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

Xu-feng Wan, MM1†, Yang Yang, MD2†, Duan Wang, MD1, Hong Xu, MD1, Chao Huang, MD1, Zong-ke Zhou, MD1, Jin Xu, MD3

1Department of Orthopaedics, West China Hospital and 2State Key Laboratory of Oral Diseases, National Clinical Research Center for Oral Diseases, West China Hospital of Stomatology, Sichuan University, Chengdu and 3Tianjin Hospital, Tianjin, China

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°±3°) was compared to residual mild varus (3°–6°) and residual severe varus (>6°). 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; I² = 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; I² = 0%) as well as higher KS-FS (M 8.20, 95% CI 4.58 to 11.82, P < 0.00001; I² = 0%). Neutral alignment was associated with similar rate of survival as mild varus alignment (95% CI 0.36 to 9.10; P = 0.48; I² = 65%) or severe varus alignment (95% CI 0.94 to 37.90; P = 0.06; I² = 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
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 alone. Postoperative function and prosthesis survival are closely related to patient satisfaction remained unsatisfaction around 20%, affecting successful outcomes. Alignment after TKA can strongly influence postoperative function and implant longevity. The gold standard for the last few decades has been postoperative overall mechanical femorotibial alignment (FTMA) of 0° ± 3°, often referred to as "neutral alignment".

However, a series of studies have called into question whether neutral alignment is necessary for optimal outcomes after TKA: some evidence suggests that deviations in lower extremity alignment do not compromise postoperative clinical and functional outcomes or prosthesis survival. 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, 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 prosthesis.

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 more. This natural alignment as constitutional varus was defined by Bellemans et al. 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° increases efficacy of TKA without increasing the rate of prosthesis failure. 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 varus. This has led to some studies comparing residual mild varus alignment (3°–6°) and neutral alignment (0° ± 3°) after TKA in patients with preoperative varus deformity, 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. Rajasekaran et al. 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 period. However, other studies have reported the opposite, one study 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 release, 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-up. Many patients undergoing TKA have varus deformity before surgery, so it is important to find the optimal postoperative alignment strategy.

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.
| Study (country) | Knees | Diagnosis | Age (years, M ± SD) | Sex (F/M) | BMI(kg/m²) M ± SD | Preoperative alignment (°) | Postoperative alignment (°) | Length of follow-up | Assessments |
|----------------|-------|-----------|---------------------|-----------|------------------|---------------------------|---------------------------|---------------------|-------------|
| Zhang (China)  | N:86  | Varus     | N68.0 ± 6.7         | N69/17    | 25.3 ± 3.2       | HKA:                       | HKA:                      | 5.2 ± 1.1           | KSS         |
|                | MV:62 | osteoarthritis | MV67.2 ± 7.1       | MV:50/12  | 26.2 ± 3.6       | varus > 3                   | MV:                       | (–3 to 3)          | WOMAC       |
|                | SV:27 |            | SV63.9 ± 7.4       | SV24/3    | 26.0 ± 3.4       | MV:                       | MV:                       | (–6 to –3)         | Survival    |
|                |       |            |                     |           |                  | SV:<6                      | SV:<6                    |                     | analysis     |
| Rajasekara (India) | N:87 | Severe varus osteoarthritis | N59.1 ± 4.4 | N:47/20 | —                | FTA:                       | FTA:                      | 12 months          | OKS         |
|                | MV:88 |            | MV64.4 ± 7.0       | MV:74/14  | 160.99 ± 3.88    | MV: 161.35                  | MV: 173-176              |                     | WOMAC       |
|                | SV:7  |            | SV62.1 ± 2.03      | SV8/1     | 157.29 ± 4.63    | MV:                       | SV: below 172            |                     |             |
| Liu (China)    | N:50  | Varus     | N66.3 ± 6.9        | N35/11    | 26.9 ± 4.2       | HKA:                      | HKA:                      | 18.4 ± 4.0 months   | HSS         |
|                | MV:20 | osteoarthritis | MV65.7 ± 7.1       | MV12/6    | 27.5 ± 4.1       | MV:                       | MV:                       | N:0 ± 3            | KSS         |
|                | SV:20 |            | SV69.0 ± 6.5       | SV15/4    | 26.6 ± 3.5       | SV:                       | SV:                       | MV:3-6            |             |
|                |       |            |                     |           |                  | N:30                        | SV:<6                    |                     |             |
| Schrinner (Germany) | N:115 | Varus     | N: 77 ± 8.2        | N61/54    | —                | HKA:                      | N: varus 8.3             | 3–5 years          | OKS         |
|                | MV:33 | osteoarthritis | MV: 77 ± 9.2       | MV:23/10  | —                | MV:                       | MV:4.1 ± 1.1             |                     | KOOS        |
|                |       |            |                    |           |                  |                             |                           |                     |             |
| Oh S. M (South Korea) | N:636 | Varus     | N6.89 ± 6.32       | N598/38   | 27.41 ± 3.52     | Varus                      | Varus                     | 8.23 ± 3.47 years   | Survival    |
|                | MV:176| osteoarthritis | MV66.93 ± 6.5      | MV174/2   | 27.35 ± 3.36     | MV:                       | MV:                       | (–3 to 3)          | rate        |
|                | SV:56 |            | SV66.25 ± 6.7      | SV52/4    | 26.38 ± 3.49     | SV:                       | MV:                       | (–6 to –3)         | Survival    |
|                |       |            |                     |           |                  | N:30                        | SV:<6                    |                     | time        |
| Rames (USA)    | N:149 | Osteoarthritis or rheumatoid arthritis | N: 63.9 ± 8.9 | N:79/19 | 31.9 ± 5.6       | HKA:                      | N: varus 8.3             | 1.3 ± 0.6 years    | SF-12       |
|                | MV:60 |            | MV: 63.2 ± 9.8     | MV22/38   | 33.3 ± 6.3       | MV:                       | MV:                       | N:0.7 ± 1.5        | OKS         |
|                | SV:28 | arthritis | SV: 63.8 ± 9.5     | SV12/18   | 36.0 ± 6.1       | MV:                       | MV:4.3 ± 0.9             |                     | FJS         |
|                |       |            |                     |           |                  | MV: varus 9.5             | MV: 7.7 ± 1.7            |                     |             |
|                |       |            |                     |           |                  | ± 4.7                      | SV: 10.5 ± 6.0           |                     |             |
| Salzmann (Germany) | N:104 | Osteoarthritis | N69.5 ± 6.3        | N58/46    | 29.8 ± 3.9       | FTA:                      | N:14 ± 1.0               | 2 years            | KSS         |
|                | MV:18 |            | MV: 69.6 ± 5.9     | MV11/7    | 29.7 ± 4.3       | FTMA:                     | MV4.3 ± 0.8              |                     | WOMAC       |
|                |       |            |                     |           |                  | (4.5–6.0)                  | MV:177-174              |                     | FJS         |
|                |       |            |                     |           |                  | (4.0–16.0)                 | MV:177-174              |                     | Survival     |
|                |       |            |                     |           |                  | (4.0–15.0)                 | MV:177-174              |                     |             |
| Nishida (Japan) | N:128 | Varus osteoarthritis | N: 73.6 ± 7.4 | N114/14 | —                | FTA:                      | N:180 ± 3                | 3.4 (range)        | KSS         |
|                | MV:61 |            | MV: 73.5 ± 6.7     | MV50/11   | 186.8 ± 5.4      | FTMA:                     | MV:180 ± 3               | 2–5 years          | ROM         |
|                | SV:15 |            | SV: 71.3 ± 7.4     | SV150/5   | 166.8 ± 5.2      | FTMA:                     | MV:177-174              |                     | Revision     |
|                |       |            |                     |           |                  | (3.5–5.5)                 | MV:177-174              |                     |             |
|                |       |            |                     |           |                  | FTMA:                     | MV:177-174              |                     |             |
| Vantommel (Belgium) | N:75  | —         | N: 74.0 ± 8.3      | N58/17    | 29.3 ± 4.6       | FTA:                      | N:180 ± 3                | 7.2 years          | KSS         |
|                | MV:46 |            | MV: 74.1 ± 8.4     | MV27/19   | 31.2 ± 4.5       | FTMA:                     | MV:177-174              |                     | WOMAC       |
|                | SV:22 |            | SV: 71.1 ± 6.5     | SV12/10   | 31.7 ± 5.5       | FTMA:                     | MV:177-174              |                     | Revision     |
|                |       |            |                     |           |                  | (3.4–6.0)                 | MV:177-174              |                     |             |

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) Statement 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**

| Study | Selection | Comparability | Exposure/outcome | Total score |
|-------|-----------|---------------|------------------|-------------|
| Zhang15 2020 | 4 | 2 | 2 | 8 |
| Rajasekaran7 2020 | 4 | 1 | 2 | 7 |
| Liu 2020 | 4 | 2 | 2 | 8 |
| Schiffter24 2019 | 3 | 1 | 3 | 7 |
| Oh, S. M. 26 2019 | 4 | 2 | 2 | 8 |
| Rames50 2018 | 4 | 2 | 2 | 8 |
| Salzmann61 2017 | 4 | 2 | 2 | 8 |
| Nishida28 2017 | 4 | 1 | 2 | 7 |
| Vanlommel56,58 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](image-url)  
**Fig. 4** Forest plot of the meta-analysis of differences in OKS between neutral alignment and either mild or severe varus alignment.

![Fig. 5](image-url)  
**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. 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 $0^\circ \pm 3^\circ$ with reference to the postoperative coronal mechanical axis; mild varus alignment, $3^\circ – 6^\circ$; and severe varus alignment, $>6^\circ$ (Fig. 1). Alignment in one study was not defined as $3^\circ – 6^\circ$ 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.
**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 diagnosis, and another included patients with rheumatoid arthritis. 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, and follow-up across all studies ranged between 1 and 9 years. Three studies 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 and between neutral and severe alignments in three studies. 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, and between neutral and severe varus alignments in two studies. 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 and between neutral and severe varus alignment in three studies. 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 and between neutral and severe varus alignments in two studies. 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; $P < 0.0001$; $I^2 = 0\%$; 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. 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 varus alignment, while four studies compared these outcomes between neutral and severe varus alignment. One study examined all-cause revision, while others considered only revision due to aseptic loosening. Two studies 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 preoperative varus knees or not. However, several studies suggest that there is no clinically significant difference between neutral alignment and misalignment. Bilgin et al. 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 TKA. The mild varus alignment in our meta-analysis was associated with better FJS than in two individual studies. FJS assesses to what extent the patient can forget about his or her joint arthroplasty while engaging in daily or recreational activities.

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 study 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 have reported similar clinical and functional outcomes for patients with postoperative varus alignment >3° 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. 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. 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.

In addition, Hatayama et al. 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. 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. found a significant correlation was found between neutral limb alignment and higher KS 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 alignment. Therefore, the available evidence suggests that excessive varus alignment can lead to poor clinical and functional outcomes.
Three studies\textsuperscript{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\textsuperscript{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

![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.](image-url)
prosthesis survival than postoperative varus alignment $>3^\circ$.
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. 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. At the same time, the authors had to be concerned about this heterogeneity. After comparison of the three articles 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 years than at 2 and 3 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 survival and improved patients’ function and satisfaction. 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 $3^\circ$–$6^\circ$ or $>6^\circ$, not only whether it is $>3^\circ$ as in previous work. Already studies have shown that kinematic alignment can improve patient satisfaction by recreating native knee kinematics, achieving similar functional, radiological, and perioperative outcomes as mechanical alignment. Advances in computer-assisted navigation, three-dimensional imaging, and patient-specific positioning can help surgeons more precisely resect bone and position components. Targeted osteotomy may also improve postoperative alignment. Such techniques may help finely optimize postoperative alignment: one study, for example, found that outcomes at $2^\circ$–$4^\circ$ 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 alignment.

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 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 one, 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 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.

Acknowledgments

We would like to thank the Department of Orthopedic Surgery, West China Hospital, for their support.

Author Contributions

FW 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.
Huang TW, Lee CY, Lin SJ, Lee MS, Hsu RWW, Shen WJ. The in...
Bellemans J, Colyn W, Vandenneucker H, Victor J. The Chitranjan Ranawat
knees. Knee Surg Sports Traumatol Arthrosc, 2013, 21: 2325
16.
15.
Arthrosc, 2014, 22: 2635
1491.
52.
188

References
1. Sloan M, Premkumar A, Sheh NP. Projected volume of primary total joint arthroplasty in the U.S., 2014 to 2030. J Bone Joint Surg Am, 2018, 100: 1455–1460.
2. Dunbar MJ, Haddad FS. Patient satisfaction after total knee replacement: new inroads. Bone Joint J, 2014, 96: 1285–1286.
3. Lu L, Xu SZ, Yang J, et al. Relationship between lower limb alignment distribution and short-term clinical results after primary total knee arthroplasty in patients with varying degrees of knee varus. Zhongguo Gu Shang, 2020, 33: 530–535.
4. Fang DM, Ritter MA, Davis KE. Coronal alignment in total knee arthroplasty: just how important is it?. J Arthroplasty, 2009, 24: 3453–3457.
5. Berend ME, Ritter MA, Meding JB, et al. Tibial component failure mechanisms in total knee arthroplasty. Clin Orthol Relat Res, 2004, 428: 26–34. https://doi.org/10.1097/01.blo.0000148578.22729.0e26-34.
6. Zhang YM, Cai HF, Xu SF, Han Y, Shi SY, Liu B. Tibial slope, mechanical axis alignment, and mechanical axis inclination of the femur in total knee arthroplasty. J Bone Joint Surg Am, 2010, 92: 2143–2149.
7. Bellemans J. Neutral mechanical alignment: a requirement for successful TKA: opposes. Orthopedics, 2011, 34: E507–E509.
8. Magnussen RA, Wepp J, Demey G, Servien E, Lustig S. Residual varus correction does not compromise results of TKAs in patients with preoperative varus. Clin Orthol Relat Res, 2011, 469: 3443–3450.
9. Matzios G, Adam J, Perka C. Varus malalignment has no influence on clinical outcome in midterm follow-up after total knee replacement. Arch Orthop Trauma Surg, 2010, 130: 1487–1491.
10. Nishikawa K, Okazaki K, Matsuda S, et al. Improved design wear decreases wear in knee total arthroplasty with varus malalignment. Knee Surg Sports Traumatol Arthrosc, 2014, 22: 2636–2640.
11. Howell SM, Howell SJ, Kuznik KT, Cohen J, Hull ML. Does a kinematically aligned total knee arthroplasty restore function without failure regarding of alignment category?. Clin Orthol Relat Res, 2013, 471: 1000–1007.
12. Parratte S, Pagnano MW, Trousdale RT, Berry DJ. Effect of postoperative coronal malalignment on the fifteen-year survival of modern, cemented total knee replacements. J Bone Joint Surg Am, 2010, 92: 2143–2149.
13. Bellemans J. Neutral mechanical alignment: a requirement for successful TKA: opposes. Orthopedics, 2011, 34: E507–E509.
14. Vasquez-Arcay S, Pagnano MW, Trousdale RT, Berry DJ. Effect of postoperative coronal malalignment on outcomes of total knee arthroplasty. J Arthroplasty, 2009, 24: 3453–3457.
15. Bellemans J, Colyn W, Vandenneucker H, Victor J. The Chitranjan Ranawat award: no difference in 2-year functional outcomes using kinematic versus mechanical alignment in TKA; a randomized controlled clinical trial. Clin Orthop Relat Res, 2011, 469: 3443–3450.
16. Matsuda S, Kawahara S, Okazaki M, Tashiro Y, Iwamoto Y. Postoperative knee joint line to horizontal. Knee Surg Sports Traumatol Arthrosc, 2016, 24: 544–549.
17. Howell SM, Wang P, Ying XZ, Zhang H. Does residual varus alignment cause increasing varus laxity at a minimum of five years after total knee arthroplasty?. Knee Surg Sports Traumatol Arthrosc, 2016, 24: 198–194.
18. Ji HM, Han J, Jin DS, Seo H, Won YY. Kinematically aligned TKA can align knee joint line to horizontal. Knee Surg Sports Traumatol Arthrosc, 2016, 24: 2436–2441.
19. Delport H, Labeby L, Innocenti B, de Corte R, Vander Sloten J, Bellemans J. Restoration of constitutional alignment in TKA leads to more physiological strains in the collateral ligaments. Knee Surg Sports Traumatol Arthrosc, 2015, 23: 2159–2169.
20. Lovejoy CO. The natural history of human gait and posture. Part 3. The knee. Gait Posture, 2007, 25: 325–341.
21. Lee S, Lee H, Lee DH, Moon YW. Slight under-correction following total knee arthroplasty for a valgus knee results in similar clinical outcomes. Arch Orthop Trauma Surg, 2018, 138: 1011–1019.
22. Sievin O, Hirschmann A, Schiaparelli FF, Amisiel F, Huegli WR, Hirschl M. Neutral alignment leads to higher knee society scores after total knee replacement.
knee arthroplasty in preoperatively non-varus patients: a prospective clinical study using 3D-CT. Knee Surg Sports Traumatol Arthrosc, 2018, 26: 1602–1609.

53. Jeffery RS, Morris RW, Denham RA. Coronal alignment after total knee replacement. J Bone Joint Surg Br, 1991, 73: 709–714.

54. Ritter MA, Davis KE, Davis P, et al. Preoperative malalignment increases risk of failure after total knee arthroplasty. J Bone Joint Surg Am, 2013, 95: 126–131.

55. Ritter MA. The anatomical graduated component total knee replacement: a long-term evaluation with 20-year survival analysis. J Bone Joint Surg Br, 2009, 91: 745–749.

56. Bonner TJ, Eardley WG, Patterson P, Gregg PJ. The effect of post-operative mechanical axis alignment on the survival of primary total knee replacements after a follow-up of 15 years. J Bone Joint Surg Br, 2011, 93: 1217–1222.

57. Ritter MA, Davis KE, Meding JB, Piorson JL, Berend ME, Malinzak RA. The effect of alignment and BMI on failure of total knee replacement. J Bone Joint Surg Am, 2011, 93: 1588–1596.

58. Nakajima A, Sonobe M, Akatsu Y, et al. Association between limb alignment and patient-reported outcomes after total knee arthroplasty using an implant that reproduces anatomical geometry. J Orthop Surg Res, 2018, 13: 320.

59. Dossett HG, Estrada NA, Swartz GJ, LeFevre GW, Kwasman BG. A randomised controlled trial of kinematically and mechanically aligned total knee replacements: two-year clinical results. Bone Joint J, 2014, 96: 907–913.

60. Mercuri JJ, Pepper AM, Werner JA, Viggodchik JM. Gap balancing, measured resection, and kinematic alignment: how, when, and why? JBJS Rev, 2019, 7: e2.

61. Luo Z, Zhou K, Peng L, Shang Q, Pei F, Zhou Z. Similar results with kinematic and mechanical alignment applied in total knee arthroplasty. Knee Surg Sports Traumatol Arthrosc, 2020, 28: 1720–1735.

62. Lombardi AV Jr, Berend KR, Ng VY. Neutral mechanical alignment: a requirement for successful TKA: affirms. Orthopedics, 2011, 34: e504-e506.

63. Ro DH, Kim JK, Lee DW, Lee J, Han HS, Lee MC. Residual varus alignment after total knee arthroplasty increases knee adduction moment without improving patient function: a propensity score-matched cohort study. Knee, 2019, 26: 737–744.

64. Miralles-Munoz FA, Rubio-Morales M, Bello-Tejada L, et al. Varus alignment of the tibial component up to seven degrees is not associated with poor long-term outcomes in a neutrally aligned total knee arthroplasty. Knee Surg Sports Traumatol Arthrosc, 2021. https://doi.org/10.1007/s00167-021-06627-3.