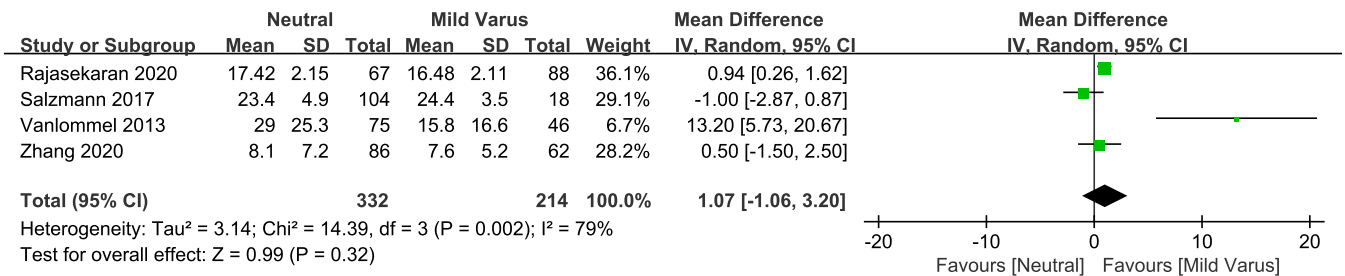


Fig. 3 Forest plot of the meta-analysis of differences in WOMAC scores between neutral alignment and either mild or severe varus alignment. SD, standard deviation.

Study Selection

Studies were selected based on the following inclusion criteria: (i) participant—patients who underwent total knee arthroplasty with preoperative varus knees; (ii) intervention—mild varus alignment postoperatively; (iii) comparison—neutral alignment postoperatively;

(iv) outcome measures—reported at least one of the following outcomes, functional and clinical outcomes, the prosthesis survival/failure; and (v) study design—randomized controlled trials or other studies. We excluded studies with the following properties: preoperative neutral or valgus knees; no distinction between mild

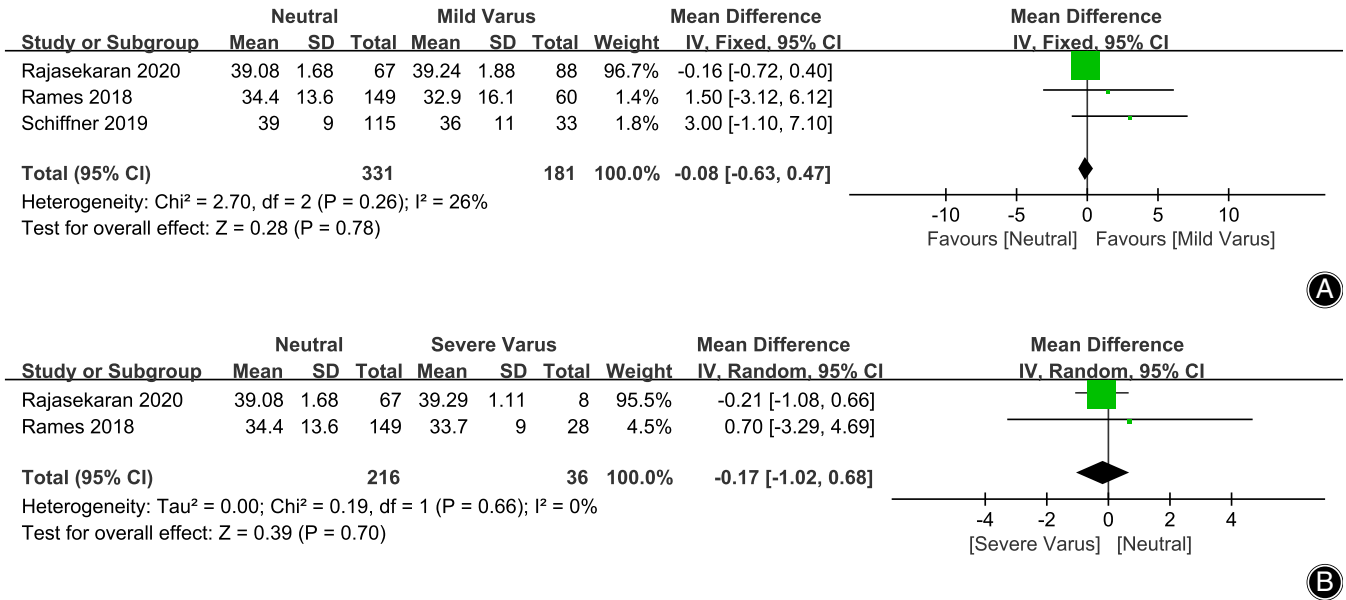


Fig. 4 Forest plot of the meta-analysis of differences in OKS between neutral alignment and either mild or severe varus alignment.

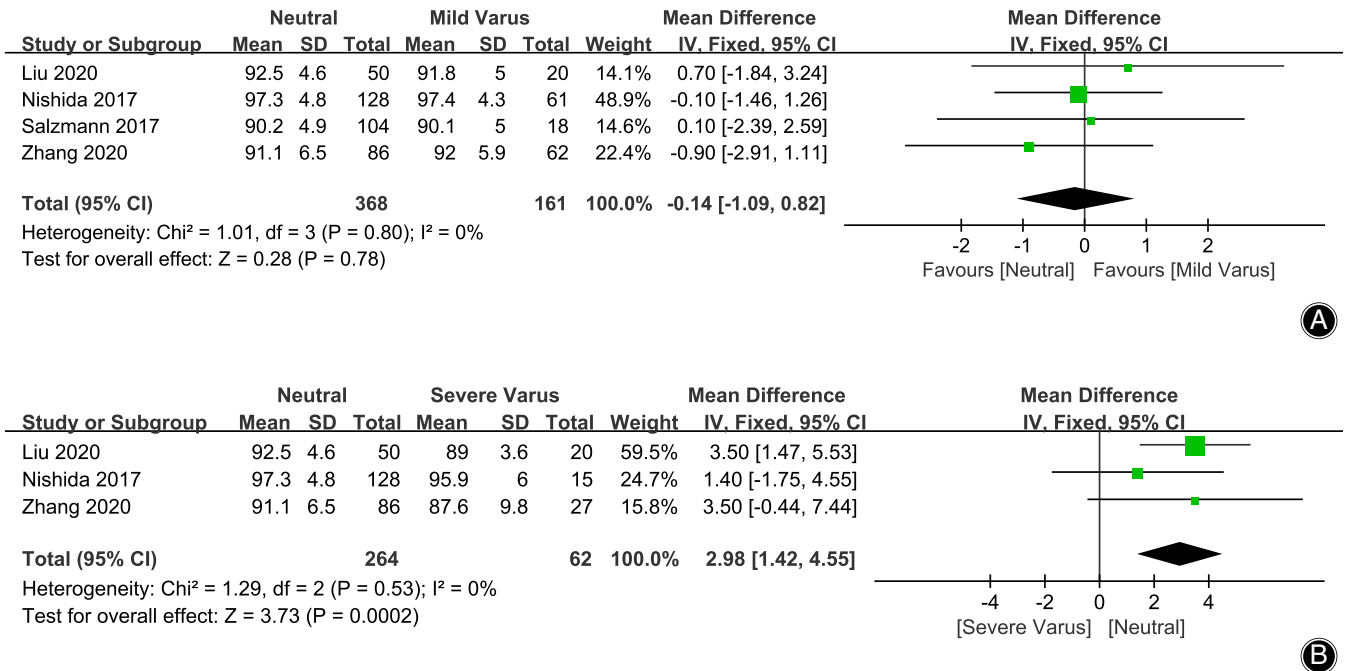


Fig. 5 Forest plot of the meta-analysis of differences in KS-KS between neutral alignment and either mild or severe varus alignment KS-KS.

and severe varus alignment postoperatively; alignment measured by FTMA; non-consecutive case series; and inadequate data.

Quality Assessment

The quality of included studies was assessed using the Newcastle–Ottawa scale (NOS) for non-randomized studies^{37,38}. This scale examines three aspects: selection of study groups (0–4 points), comparability of the groups (0–2 points), and ascertainment of either the exposure or outcome of interest (0–3 points). A total score of 9 points indicates the highest possible quality.

Data Extraction

The following data were extracted independently by two reviewers using a predefined form: first author, year of publication, country, sample size, preoperative diagnosis, age, sex, body mass index (BMI), pre- and post-operative alignment, length of follow-up, and methods used to assess knee function and survival. To ensure uniform descriptions of the coronal limb axis, the hip–knee–ankle angle (HKA) and

mechanical femorotibial alignment (FTMA) were defined as the angle between the mechanical axis of the femur and the reversed extension line of the mechanical axis of the tibia. Varus was defined as positive and valgus as negative. Neutral alignment was defined as 0° ± 3° with reference to the post-operative coronal mechanical axis; mild varus alignment, 3°–6°; and severe varus alignment, >6° (Fig. 1). Alignment in one study²⁴ was not defined as 3°–6° by the authors but the 95% confidence interval (CI) of the alignment fell within that range, so it was classified as mild varus alignment for the present meta-analysis. When outcomes were reported for multiple time points, only data for the longest time point were included. If outcome data were unclear, the corresponding author was contacted for clarification.

Publication Bias

Funnel plots were applied to assess for publication bias (Appendix S1). The funnel plot was visually reviewed, and analyses by sUA quartiles showed funnel plots asymmetry, indicating a publication bias.

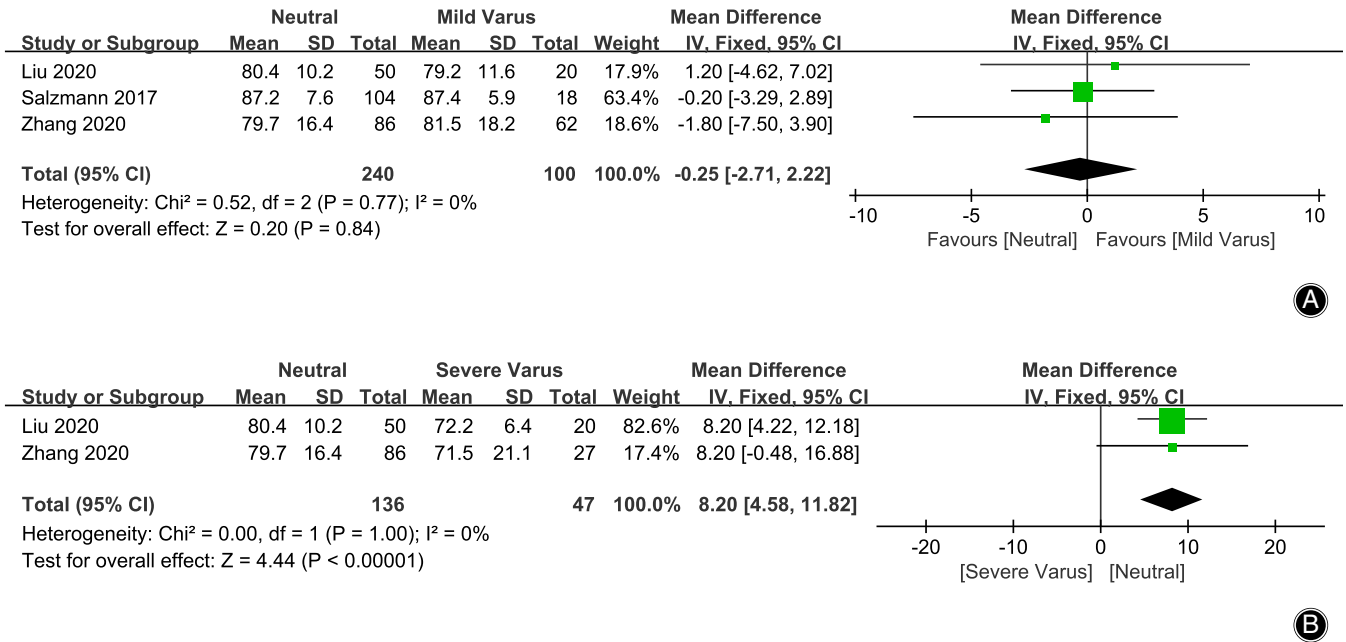


Fig. 6 Forest plot of the meta-analysis of differences in KS-FS between neutral alignment and either mild or severe varus alignment KS-FS.

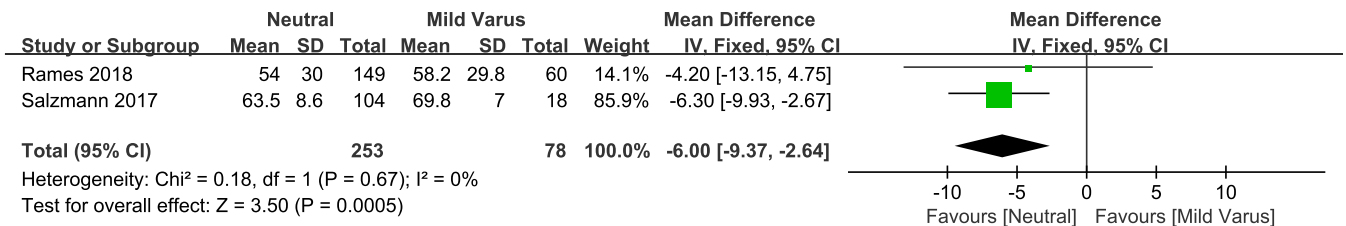


Fig. 7 Forest plot of the meta-analysis of differences in FJS between neutral alignment and mild varus alignment.

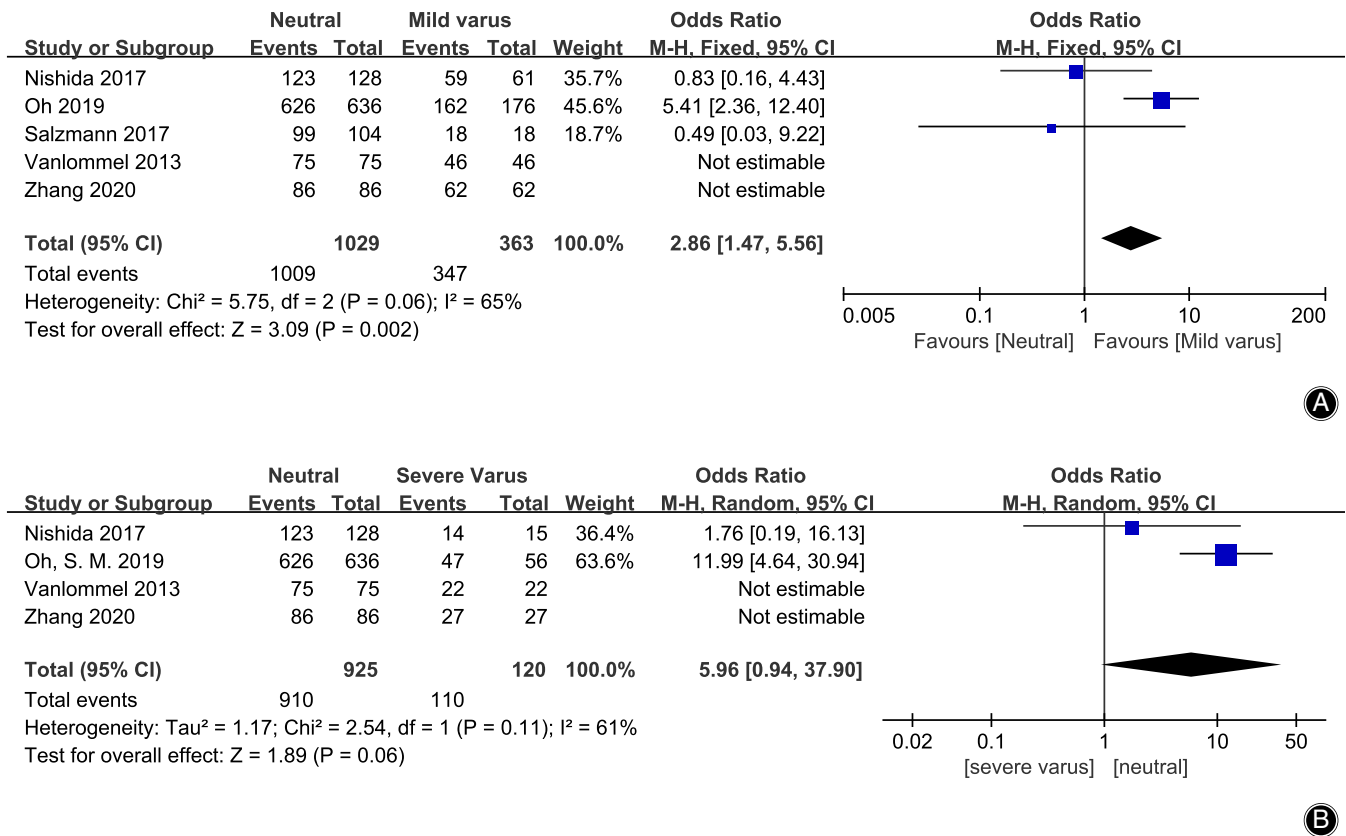


Fig. 8 Forest plot of the meta-analysis of differences in survival between neutral alignment and either mild or severe varus alignment.

Data Analysis

Meta-analysis was performed using Review Manager 5.3 (The Nordic Cochrane Center, Copenhagen, Denmark). Outcomes of interest were Oxford Knee Score (OKS), Western Ontario and McMaster Universities Arthritis Index (WOMAC), Knee Society Knee Score (KS-KS), Knee Society Function Score (KS-FS), Forgotten Joint Score (FJS), and prosthesis survival. The I² test was used to assess heterogeneity based on the thresholds reported in the Cochrane handbook for systematic reviews of interventions: 0%–40% might not be important, 30%–60% may represent moderate heterogeneity, 50%–90% may represent substantial heterogeneity, and 75%–100% may represent considerable heterogeneity. When I² was less than 50%, the fixed-effect model was applied for the meta-analysis; on the contrary, when I² was greater than 50%, the random-effect model should be adopted.

Results

We identified a total of 2436 studies, including 1063 from PubMed, 559 from Embase, 688 from Web of Science, and 67 from the Cochrane Library. We identified another 59 studies through manual searching (Fig. 2). In the end, nine studies were included in the review and meta-

analysis, all of which had a cohort design and were published after 2013.

One study did not mention preoperative diagnosis¹⁵, and another included patients with rheumatoid arthritis³⁰. Patients in the remaining studies were diagnosed with osteoarthritis. The nine studies included 1,410 cases of postoperative neutral alignment, 564 of residual mild varus alignment and 175 of residual severe varus alignment following TKA (Table 1). Three studies showed a mean follow-up longer than 5 years^{15,16,32}, and follow-up across all studies ranged between 1 and 9 years. Three studies^{24,27,28} scored 7 points on the NOS, while the remaining studies scored 8 points, suggesting high quality (Table 2).

Clinical and Functional Outcomes

WOMAC score, OKS, KS-KS, KS-FS, and FJS were meta-analyzed to compare neutral with mild or severe varus alignment. WOMAC scores were compared between neutral and mild varus alignments in four studies^{15,16,27,31} and between neutral and severe alignments in three studies^{15,16,27}. The respective pooled mean differences (MDs) were 1.07 [95% confidence interval (CI) −1.06 to 3.20; P = 0.32; I² = 79%] and −0.35 (95% CI −5.02 to 4.33; P = 0.88; I² = 67%; Fig. 3).

OKS was compared between neutral and mild varus alignments in three studies^{24,27,30} and between neutral and severe varus alignments in two studies^{27,30}. The respective pooled MDs were -0.88 (95% CI -0.63 to 0.47 ; $P = 0.78$; $I^2 = 26\%$) and -0.17 (95% CI -1.02 to 0.68 ; $P = 0.70$; $I^2 = 0\%$; Fig. 4).

KS-KS was compared between neutral and mild varus alignments in four studies^{3,15,28,31} and between neutral and severe varus alignment in three studies^{3,28}. The respective pooled MDs were -0.14 (95% CI -1.09 to 0.82 ; $P = 0.78$; $I^2 = 0\%$) and 2.98 (95% CI 1.42 to 4.55 ; $P = 0.0002$; $I^2 = 0\%$; Fig. 5). KS-FS was compared between neutral and mild varus alignments in three studies^{3,15,31} and between neutral and severe varus alignments in two studies^{3,15}. The respective pooled MDs were -0.25 (95% CI -2.71 to 2.22 ; $P = 0.84$; $I^2 = 0\%$) and 8.20 (95% CI 4.58 to 11.82 ; $P < 0.00001$; $I^2 = 0\%$; Fig. 6).

Neutral and mild varus alignments did not differ significantly in WOMAC score, OKS, KS-KS, or KS-FS. Neutral and severe varus alignments did not differ significantly in WOMAC score or OKS, but neutral alignment was associated with significantly higher KS-KS and KS-FS.

FJS was compared between neutral and mild alignments in two studies^{30,31}. The pooled results indicated lower score for neutral alignment (-6.00 , 95% CI -9.37 to -2.64 ; $P = 0.0005$; $I^2 = 0\%$; Fig. 7).

Survival

Five of the studies compared revision rate or prosthesis survival between neutral and mild alignments^{15,16,28,31,32}, while four studies compared these outcomes between neutral and severe alignments^{15,16,28,32}. One study³² examined all-cause revision, while others^{15,16,28,31} considered only revision due to aseptic loosening. Two studies^{15,16} reported 0% revision rates. Neutral alignment was associated with similar rate of survival as mild varus alignment (95% CI 0.36 to 9.10 ; $P = 0.48$; $I^2 = 65\%$) or severe varus alignment (95% CI 0.94 to 37.90 ; $P = 0.06$; $I^2 = 61\%$; Fig. 8).

Publication Bias

The funnel plots were applied to all the outcomes (Fig. 9). The funnel plots revealed symmetry except the WOMAC score, suggesting that publication bias was minimal. As for the WOMAC score, the funnel plots showed that one study was not included inside, indicating that publication bias existed.

Discussion

To our knowledge, this is the first meta-analysis to compare clinical and functional outcomes as well as prosthesis survival in patients with varus knees following TKA. Our main finding is that residual mild varus alignment is associated with similar or superior outcomes as neutral alignment, while residual severe varus alignment is associated with worse outcomes than neutral alignment.

Neutral alignment is currently the gold standard in TKA, based on studies that it can lead to better outcomes than varus alignment, regardless of whether patients had pre-operative varus knees or not^{7,39}. However, several studies suggest that there is no clinically significant difference between neutral alignment and misalignment^{18,40}. Bilgin *et al.*²¹ reported that the differences in clinical outcomes between well-aligned knees and those of outliers were not found to be statistically significant.

Our analysis showed that neutral and mild varus alignments were associated with similar WOMAC scores, OKS, KS-KS, and KS-FS, which are useful for evaluating the success of TKA⁴¹. The mild varus alignment in our meta-analysis was associated with better FJS than in two individual studies^{30,31}. FJS assesses to what extent the patient can forget about his or her joint arthroplasty while engaging in daily or recreational activities^{42,43}. Although we found that mild varus alignment offered a few advantages in the forgotten extent, it did not offer advantages in objective outcomes or prosthesis survival. One study²⁴ in our meta-analysis reported that total knee injury and osteoarthritis outcome score were significantly better with residual mild varus alignment than with neutral alignment.

Consistent with our meta-analysis, several studies^{12,44,45} have reported similar clinical and functional outcomes for patients with postoperative varus alignment $>3^\circ$ and those with neutral alignment, while several others have reported similar or superior outcomes for patients with residual mild varus alignment 3° – 6° than for those with neutral alignment^{24,27–29,46}. In fact, some studies suggest that post-TKA neutral alignment of patients with “constitutional” varus, which occurred after skeletal growth was complete, can lead to excessive release of medial soft tissue^{17,29,47}. Residual mild varus alignment can result in a more physiological tension in the soft tissue tension than neutral alignment, leading the patient to experience a “natural feeling” in the knees, improving function and satisfaction^{46,48–50}. In addition, Hatayama *et al.*⁴⁴ found postoperative residual varus limb alignment did not lead to increasing varus laxity after TKA in the mid-term. Not only that, but the valgus knee has the same results as the varus knee, Lee *et al.*⁵¹ reported 93 knees with pre-operative valgus alignment and found postoperative slight valgus alignment following TKA resulted in similar clinical outcomes compared with neutral alignment. Furthermore, a study by Slevin *et al.*⁵² found a significant correlation was found between neutral limb alignment and higher KSS only in patients with preoperative non-varus alignment. Although our meta-analysis showed no significant difference between neutral and severe varus alignments in OKS or WOMAC score, it did find significantly lower KS-KS and KS-FS with severe alignment. Indeed, one study reported significantly lower postoperative scores on the Short Form-12 after severe alignment than after neutral alignment³⁰. Therefore, the available evidence suggests that excessive varus alignment can lead to poor clinical and functional outcomes.

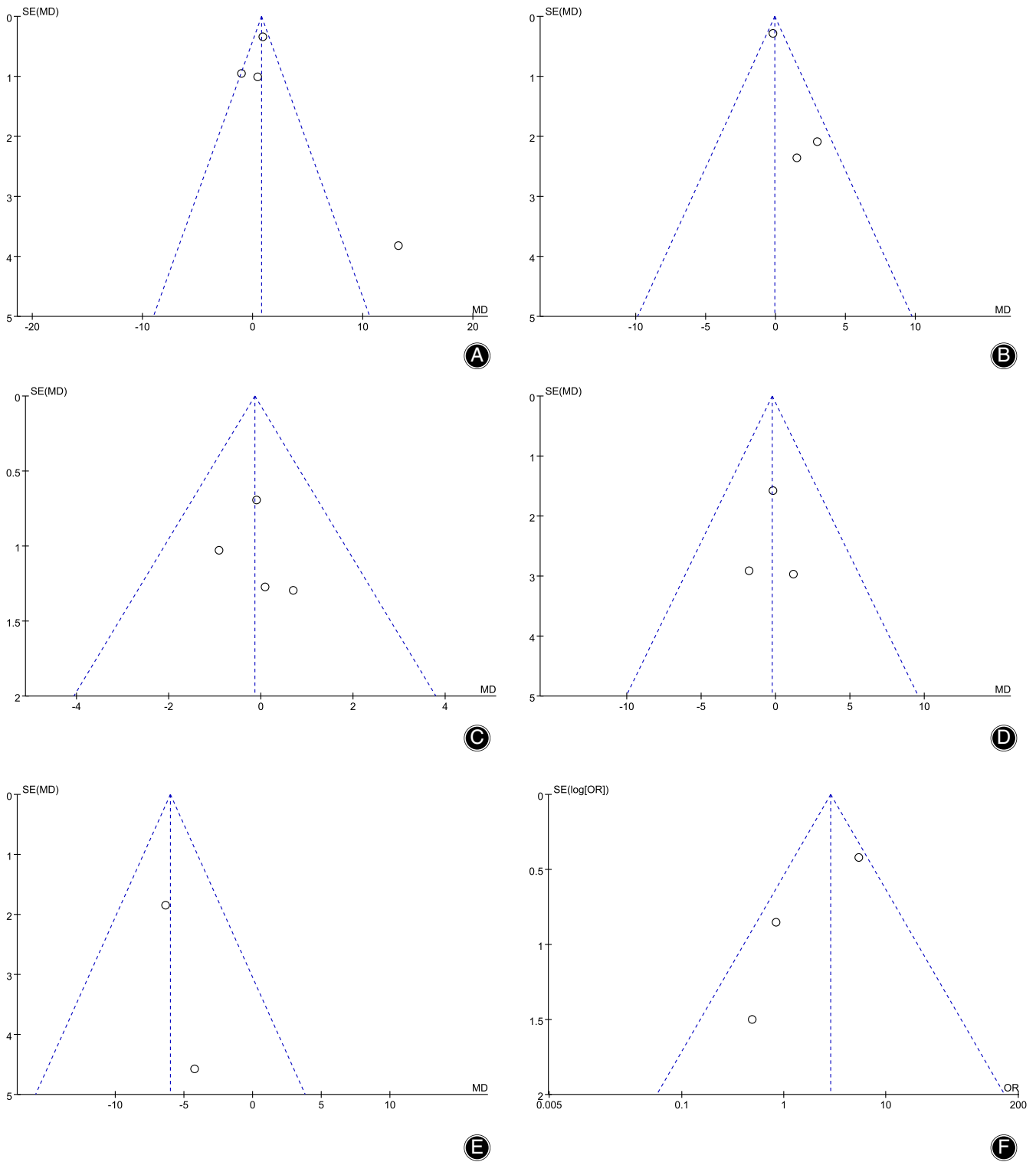


Fig. 9 Fig. Funnel plots of postoperative outcomes between neutral alignment and mild varus alignment. (A) For WOMAC score; (B) for OKS score; (C) for KS-KS score; (D) for KS-FS score; (E) for FJS score; (F) for survival rate.

Three studies^{28,31,32} in our meta-analysis showed that neutral alignment was associated with similar prosthesis survival rates as mild varus alignment, while another two

studies^{15,16} reported 0% rates of prosthesis failure. In contrast to our findings, a previous meta-analysis concluded that neutral alignment was associated with significantly longer

prosthesis survival than postoperative varus alignment $>3^{\circ}$ ²³. Misalignment in the lower extremity may result in an imbalance of forces between the medial and lateral tibial plateaus, which may accelerate wear on the polyethylene insert and increase the risk of osteolysis and prosthesis loosening^{6,53–55}. However, there are several differences between the previous meta-analysis and the current study. First of all, the patients included in the previous meta-analysis include not only preoperative varus knees but also valgus and neutral knees. Comparison of postoperative results did not distinguish varus from mild varus and severe varus. In addition, the previous meta-analysis only compared the prosthesis survival, the current study not only compared the survival, but also compared the clinical and functional outcomes. Several studies suggest that, at least among patients with preoperative varus knees, neutral alignment is associated with similar prosthesis survival as mild varus alignment^{10,13,56}. At the same time, the authors had to be concerned about this heterogeneity. After comparison of the three articles^{28,31,32} included in the survival analysis, the authors found that the biggest difference was in the duration of follow-up, which was much greater at 8 years³² than at 2³¹ and 3²⁸ years. In addition, no significant differences were found in the surgical approach, type of prosthesis, and imaging assessment modalities of the three studies.

Studies have reported that the combination of optimal alignment and soft tissue balancing prolonged implant survival⁵⁷ and improved patients' function and satisfaction⁷. Further research is needed on how to optimize treatment and management of patients with preoperative varus knees, particularly as a function of whether the alignment is 3° – 6° or $>6^{\circ}$, not only whether it is $>3^{\circ}$ as in previous work^{13,58}. Already studies have shown that kinematic alignment can improve patient satisfaction by recreating native knee kinematics^{17,59,60}, achieving similar functional, radiological, and perioperative outcomes as mechanical alignment⁶¹. Advances in computer-assisted navigation, three-dimensional imaging, and patient-specific positioning can help surgeons more precisely resect bone and position components⁶². Targeted osteotomy may also improve postoperative alignment. Such techniques may help finely optimize postoperative alignment: one study⁶³, for example, found that outcomes at 2° – 4° were similar or better than those at $0^{\circ} \pm 1^{\circ}$, which provided a basis for determining the optimal alignment in a smaller area. Based on the booming robot-assisted TKA technology, it is possible to create an individualized, optimized alignment³⁴.

The current meta-analysis has several limitations. First, all of the included studies had a cohort design and provide a relatively low level of evidence. Second, the heterogeneity was unsatisfactory in the meta-analyses of survival rate and WOMAC score. For the heterogeneity of WOMAC, among the four studies^{15,16,27,31} included, the study by Vanlommel *et al.* comprised patients who underwent surgery around 2003, and the rest were patients who underwent surgery after 2008. After the authors excluded the study from Vanlommel *et al.*, I^2 decreased from 79% to 46%. The authors believe

that this is the main reason. As Table 1 shows, the inconsistency of preoperative varus alignment may be another reason. All in all, the same osteotomy was used except for the one⁶⁴, which used a two-dimensional osteotomy templating, which may have an impact on prosthesis location. Although the HKA reflects the full-length alignment of the lower limb, it does not fully reflect the respective alignment of the tibia and femur. Third, lack of reporting prevented us from meta-analyzing patient-reported outcomes, such as pain, range of motion, or satisfaction. Lastly, studies examined relatively small samples, and two studies^{28,31} did not follow up longer than 5 years. Larger well-designed studies with longer follow-up are needed to confirm our findings and assess whether prosthesis failure rates correlate with postoperative mild varus alignment.

Conclusion

The available evidence suggests that postoperative residual mild varus alignment is associated with similar or even better outcomes than neutral alignment in patients with preoperative varus knees who have undergone TKA. Our results suggest that postoperative residual mild varus alignment is acceptable for such patients, while severe varus alignment should be avoided.

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Author Contributions

XFW conceived the methods of the study, performed the database search, the article selection and data extraction processes, performed the statistical analysis and drafted the manuscript. YY and DW conceived the methods of the study, performed the database search, the article selection and data extraction processes. HX and CH conceived the methods of the study and analyzed data. ZKZ and JX helped to perform data extraction processes and draft the manuscript. All authors reviewed the final manuscript. All authors agree to be accountable for all aspects of the work.

Availability of Data and Material

The data sets used and/or analyzed during the current study are fully available on reasonable request.

Consent for Publication

All authors have stated for their consent for publication.

Supporting Information

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

Appendix S1. Funnel plots of postoperative outcomes between neutral alignment and severe varus alignment. A. for WOMAC score; B. for survival rate; C. for KS-KS score; D. for KS-FS score.

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