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Knee arthroplasty: Techniques and complications

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Knee arthroplasty: Techniques and complications

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Editorial: Knee arthroplasty: techniques and complications

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Editorial on the Research Topic
Knee arthroplasty: techniques and complications

Knee arthroplasty is considered the most successful surgery of the past decade. Even then, 10%–20% of patients remain dissatisfied following the procedure (1). The understanding of this technique has developed from mechanical to kinematic alignment, and the accuracy has been enhanced from conventional manual technique to computer navigation, patient-specific implantation (PSI), and robotic-assisted surgery. Using various parameters, researchers are trying to predict the complications, such as fever, infection, loosening, and hospital stay. The collection of articles in this special issue has published many such innovative concepts that will be helpful to arthroplasty surgeons.

The restricted kinematic alignment (RKA) restores the pre-arthritic constitutional lower limb alignment in TKA Vendittoli et al. The principles aim at hip-knee-ankle (HKA) angle restoration of 3 degrees on either side, joint line obliquity within 5 degrees of neutral, restoration of knee soft tissue tension, preservation of femoral anatomy, and making the pivot point on the less damaged condyle. As nearly half of the patients need anatomic modifications to fit within the restricted kinematic alignment boundaries, the technique can be best adopted using PSI, computer navigation, or a robot. The clinical report suggested better mid-term function, a higher patient-reported outcome score, and a gait pattern equivalent to a non-arthritic limb. Unlike mechanical alignment, RKA avoids extensive corrections and soft tissue releases. RKA can also be applied to revision TKA, particularly in early, non-wear-related, unsuccessful mechanically aligned TKAs Kostretzis et al.

The article "Clinical and Radiological Changes of the Ankle in Knee Osteoarthritis with Varus After Total Knee Arthroplasty: A Systematic Review" provides a comprehensive overview of the clinical and radiological changes that occur in the ankle joint and hind foot following total knee arthroplasty (TKA) in patients with knee osteoarthritis and varus alignment Feng et al. The authors systematically reviewed the literature and analyzed the results of 8 studies involving 913 patients with 1,157 knees. TKA in patients with varus knee osteoarthritis significantly improved ankle function and hindfoot alignment. However, the ankle pain increased after TKA in patients with osteoarthritis ankle, hindfoot stiffness, and residual knee deformity. The authors suggested that patients with residual knee deformity and pain in the hindfoot should receive treatment for the foot problem after six

weeks of TKA as further improvement is remote. The authors concluded with a message to the arthroplasty surgeons that all patients should have thorough clinical and radiological examinations of the ankle/hindfoot before TKA. Symptomatic ankle or hindfoot problems with radiological changes can receive treatment in the preoperative or postoperative periods of TKA. However, patients without ankle/hindfoot problems before TKA may also develop foot symptoms after TKA, and they can be treated when discomfort occurs.

Noninfectious fever (NIF) after TKA is a serious issue for orthopedic surgeons. It is defined as a raised body temperature equal to or higher than 38.0°C with a negative bacterial culture of blood, urine, sputum, and synovial fluid aspirate. It leads to prolonged antibiotic use and hospital stay, thus increasing the medical cost of treatment. The retrospective data published in this special issue reported a 39% incidence of NIF in 146 patients of TKA Xu et al. The proposed nomogram by the team predicted NIF within seven days of TKA from three parameters:

- Intraoperative blood loss
- The volume of postoperative drainage fluid
- Frequency of blood transfusion

The author proposed that this nomogram had a sensitivity of 54% and a specificity of 82%. While the nomogram can predict fever of noninfectious origin, the study suggests surgeons pay more attention to perioperative bleeding control measures and judicious use of blood transfusion to minimize the incidence of NIF.

An exciting article predicted the length of hospital stay after TKA from a nomogram Liu et al. The parameters were age, Hb, surgical duration, procedure description, diabetes mellitus, day of operation, blood transfusion, and repeat surgery within 30 days. Three quartiles of patients (Q3) had a hospital stay of six days, and 20% had an extended stay.

In an innovative model, the Polyetheretherketone (PEEK) based TKA allowed computed tomographic assessment of the underlying bone with bone mineral density (BMD) measurement Cai et al. The authors noted a reduction in BMD in a lateral tibial plateau at three months follow up and noted tibial prosthesis overhang in 2 of 10 patients. PEEK may offer the advantages of accurately measuring periprosthetic bone changes and prosthesis overhang while avoiding metal-related reactions.

Prosthetic joint infection (PJI) is alarming as the incidence is increasing because of increased primary TKA. The available serum biomarkers lack specificity, and synovial fluid markers play a more significant role in diagnosis (2). The prospective study on PJI reported that both synovial fluid IL-4 (SF-IL4) and polymorphonuclear cell percentage (SF-PMN %) could diagnose PJI with 97% specificity and 96% accuracy when the cut-off values were 1.7 pg/ml and 75%, respectively Huang et al.

The data from Richmond, USA, about stem survivorship in revision TKA ($n = 133$ revision in 122 patients) revealed that hybrid (primary fixation through diaphyseal stem-bone fixation and secondarily with epiphyseal or metaphyseal cement) and fully cemented techniques of both femoral and tibial stem implantations have similar survival rates Kemker et al. The stem survivorship was 81% in the hybrid group and 85% in the cemented groups at a minimum follow-up of 2 years. The authors did not find an association between age, sex, and BMI with the failure in either group. There were no differences in length of hospital stay and hemoglobin drop in both the groups suggesting no difference in early postoperative complications rate.

The technique of fusiform capsulectomy of the posterior capsule and percutaneous flexion tendon release for TKA in the bony ankylosed knee with severe flexion contracture (>80°) has shown promising results without neurovascular complications or infection. At medium-term follow-up, the authors reported a significantly improved knee society score with a mean range of motion of 100 degrees Chen et al.

The articles in this special issue are blended with research articles, new technology, and systematic review. Information provided through these articles will be helpful to arthroplasty surgeons for better patient care, precision in surgery and future development.

Author contributions

ST prepared the initial draft of the editorial. SS, JS, and SB provided intellectual input. All authors read the articles and approved for publication. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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METHODS
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Restricted Kinematic Alignment, the Fundamentals, and Clinical Applications

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Introduction: After a better understanding of normal knee anatomy and physiology, the Kinematic Alignment (KA) technique was introduced to improve clinical outcomes of total knee arthroplasty (TKA). The goal of the KA technique is to restore the pre-arthritic constitutional lower limb alignment of the patient. There is, however, a large range of normal knee anatomy. Unusual anatomies may be biomechanically inferior and affect TKA biomechanics and wear patterns. In 2011, the leading author proposed the restricted kinematic alignment (rKA) protocol, setting boundaries to KA for patients with an outlier or atypical knee anatomy.

Material and Equipment: rKA aims to reproduce the constitutional knee anatomy of the patient within a safe range. Its fundamentals are based on sound comprehension of lower limb anatomy variation. There are five principles describing rKA: (1) Combined lower limb coronal orientation should be ± 3° of neutral; (2) Joint line orientation coronal alignment should be within ± 5° of neutral; (3) Natural knee's soft tissues tension/ laxities should be preserved/restored; (4) Femoral anatomy preservation is prioritized; (5) The unloaded/most intact knee compartment should be resurfaced and used as the pivot point when anatomical adjustment is required. An algorithm was developed to facilitate the decision-making.

Methods: Since ∼50% of patients will require anatomic modification to fit within rKA boundaries, rKA is ideally performed with patient-specific instrumentation (PSI), intra-operative computer navigation or robotic assistance. rKA surgical technique is presented in a stepwise manner, following the five principles in the algorithm.

Results: rKA produced excellent mid-term clinical results in cemented or cementless TKA. Gait analysis showed that rKA TKA patients had gait patterns that were very close to a non-operated control group, and these kinematics differences translated into significantly better postoperative patient-reported scores than mechanical alignment (MA) TKA cases.

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Discussion: Aiming to improve the results of MA TKA, rKA protocol offers a satisfactory compromise that recreates patients' anatomy in most cases, omitting the need for extensive corrections and soft tissue releases that are often required with MA. Moreover, it precludes the reproduction of extreme anatomies seen with KA.

Keywords: knee-surgery, alignment, kinematic, personalized medicine, anatomical, arthroplasty (replacement), mechanical, restricted

INTRODUCTION

Mechanical Alignment Limitations

Most patients following mechanically aligned (MA) total knee arthroplasty (TKA) do not report a natural joint (1). Every fifth patient is dissatisfied (2), every second patient presents residual symptoms (3), and every fourth one would not undergo the same surgery again (4). Following TKA, patients walk with a diminished total range of knee motion and significant kinematic discrepancies, as demonstrated by gait analysis studies (5). Historically, TKA implantation lacked instrument precision, and technical errors were frequent. Surgeons focused mainly on implant survivorship rather than on recreating a normal knee function (6). To ensure satisfactory prosthetic survivorship, the mechanical alignment (MA) technique was introduced. Neutral femoral and tibial cuts with adjusted femoral rotation and ligamentous releases to create equal flexion and extension gaps were the foundation of this simple method of knee alignment. This "one size fits all" philosophy, albeit reproducible, does not incorporate the full range of normal knee anatomy (7).

Even though the mean hip-knee-ankle angle (HKA) is close to neutral, in a study of 4,884 lower limb CT-scans of patients scheduled for TKA, we found that only 0.1% of patients had both a mechanical proximal tibial angle (mPTA) and mechanical distal femoral angle (mDFA) at neutral, which is MA goal. Such modifications of the bony anatomy will affect the soft tissue laxities and knee balance (**Figure 1**).

Simulating MA bone cuts on 1,000 knee CT scans, we found that MA results in many cases of gap asymmetries (8, 9). Mediolateral imbalances of more than 3 mm were observed in 25 and 54% of varus and valgus knees, respectively. Only 49% of varus and 18% of valgus knees had <3 mm of imbalance in mediolateral and flexion/extension gaps when employing trans-epicondylar axis for femoral rotation. Some imbalances might not be surgically correctable and may result in residual instability and poor results in knee replacement patients. A better understanding of normal knee joint functional anatomy led to the introduction of Kinematic Alignment (KA) technique to improve clinical outcomes after knee arthroplasty. It intends to restore the patient's pre-arthritic constitutional lower limb alignment and the orientation of its joint surfaces. The KA TKA technique is a joint resurfacing procedure rarely requiring soft tissue release (10–12). On the other hand, concerns remain about restoring "outlier" or "pathological" anatomies, which may be incompatible with current TKA prostheses and fixation methods.

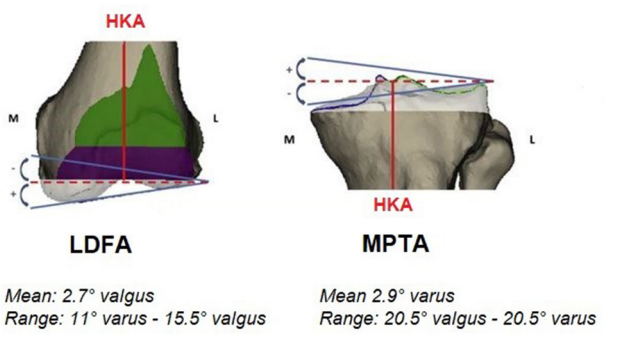

FIGURE 1 | Anatomic modification linked to mechanical alignment technique on the distal femur and proximal tibia.

Are All Observed Anatomies Physiologic?

The human knee anatomy is highly variable, and pathological changes increase this fluctuation even further (7, 13, 14). In 4,884 lower limb CT-scans of patients scheduled for TKA: arithmetic HKA (aHKA) was >3° in 40%, >5° in 19%, and >10° in 3% (7). The mDFA mean was 2.7° valgus, ranging from 11° varus to 15.5° valgus. The mPTA mean was 2.9° varus within 20.5° varus and 20.5° valgus range. This large spectrum of mPTA and mDFA values exhibits the vast variability in patient anatomy. The more outlying alignment may be inherently biomechanically inferior. It may have been altered by different conditions that might expedite the degenerative changes, such as trauma, developmental deformity, tumors or previous surgery.

The existence of patho-anatomies can be demonstrated by their unilateral occurrence or bilateral asymmetry in some patients (**Figures 2**, **3**). The surgeon should not blindly reproduce the identical anatomy of outlier patients as it might negatively affect the TKA biomechanics and increase wear. On the other hand, these extreme cases are the most impacted by a MA technique as it significantly modifies their anatomy and likely causes soft tissue imbalances, variation of the femoral flexion axis, changes in joint line orientation, and alteration of knee kinematics.

A computer simulation study comparing the effects of MA or KA on a single knee joint replacement model showed that KA TKA produced near-normal knee kinematics, including higher femoral rollback and external rotation of the femoral component (15). However, it demonstrated increased contact stresses, questioning long-term results. A study of 178 MA knee arthroplasty revisions found that knees with higher varus alignment had greater total damage of the retrieved polyethylene

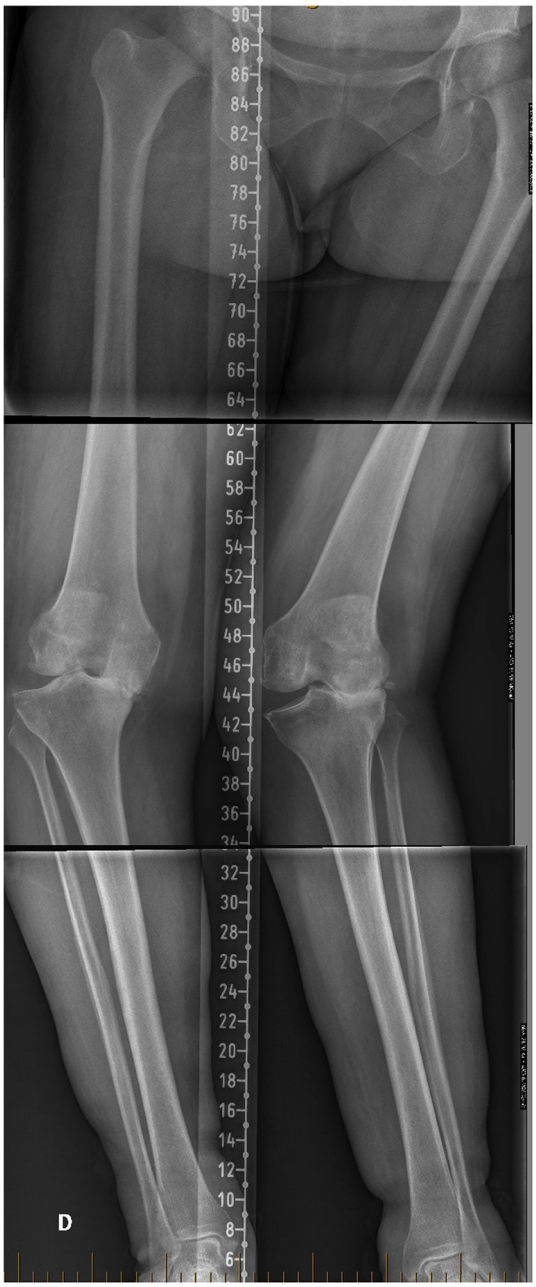

FIGURE 2 | Lower limb full-length radiographs showing lower limbs with windswept deformity. Her mechanical distal femoral angle (mDFA) is 10° valgus on the right femur vs. 1° on the left side. Regarding tibial anatomy, her right mechanical proximal tibial angle (mPTA) is at 0° vs. 5° varus on the left. Because of her important lower limb asymmetry, we consider her lower limb anatomy to be pathologic. Applying unrestricted KA technique would reproduce her lower limbs malalignment.

components (16). They also demonstrated that MA-TKAs tended to drift away from a neutral mechanical alignment toward the preoperative varus deformity. Other clinical and simulator studies have found an association between polyethylene wear and varus alignment (17–19). Tibial baseplate migration and greater

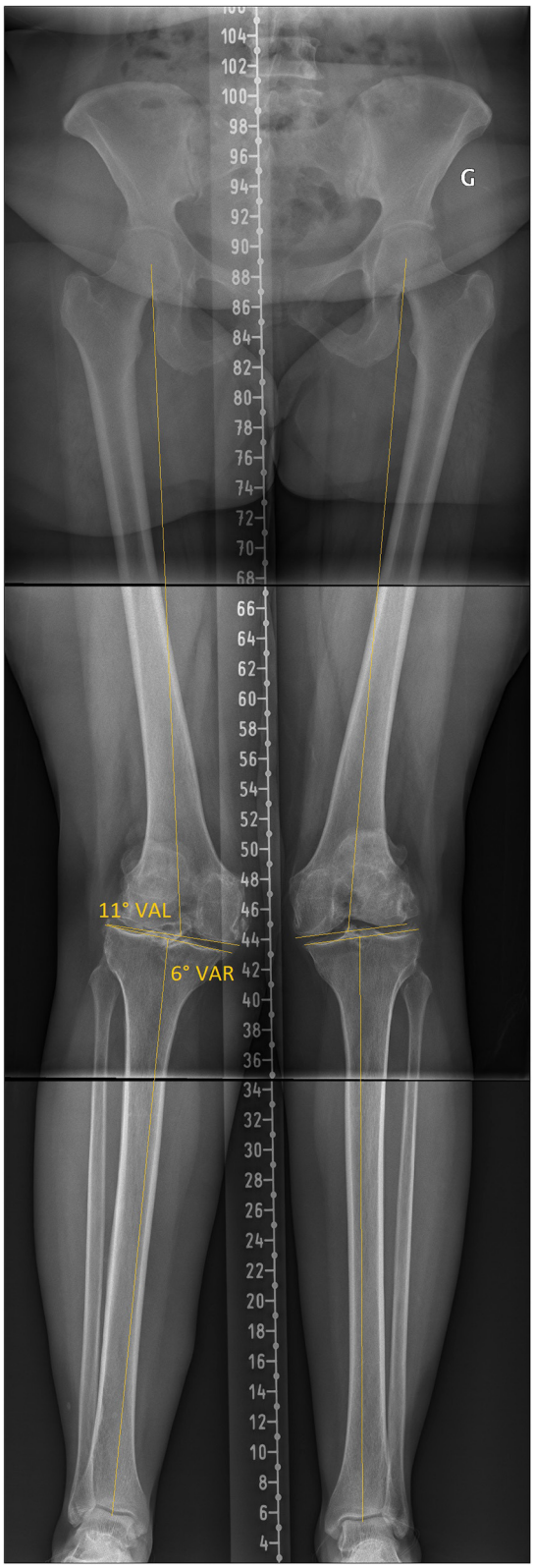

FIGURE 3 | Lower limb full-length radiographs show bilateral valgus lower limbs with severe right knee OA. Her mDFA is 11° valgus and her mPTA is 6°

(Continued)

FIGURE 3 | varus. Applying unrestricted KA technique would reproduce her right lower limb alignment, reproducing extreme joint orientation (obliquity) and a lower limb arithmetic HKA (aHKA) in 5° of valgus. Such outlier anatomy might not be compatible with current TKA implant bearing and fixation methods.

tibial varus were weakly correlated ($r^2 = 0.45$) in a study with a 10-year follow-up (20). Interestingly, baseplate migration was not affected by overall limb alignment (HKA of 1.3° valgus to over 10° varus). No difference was shown between those within ± 3° of neutral and those higher than 3°. These studies suggest that systematic replicating the patho-anatomy of all patients might not be suitable for survivorship of the TKA using current materials and fixation methods.

FUNDAMENTALS OF RESTRICTED KINEMATIC ALIGNMENT

Five rKA Principles

The rKA protocol has been developed as an alternative to the unrestricted KA proposed by Howell (11, 21) for patients with an outlier or atypical knee anatomy. The concept of rKA aims to reproduce patient's constitutional knee anatomy within a safe range while avoiding extreme or pathological anatomies that have been demonstrated to exist (7). The five principles to perform rKA TKA are explained by its designer (PAV) in Video 1. https://youtu.be/k6qdpyh80Tc

rKA Principle 1: HKA Boundaries

Historically, the hip-knee-ankle (HKA) angle serves as a reference for knee alignment. MA TKA data has demonstrated that the survivorship of the implant is not affected if the values of HKA are kept within 3° (22). In a population of 4,884 patients awaiting a TKA, a total of 40% of patients had an aHKA >3°, and 3% had extreme anatomy with an HKA of >10° in varus or valgus (7) (**Figure 4**). Aiming at reproducing individual lower limb anatomy while keeping aHKA within ± 3° range establishes the first rKA principle.

rKA Principle 2: Joint Line Orientation

It is very rare (0.1%) for the human knee to have a neutral joint line (neutral mDFA + neutral mPTA) (7). In fact, the mean mPTA is in 2.9° varus, and the mean mLDFA is in 2.7° valgus. Furthermore, we found that 80% had an mDFA and mPTA below 5° (**Figure 5**). Keeping in mind the mean values and aiming to include the vast majority of patients, the second rKA principle strives to reproduce individual anatomy while keeping the LDFA and the mPTA within ± 5°. By this second principle, rKA limits the joint obliquity to 5°. Selecting 5° also includes all patients with ± 2° from the mean values (80% of the population).

Applying the first two rKA principles, 51% of the population would undergo a classic KA without any modification. Another 30% would have a correction of <1° (mean tibia 0.5° and mean femur 0.3°). The remaining 20% of patients would require more substantial adjustments (7). Awaiting further evidence regarding the acceptable limb alignment boundaries, the proposed rKA boundaries are sound and reasonable but may evolve with time.

rKA Principle 3: Preservation of Soft Tissue Laxities

The third rKA principle is to preserve/restore the natural knee's soft tissue tension. Physiologic soft tissue laxities, including ligaments, tendon and capsular structures, play a key role in knee kinematics. It has been shown that collateral ligaments are not isometric, and their laxities change over the arc of motion. The medial collateral ligament (MCL) is tighter than the lateral collateral ligament (LCL), and both ligaments are tighter in extension than in flexion (23). Furthermore, ligamentous laxity is higher in females than in the male population, and the inter-individual variation is wide. Following this notion, MA or any other technique that includes ligaments tensioning or gap balancing aiming to create an equal tension of medial and lateral collateral structures does not restore the correct kinematics of the knee (24, 25). With rKA, soft tissue release should only be performed in cases outside the boundaries of principles 1 and 2; i.e., a systematic deep MCL release at exposure should be avoided. In the senior author's experience, soft tissue releases are required when rKA boundaries necessitate an anatomy correction of more than 2-3°. For example, in a varus knee where the mPTA is modified from 8° to 5°, a deep MCL release should be enough to balance the gap modification in most cases.

rKA Principle 4: Femoral Anatomy Preservation

In consensus with numerous scientists, we consider the femoral anatomy to be fundamental to knee kinematics (26–28). The fourth rKA principle states that in cases where the patient's anatomy is outside the rKA boundaries described in principles 1 and 2, femoral anatomy preservation is prioritized over the tibia. The rKA algorithm (**Figure 6**) advocates correcting the most contributing bone to the alignment's deviation. In most mild varus knees, the tibia is the main contributor, whereas it is the femur in valgus cases. In more extreme cases (e.g., aHKA>10°), both the femur and the tibia contribute to the outlying anatomy (i.e., severe varus with the femur and tibia in varus). In such varus cases, we limit the femoral anatomy modification to 2°, and in severe valgus cases, after reducing the mDFA to 5°, no further modification to the femur is added. The tibia will have to be in 2° of varus to keep the overall aHKA within ± 3° (Principle 1).

Furthermore, no external femoral rotation is set when using the rKA protocol. For posterior condyles resurfacing, a posterior referencing guide is set to neutral rotation, thus resecting only the implant thickness of the posterior condyles matching each patient's native femoral orientation (**Figure 7**).

In cases where tibial anatomy is modified, e.g., mPTA of 8° is reduced to 5°, both the extension and flexion gaps will be affected (tightening), MCL release should be performed to restore the mediolateral gap balance in both extension and flexion. As described above, rKA does not aim toward MCL/LCL isometry since it would compromise natural knee kinematics, neither does

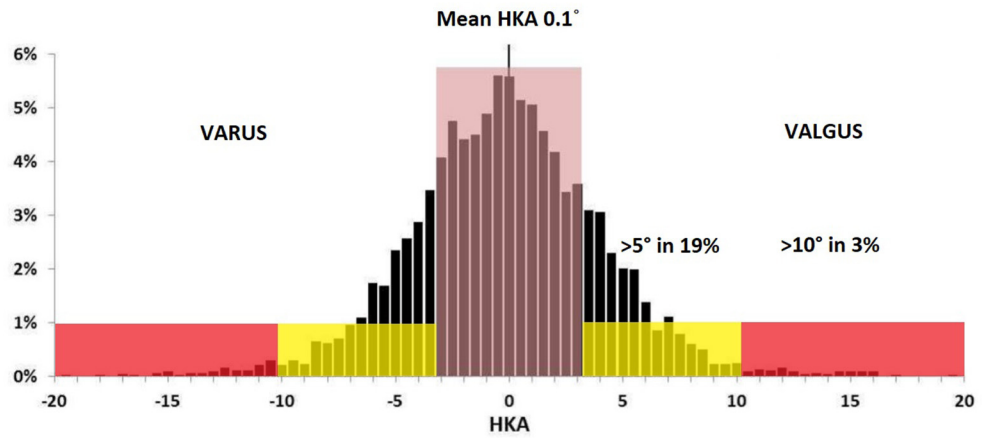

FIGURE 4 | Lower limb Ct-Scan, preoperative aHKA distribution from a population of 4,884 patients scheduled for a TKA (7).

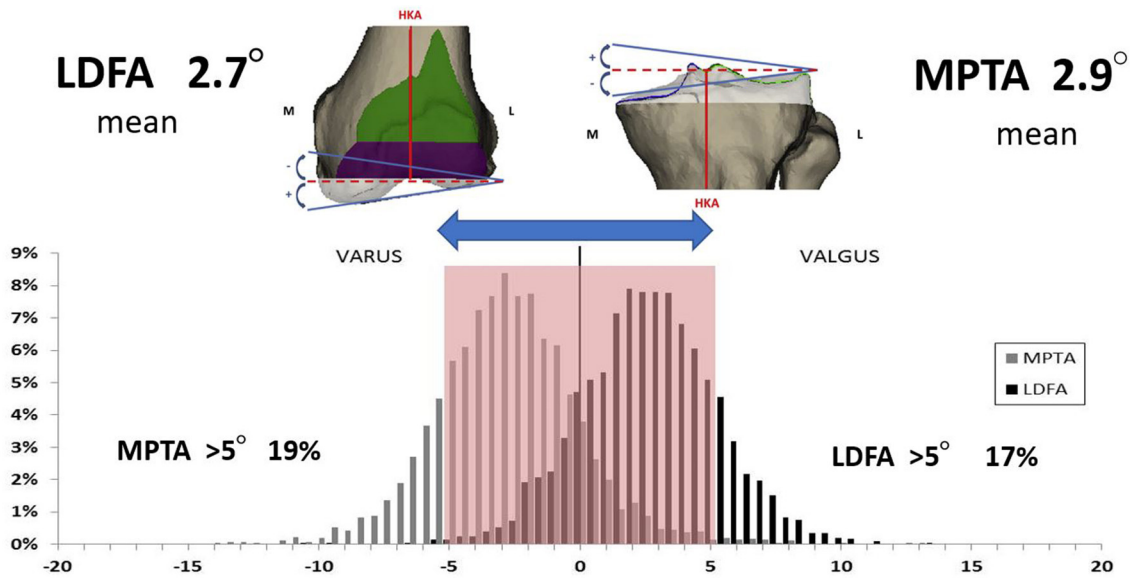

FIGURE 5 | Lower limb Ct-Scan preoperative mDFA and mPTA distribution from a population of 4,884 patients scheduled for a TKA (7).

it modify femoral bone cuts to create balanced gaps (as in gap balancing or functional alignment techniques).

rKA Principle 5: Pivot Point

When outside the boundaries set in principles 1 and 2, the surgeon needs to decide where the anatomical modification (bone resection changing patient's anatomy) should be; medial, lateral or balanced on both sides. Cut orientation can be adjusted using 3 different pivot points: medial, central or lateral. A medial pivot point would resurface the medial compartment and modify the resection thickness on the lateral side (vice versa for a lateral pivot). A central pivot would change cut thicknesses on both compartments. The fifth rKA principle proposes to resurface (resection thicknesses equal to those of the implant) the unloaded knee compartment, and cut adjustment is performed on the worn side. This will modify the resection thickness on the worn side: medial in varus (**Figure 8**), lateral in valgus (**Figure 9**).

By following this principle, the intact compartment is resurfaced by cutting the exact thickness of bone matching the implant thickness, thus preserving the joint line level and preserving bone. As in MA, this leaves a tighter damaged compartment. Most surgeons will then feel comfortable performing the required ligamentous release as they would do with MA. A balanced resection with a central pivot is appealing but hard to manage without sophisticated preoperative planning or intra-operative automated decision tool.

rKA Algorithm

To facilitate decision-making, an rKA algorithm following the five rKA principles is presented in **Figure 6**. As stated above,

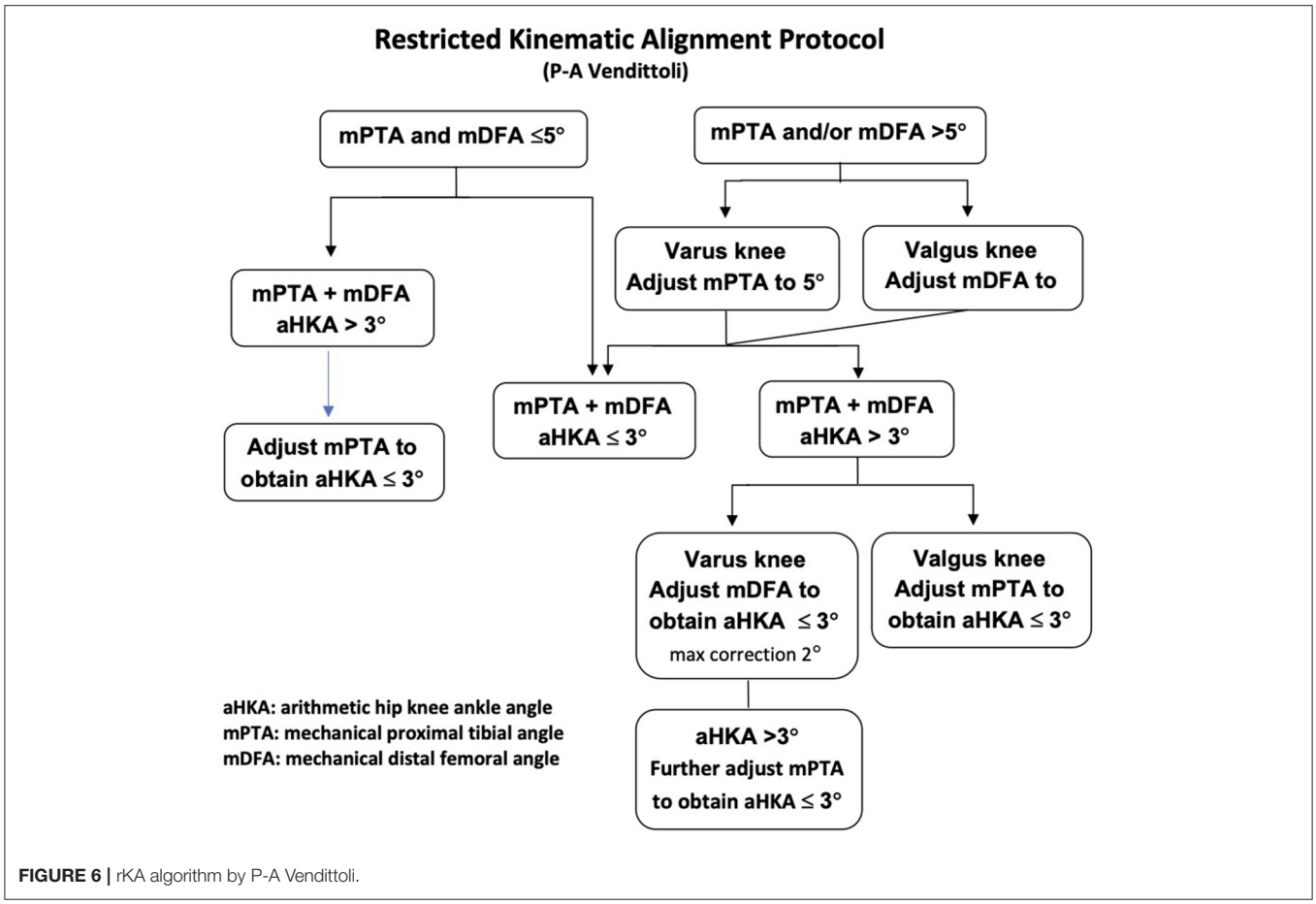

FIGURE 6 | rKA algorithm by P-A Vendittoli.

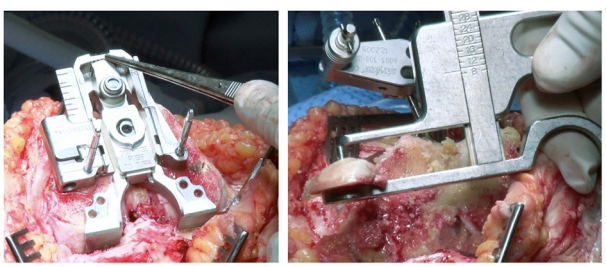

FIGURE 7 | Intraoperative photograph of posterior referencing guide placed in neutral femoral rotation (left). The resected posterior femoral condyle measurement shows 9 mm corresponding to femoral component thickness (right).

51% of the patients present aHKA 3° and with both mPTA and mDFA ≤5°, implying that no adjustment is needed for those knee arthroplasties.

If the mPTA and mDFA are <5° but the aHKA is >3° varus (in 8% of the cases) or >3° valgus (in 7% of cases), then, following the fourth rKA principle of femoral anatomy preservation, the mPTA should be corrected to fall within 3° of aHKA. In cases with mPTA and/or mDFA >5° (right side of the algorithm), in varus knees, the mPTA needs to be adjusted to 5°; whilst in valgus knees, the mDFA should be brought to 5°. If those resections bring the aHKA ≤ 3°, the rKA objective is achieved. If the resultant aHKA is >3°, the previously unchanged parameter should be corrected, namely mDFA in varus knees and mPTA in valgus until the aHKA is ≤ 3°. In rare cases, where the above-mentioned steps do not lead to the desired aHKA ≤ 3°, MPTA should be further corrected. Ligamentous releases are rarely needed in cases with anatomic modifications of <3°. In more significant corrections, minimal releases can be done (usually, to a much lesser extent than in MA).

In our simulation study, unusual anatomy was observed in 17% of knees, with both the femur and tibia articular surfaces orientation in varus or valgus (7). As both bones contribute to the same overall HKA deviation, the surgeon has to decide which one to correct to reach the safe range. In our opinion, the femoral flexion axis plays a more significant role in knee kinematics; hence our practice maximally preserves femoral anatomy and performs most modifications of the tibia. For example, a valgus knee (aHKA 10° valgus) with a femur in 9° valgus and a tibia in 1° valgus, the femoral cut is modified to a maximum of 5° valgus and the tibial cut corrected to 2° varus, creating an aHKA of 3° valgus. Similarly, in severe varus knee (aHKA of 8° varus), with a femur 2° varus and tibia 6° varus, the femoral orientation is

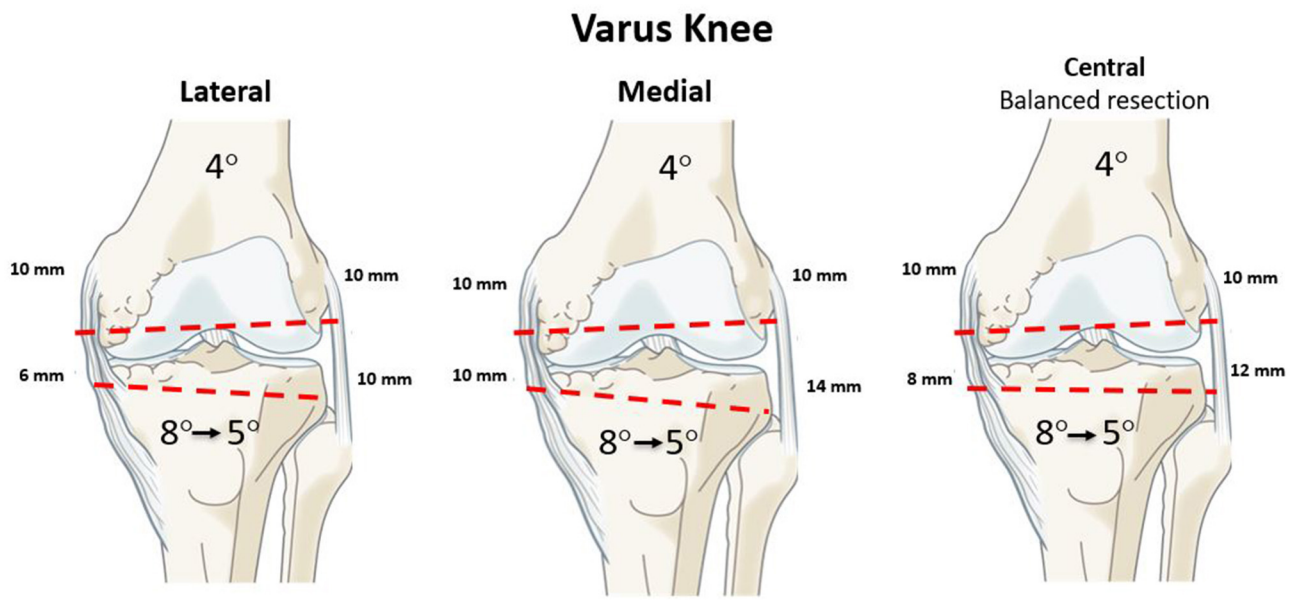

FIGURE 8 | An example of varus knee with mDFA 4° valgus, mPTA 8° varus and aHKA 4° varus. Following rKA principles, the mPTA is adjusted to 5°, consequently changing aHKA to 1° varus. Using a lateral pivot point (shown on the left), the intact (lateral) compartment is resurfaced to accommodate an implant thickness (10 mm), creating a tighter medial gap which might require a deep MCL release. The medial pivot (central image) would result in thicker bone resection of the intact compartment and enlarging the lateral gap. The right figure shows a balanced bone resection with a central pivot. It complexifies the decision-making and requires PSI or robotics.

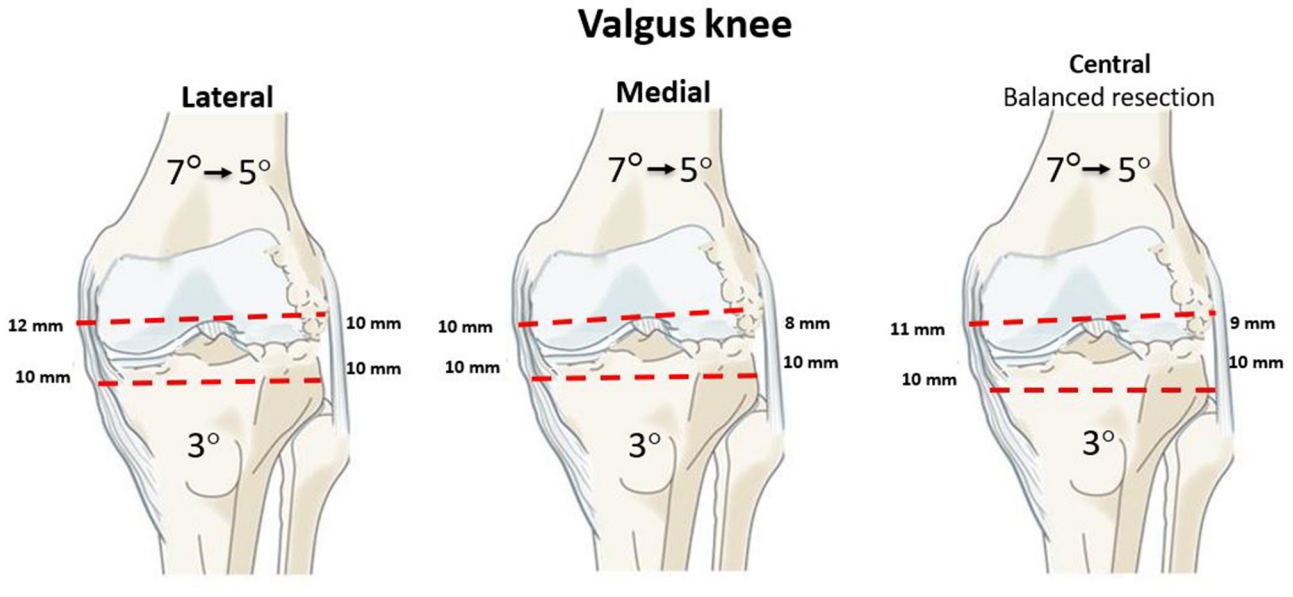

FIGURE 9 | A valgus knee example with mDFA 7° valgus, mPTA 3° varus and aHKA 4° valgus. According to rKA protocol, aHKA should be ± 3°; thus mDFA is modified to 5° valgus. The left image presents a lateral pivot resulting in a 2 mm medial compartment imbalance, which may be detrimental for a valgus knee. The central image demonstrates the medial pivot creating tightness in the damaged lateral compartment while maintaining medial stability. The right figure shows a balanced bone resection with a central pivot. It complexifies the decision-making and requires PSI or robotics.

maintained (2° varus), and the tibial varus is reduced to from 6° to 1°, resulting in overall aHKA of 3° varus. It must be kept in mind that most of these cases have associated extra-articular deformities explaining these extreme alignments. The severe valgus is often due to diaphyseal tibia valga deformity, and the severe varus may be due to a femoral bowing creating this lower

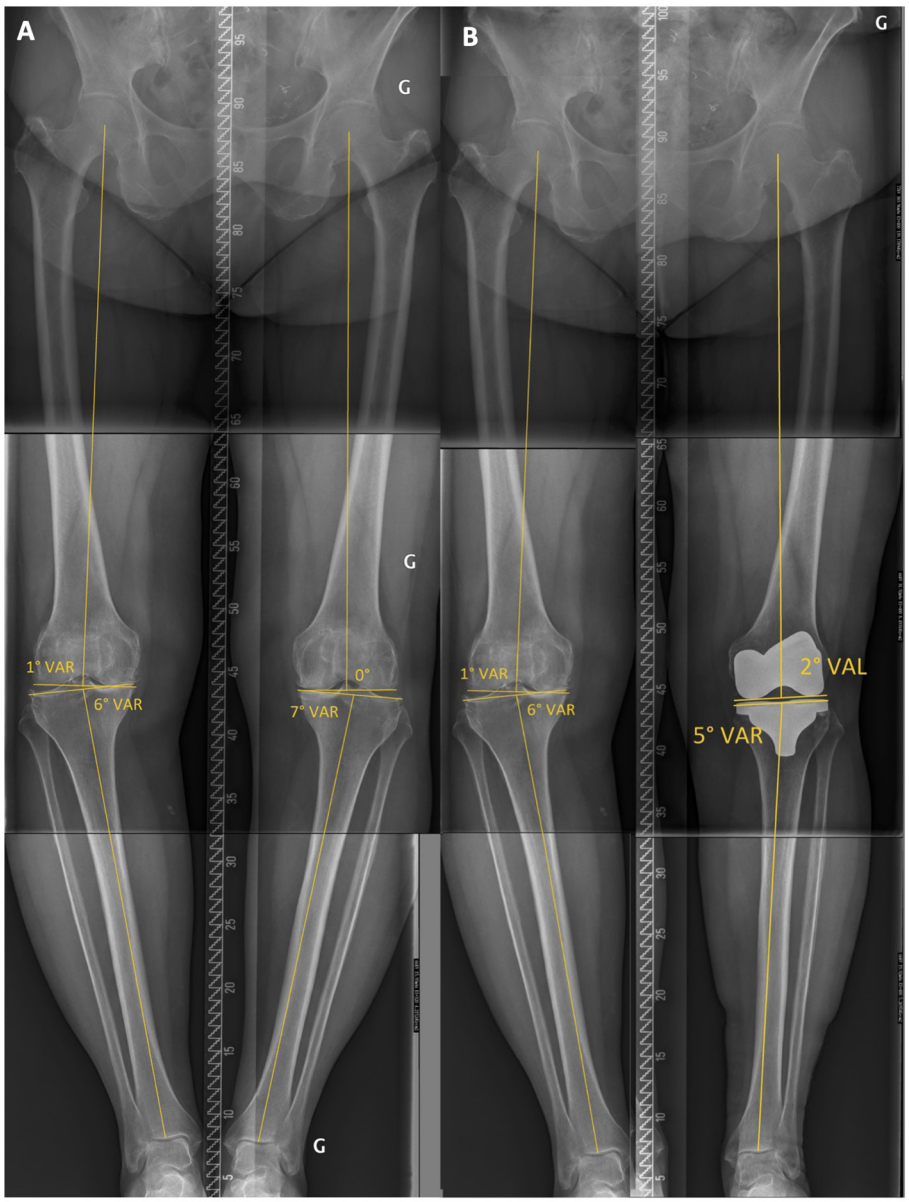

FIGURE 10 | Case example 1, **(A)** preoperative standing long radiograph of a patient with a left lower limb mDFA of 0° and a mPTA of 7° varus, resulting in an aHKA of 7° varus. **(B)** on the postoperative radiograph, following the rKA algorithm, the implants mDFA is 2° valgus and mPTA is 5° varus.

limb alignment (29). In these cases, KA (resurfacing the knee joint) will facilitate the preservation of ligament laxities but will not address the lower limb deviation caused by the extra-articular deformity. Performing the restricted KA protocol will correct the extra-articular deformity with intra-articular cuts and may require ligament adjustment to avoid secondary instability.

METHOD: rKA SURGICAL TECHNIQUE

In cases where the patient's anatomy fits into the rKA boundaries (51% of the cases), surgery could be performed using measured resection techniques with a caliper, as described by Howell (30). Doing so would require very meticulous preoperative radiographic planning to preserve the patient's anatomy. Since many patients will require anatomic modification to fit within rKA boundaries, rKA is ideally performed with patient-specific instrumentation (PSI), intra-operative computer navigation or robotic assistance (31). The following surgical technique applies to surgery with computer navigation or robotic assistance. A video is available for the PSI technique (Video 2) https://youtu.be/wKoSkbHmikI and computer navigation technique (Video 3) https://youtu.be/M8n-5l3Hzvo

After joint exposure, cartilage and bone loss thicknesses are estimated by comparing them to the intact areas. The

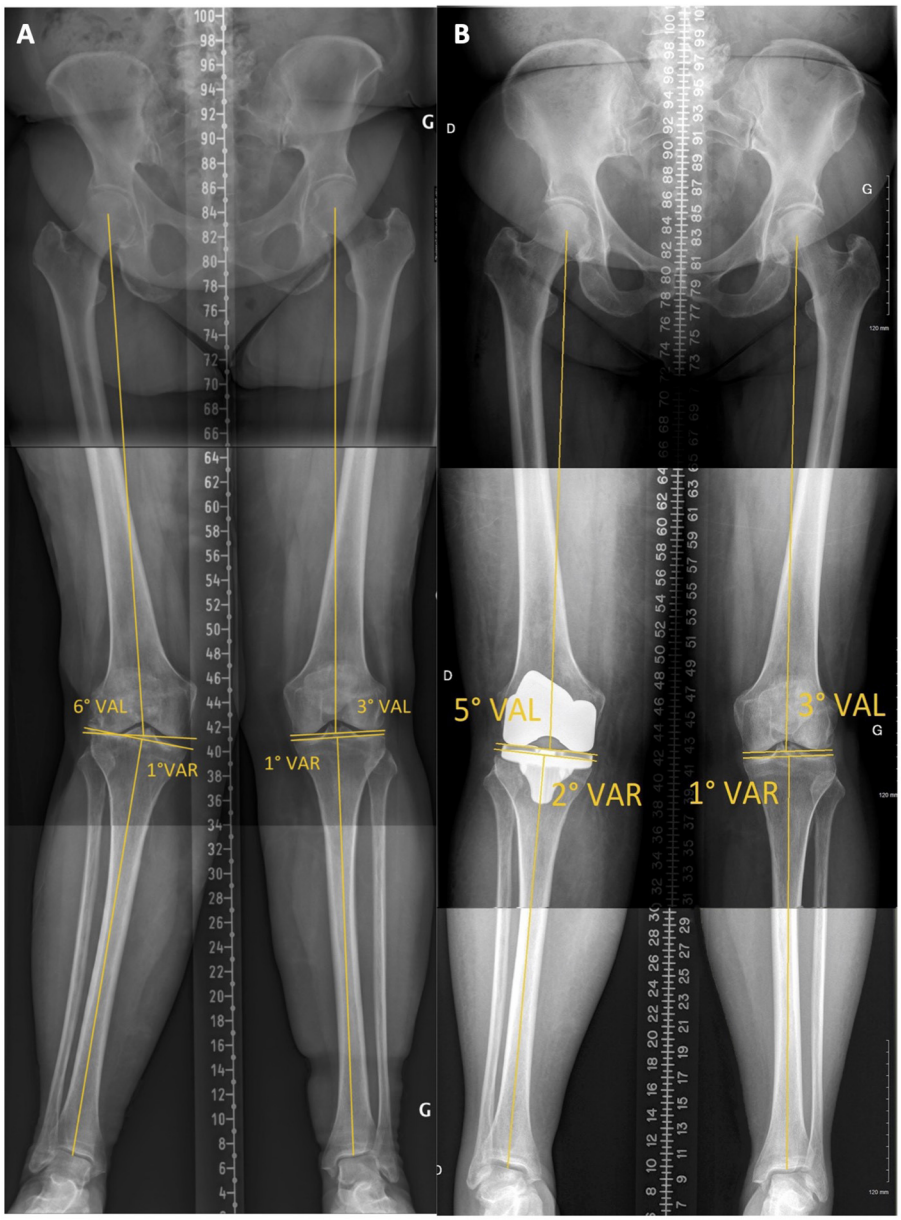

FIGURE 11 | Case example 2, **(A)** preoperative standing long radiograph of a patient with a left lower limb mDFA of 6° valgus and a mPTA of 1° varus, resulting in an aHKA of 5° valgus. **(B)** on the postoperative radiograph, following the rKA algorithm, the implants mDFA is 5° valgus and mPTA is 2° varus.

intention is to restore the patient's pre-arthritic joint surfaces and lower limb alignment. For example, in a varus knee, for the unworn compartment (lateral), the distal femoral and proximal tibial cut resections are set at each implant's thickness (10 mm) (lateral pivot, rKA principle 5). Then, the cartilage wear thickness on the medial side of bone surfaces is assessed (intact cartilage = 0 mm, partial cartilage thickness wear = 1 mm, and exposed subchondral bone = 2 mm) (31). The cut angle is then adjusted to reach the desired medial resection thickness (e.g., a case with 2 mm of medial tibial wear (subchondral bone exposed), an 8-mm medial resection, and a 10-mm lateral resection should be performed.

Resections only differ from patient anatomy when the measured angles fall outside the pre-defined "safe range" as described in the rKA algorithm (rKA principles #1 and 2, **Figure 6**).

To preserve femoral anatomy (posterior and anterior joint surface orientations), the surgeon should aim to resurface the posterior condyles. Using a posterior referencing guide set to neutral rotation, the implant thickness on both posterior condyles will be ressected without modifying femoral rotation

(**Figure 7**). Tibial component's rotation is set by its alignment with the femoral trial component, keeping the knee in 10 degrees of flexion. If the resected pieces do not match the computer plan or ligament laxities assessed with trial implants fall outside the expected native ligament laxity range (24), the resection accuracy can be confirmed by caliper measurement and cut adjustment is performed when needed (**Figure 7**).

CLINICAL RESULTS USING rKA

The rKA protocol aims to bring the extreme anatomies toward acceptable values by correcting the deformities and providing an implant orientation that is compatible with current materials and fixation methods. Comparing the required anatomy correction between MA and rKA in a cohort of 4,884 arthritic patients, significantly larger corrections were necessary with MA (7). The mean mPTA correction was 0.5° for rKA vs. 3.3° for MA ($p < 0.001$). Similarly, the mean mDFA correction was 0.3° for rKA vs. 3.2° for MA ($p < 0.001$). This highlights that MA introduces significant changes to normal anatomy. Consequently, these modifications of anatomy require larger soft tissue releases to balance the knee, which may have an unfavorable effect on normal biomechanics. The mediolateral and flexion-extension gap asymmetries were compared between measured resection MA and rKA protocol bone cut simulations in another study of 1,000 preoperative CT scans of patients awaiting knee arthroplasty. Greater than 2 mm extension space mediolateral (ML) imbalances occurred in 33% of TKA with MA technique vs. 8% of the knees with rKA. Imbalances of more than 4 mm were present in 11% of MA knees vs. 1% in rKA ($p < 0.001$). With MA, a higher rate of flexion space imbalance was created by the transepicondyar axis (TEA) technique ($p < 0.001$), compared to external rotation of 3° to posterior condyles (PC). rKA again performed better than both techniques ($p < 0.001$). MA with either TEA or PC, only 49 and 63% of the knees, respectively, had < 3 mm of imbalance throughout the extension and flexion spaces and medial and lateral compartments, vs. 92% with rKA ($p < 0.001$). A wide spectrum of complex collateral ligament imbalances, incorrigible by collateral ligament releases, caused by the significant anatomical modifications inherent in the MA technique, has been reported in the literature (7, 32).

A clinical series of the first 100 cemented TKA patients operated on using the rKA protocol demonstrated satisfactory functional outcomes at 2.4 years follow-up (33). Minor ligamentous releases were required in only 5% of the knees. Another study presented 100 cementless TKAs operated on using rKA protocol without any revision for aseptic loosening at 49 (32–60) months of follow-up (34). It also demonstrated excellent osseointegration of the implants, both on radiographic evaluation and on direct examination of implants in three revised patients-one following trauma that caused a tibial implant shift, one due to deep infection at 21 months after the index TKA, and one for instability due to implant under-sizing. The WOMAC, KOOS, and Forgotten Joint scores reported in this study were similar to those reported for cemented KA TKAs.

A study comparing the gait patterns of patients operated on with rKA vs. MA techniques found that the rKA TKA kinematics were significantly closer to healthy controls than in MA TKAs (33). When comparing the MA and control (healthy) groups, the former displayed a decreased maximum flexion (52° vs. 58°, $p = 0.002$), less sagittal plane range of motion (49° vs. 54°, $p = 0.020$) and increased adduction angle (2.0–7.5° vs. −2.8–3.0°, $p < 0.05$). KA group presented a significantly higher postoperative KOOS score when compared to the MA group (74 vs. 61, $p = 0.034$).

DISCUSSION: rKA VS. TRUE KA, A COMPROMISE?

Many surgeons are concerned about allowing too much varus or valgus with the KA technique. Howell et al. (35) reported 97.5% implant survivorship in a cohort of 222 KA TKAs at 10-year follow-up. There was no increased failure rate in patients with greater varus. The radio-stereometric analysis of TKAs randomized to MA or KA did not detect differences in implant migration between groups (31). There are few long-term follow-up studies on KA knee replacement, whereas MA TKAs have a long history of good survivorship (36–38). A mechanical axis ±3° of neutral has demonstrated better functional outcomes than TKAs with more extreme values (39–41). Increased rates of aseptic loosening related to malaligned components have been published (22, 42, 43). However, more recent studies have failed to demonstrate better survivorship or functional outcomes in prostheses aligned within ± 3° of neutral compared to malaligned ones (44–47). Caution should be taken, not transposing the results of these studies to KA. It is important to understand that an accurate KA, aiming for an HKA other than neutral, is inherently different from a failed MA TKA, targeting a neutral alignment. There are other factors than coronal alignment that affect the dynamic loading of the prosthetic knee. The joint line tends to remain parallel to the ground when standing, despite a range in alignment, in studies of both healthy, asymptomatic knees and in kinematic TKA patients (48, 49). The resultant functional joint line orientation may be favorable for the overall load profile of the prosthetic joint.

Some authors advise against widespread adoption of the KA technique due to the lack of long-term studies of KA TKAs (50). We believe the rKA protocol is an appealing compromise that allows the restoration of normal patient anatomy in the majority of cases. It averts the excessive corrections and ligamentous releases often required with MA but precludes the extremes of implant positioning that can be seen in unrestricted KA technique.

CASE ILLUSTRATIONS

Case Example 1

A 62-year-old female with bilateral symptomatic varus knee osteoarthritis (**Figure 10A**). A preoperative radiograph shows a left lower limb mDFA of 0° and mPTA of 7° varus, resulting in an aHKA of 7° varus. Following the algorithm (**Figure 6**), we should correct the mPTA from 7° to 5° (Principle 2). Her

neutral mDFA, would lead to an aHKA of 5°, which is >3° (Principle 1). Further tibial varus reduction (down to 3°) would impact the knee's flexion gaps balance. Instead, following the algorithm, we suggest adding 2° of valgus to the distal femoral cut. No femoral rotation modification is needed, and femoral anatomy modifications are minimized (Principle 4). The overall angle correction was 4° (2 on de femoral side and 2 on the tibial side). We resurfaced the lateral compartment (lateral pivot point, Principle #5) and reduced medial compartment resection thicknesses (∼2 mm thinner cuts on both the femur and tibia). To achieve medio-lateral ligament balance, we had to perform a deep MCL release alone. The postoperative radiograph confirms the achievement of our goals with a mDFA of 2° valgus and a mPTA of 5° varus (**Figure 10B**).

Case Example 2

A 79-year-old female with a painful osteoarthritic right knee with a valgus deformity (**Figure 11A**). The patient has an aHKA of 5° valgus, resulting from a mDFA of 6° valgus and mPTA of 1° varus. Following rKA algorithm (**Figure 6**), the mDFA of 6° valgus must be brought to 5° (Principle 2). To obtain an aHKA is <3° (Principle 1) and minimize femoral anatomy modification (Principle 4), further correction is required on the tibial side. A slight tibial varisation from 1° to 2° would lead to an acceptable aHKA of 3° valgus. We resurfaced the intact medial compartment (medial pivot point, Principle #5) and reduced lateral compartment resection thicknesses. Overall anatomy modification for this patient was 2° (1° on both the femur and tibia), and no ligamentous release was required to obtain satisfactory joint laxities. Postoperative radiograph confirms that we achieved our implant alignment goals using computer navigation (**Figure 11B**).

Further clinical examples are available in Video 4. https://youtu.be/GTi5me1tN4M. Surgeons should also understand how to manage specific/challenging cases (51, 52).

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

P-AV contributed to the conception and design of the method. WB wrote the first draft of the manuscript. P-AV, WB, and SM wrote sections of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Revision Total Knee Arthroplasty With the Use of Restricted Kinematic Alignment Protocol: Surgical Technique and Initial Results

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Purpose: Kinematic alignment (KA) for primary total knee arthroplasty (TKA) has been shown to provide equivalent or better results to mechanical alignment (MA). The use of KA in revision TKA to restore the individual knee anatomy, kinematics, and soft-tissue balance, has not been documented yet. The purpose of this study is to describe the technique for performing TKA revision using the restricted KA (rKA) protocol and to report (1) rerevision rate and adverse events, (2) patient-reported outcome measures (PROMs), and (3) radiological signs of implant dysfunction related to this technique.

Methods: The rKA protocol was used in 43 selected TKA revisions cases suitable for the technique. Adverse events, reoperation, revision, and their causes were recorded. In addition, PROMs assessed by WOMAC score and radiographic evaluation to identify signs of implant dysfunction were documented at last follow-up.

Results: After a mean follow-up of 4.0 years (0.9–7.7, ±2), only one rerevision (2.3%) was required for persisting instability (polyethylene liner exchange from posterior stabilized to a semi-constrained). Short-cemented stems were used for both the femur and tibia in 28 (65%) cases, for the femur alone in 13 (30%) cases, and no stems in two cases. In 31 (72%) cases, a standard posterior stabilized tibial insert was used, while 12 (28%) cases required a semi-constrained insert. The mean WOMAC score was 34.4 (0–80, ±21.7). Mean postoperative arithmetic hip-knee-ankle angle (HKA) was 0.8° varus (from 5° varus to 4° valgus), mean mechanical distal femoral angle was 1.7° valgus (from 2° varus to 5° valgus), and mean mechanical tibia proximal angle was 2.2° varus (from 5° varus to 1° valgus). No radiological evidence of aseptic loosening or periprosthetic radiolucencies were identified.

Conclusion: Although current revision TKA implants are not ideal for revision TKA performed with rKA, they are an appealing alternative to MA, especially in cases of early, non-wear-related, unsuccessful MA TKAs. rKA TKA revision using short-cemented stems in conjunction with meticulous preoperative planning is safe in the mid-term.

Level of evidence: IV

Keywords: revision, knee, arthroplasty, technique, patient reported outcome measures, restricted kinematic alignment, mechanical alignment, kinematic alignment

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INTRODUCTION

The number of total knee arthroplasties (TKAs) performed worldwide is constantly increasing as the population is growing and indications for TKAs are widened to include younger patients (1). It has been estimated that revision knee surgeries could increase by 601% in the USA (2), and up to 332% in England and Wales (3), by 2030. Revision TKA procedures are highly complex procedures and have inferior survival rates and poorer functional outcomes than primary arthroplasties (4, 5). Currently, the main reasons for revision include infection, loosening, instability, and pain (6). As TKA implants have improved over the years, rates of aseptic loosening have gradually lowered, and it is now the second main reason for revision (7).

Despite the advances in implant technology, patient dissatisfaction has remained relatively high at 15–20% (8). In addition, up to 50% of patients report persisting residual symptoms such as pain, stiffness, and instability (9, 10). Some authors believe that many unsatisfactory outcomes may be due to anatomical changes linked to the mechanical alignment technique (11–13). In primary arthroplasty, kinematic alignment (KA) is proposed as an alternative to MA to minimize these issues. KA has shown equivalent or better functional outcomes and survival rates in the mid-term than MA (14). The logical next step is to apply the principles of KA in revision surgeries. The goal of KA is to restore or preserve the patient's pre-arthritic knee anatomy by resurfacing the native joint and maintaining the soft tissue envelope (11). As in primary TKA, KA principles could be applied to revision TKA. However, multiple challenges intrinsic to revision surgeries and the MA technique will need to be addressed: bone loss, loss of some anatomical landmarks, soft tissue management, revision implants, and instruments designed for MA.

The senior author (PAV) has used restricted KA (rKA, **Figure 1**) since 2011 when performing primary TKAs, and started using rKA for TKA revision in February 2013. The study objective is to describe the technique used to perform TKA revision using rKA principles and to report early outcomes, including (1) the rerevision rate, (2) patient-reported outcome measures (PROMs) assessed with WOMAC score and, (3) radiological signs of implant dysfunction. The hypotheses for the study were that revision TKA with the use of the rKA protocol would produce favorable outcomes in PROMs, while achieving low (<10%) rerevision rates at early follow-up.

MATERIALS AND METHODS

Patients

All revision TKAs performed by the senior author between February 2013 and November 2020 were retrospectively reviewed for inclusion in this study ($N = 85$). The following cases were excluded: revision surgeries for polyethylene liner exchange (4), for patellar resurfacing (2), with associated extra-articular deformities (1), that required long uncemented diaphyseal fixation (major metaphyseal bone loss) (15), that required hinged components (5), and 13 patients who did not want to participate in the study. A total of 42 patients (43 TKAs, one bilateral) gave their consent to participate in the study. There were 12 males and 31 females who had a mean age at the primary surgery of 67.7 years (55–85, ±7.2). Our scientific and ethics review committees approved the study, and all patients consented to include their case.

Methods of Assessment

A retrospective review of patients' charts was used to record any rerevisions and adverse events during the follow-up period. Adverse events were recorded using the Knee Society standardized TKA complication list (16). At the last follow-up, a single research assistant assessed patients' functional outcomes using the WOMAC score (15). The post-revision anteroposterior and lateral radiographs obtained during follow-up visits were evaluated following the modern Knee Society Radiographic Evaluation System (16) to assess radiolucent lines, osteolysis, and signs of component loosening. Radiographic pre- and post-revision coronal orientation measurements were calculated in AP standing long leg x-rays using the mechanical distal femoral angle (mDFA), the mechanical proximal tibial angle (mPTA), and the arithmetic hip-knee-ankle angle (aHKA = mDFA + mPTA). Using digitized image and measurement tools, the same evaluator (LK) performed all measurements. The preoperative rotational alignment of the femoral and tibial components were measured with the use of epicondylar axis and tibial tubercle as references on CT scans as described by Berger and Crossett (17).

Statistical Analysis

Continuous data are presented using mean, minimum, maximum, and standard deviation. Comparisons of the preoperative and postoperative continuous data were analyzed using a paired Wilcoxon test (pre- and post-revision mDFA, mPTA, aHKA). Categorial variables are presented as numbers and percentages. A significance level of $p = 0.05$ (two-sided) was used for all tests. The analyses were performed using the SPSS software version 26 (SPSS Inc., Chicago, IL, USA). No sample size calculation was done for this study as it is a cohort report with no comparison group.

Prosthesis

The implant used in all patients for this study was the Triathlon TS Knee System (Stryker Orthopedics, Mahwah, NJ). This prosthesis is a revision system that features a single radius femoral articulating design. Tapered uncemented or cemented femoral and tibial stems are available and come in 50-, 100-, and 150-mm lengths. The stems have a fixed angle of 6° of valgus to the femoral component and neutral alignment to the tibial component. 360° of stem offset of 2–8 mm for both the femur and the tibia are available.

Abbreviations: aHKA, Arithmetic hip–knee–ankle angle; BMI, Body mass index; KA, Kinematic alignment; MA, Mechanical alignment; mDFA, Mechanical distal femoral angle; mPTA, Mechanical proximal tibial angle; PROMs, Patient reported outcome measures; PS, Posterior stabilized; RCT, Randomized controlled trial; rKA, Restricted kinematic alignment; TKA, Total knee arthroplasty; TS, Total stabilizer; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

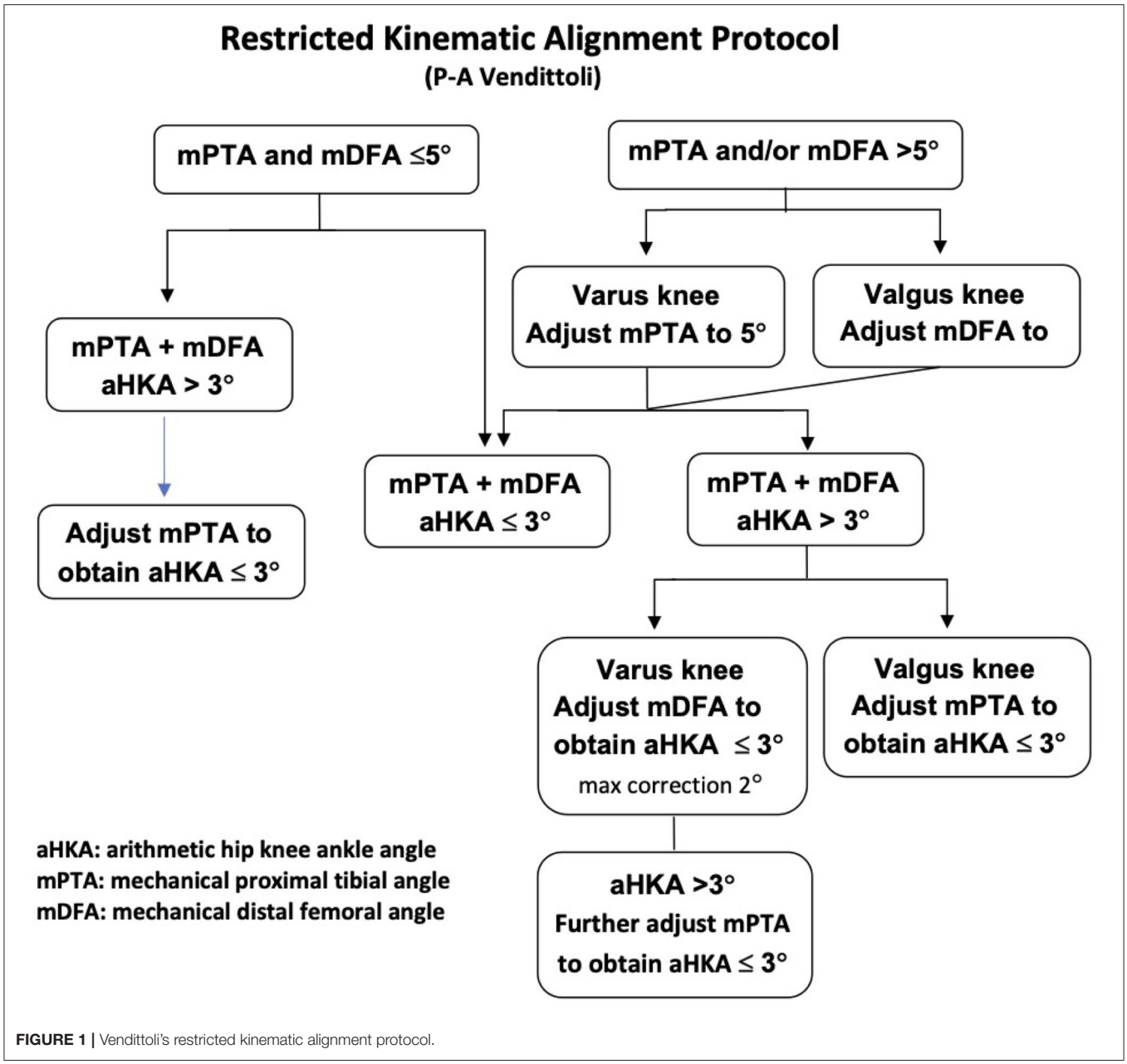

FIGURE 1 | Vendittoli's restricted kinematic alignment protocol.

Analysis of Failure to Plan rKA Reconstruction

Patients' preoperative clinical and radiographic assessments are crucial for determining the cause of failure, especially for patients with well-fixed implants, and planning the rKA reconstruction. Knees were examined for range of motion limitations and ligamentous instability. Implant size, position, orientation, and joint-line were compared with preoperative radiographic images when available or with the contralateral side. Computed tomography scans were performed to evaluate the axial rotation of the components when malrotation was suspected (17, 18). The coronal alignment was planned preoperatively using the restricted rKA protocol (**Figure 1**). As TKA revision systems were designed for MA with fixed coronal implant-stem angle (6° valgus on the femur and 0° on the tibia for most systems), stem relation to the meta-diaphyseal region is templated.

In most cases, to achieve the proper rKA coronal alignment, short-cemented stems are planned without interfering with the meta-diaphyseal cortex. Distal augments or bone resections needed to achieve the correct coronal angle for components was estimated. The amount of angulation achieved depends on the thickness of the augment and the size of the component (**Figure 2**). The approximate angular correction at the tibia for the 5- and 10-mm augments for each tibial component size are provided in **Table 1**. The approximate angular correction at the distal femur for the 5-, 10-, and 15-mm augments for

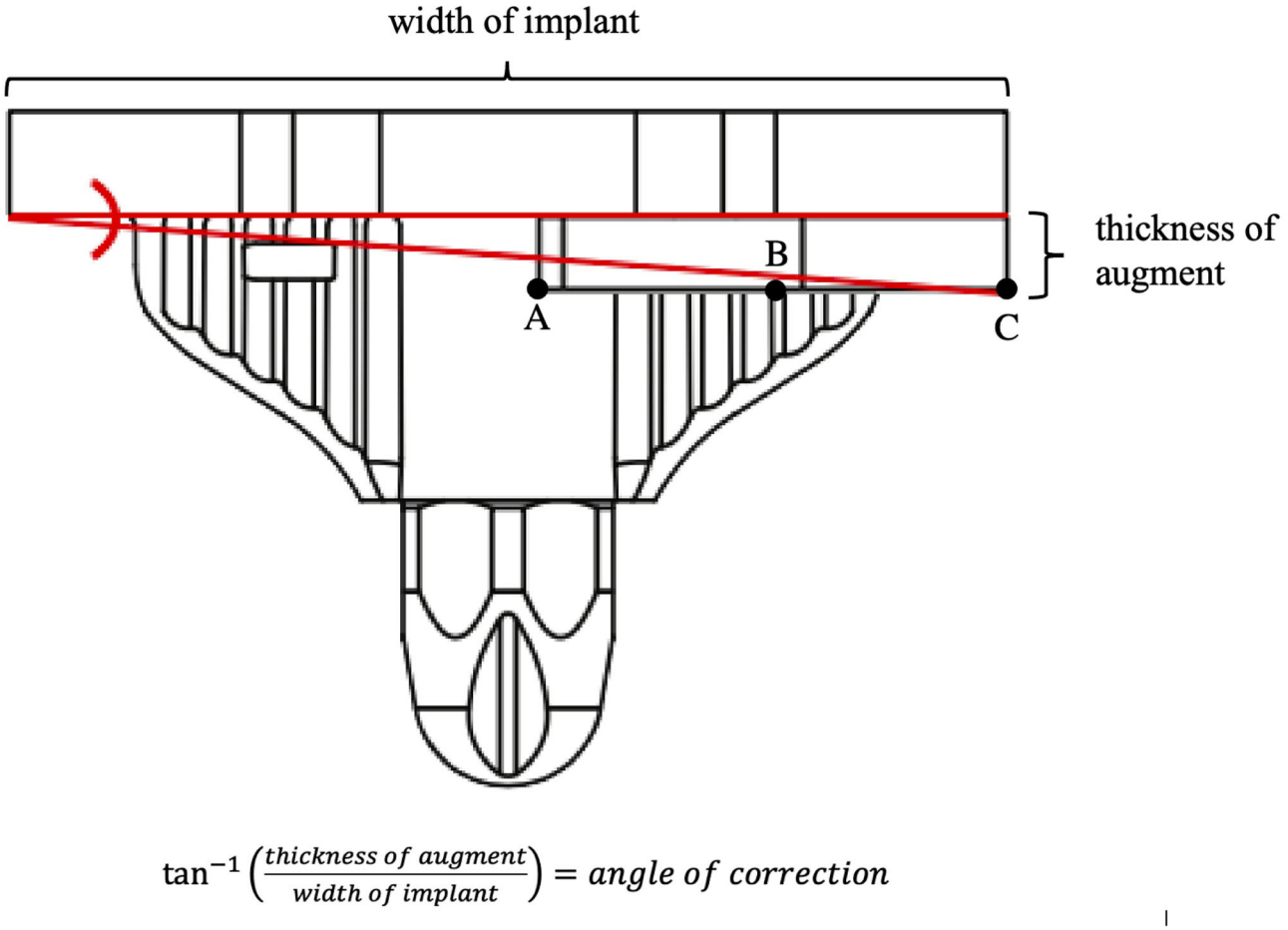

FIGURE 2 | The inverse tangent of the augment's thickness over the implant's width can be used to approximate the angular correction given by apposing the component with a unilateral augment to a uniformly flat bone surface. In a purely mathematical sense, the augment would first contact a flat surface at point A. However, from a practical point of view, because of the use of cement and partial impaction in cancellous bone, using point A to calculate the angular correction would overestimate the correction. Thus point B, in the middle of the augment, was assumed to be where a flat plane would intersect the augment. The length of the segment BC was subtracted from the width of the implant in the calculations.

each femoral component size are provided in **Table 2**. Posterior augments were utilized in a similar fashion to achieve the desired rotational alignment for the femoral component. The resulting rotational angular corrections are the same as the coronal angular corrections for the distal femoral augments already described in **Table 2**. If less angular correction is required, the selected augment will be combined intra-operatively with a bone resection (1–3 mm). **Table 3** summarizes common problems encountered with failed primary arthroplasties and how to address them during rKA revision.

Surgical Technique to Apply rKA in the Revision Setting

The rKA TKA revision aims to recreate the pre-arthritic native knee anatomy and soft tissues laxities. To confirm or optimize our preoperative plan, at surgical exposure, a careful knee examination is performed to assess soft tissues laxity, knee range of motion, and the position, orientation, and fixation of the implant. After removing the implant and bone loss assessment, we used a distal femoral cutting jig connected to an intramedullary rod kept loose in the metaphysis (not deeply inserted, to avoid a tight fit in the diaphysis). We performed the distal femoral refreshing cuts including the planned supplemental bone resection and/or metallic augments to modify the mDFA adjust the joint line level when required (**Table 2**). In practice, a 5-mm augment angulates the component by 5°. When dealing with the smallest sizes, this angle would be closer to 6° and 4° with the largest components. Using an anterior referenced 4-in-1 femoral cutting block of the appropriate size, and positioned to correct any malrotation, we performed the anterior, chamfer, posterior, and posterior stabilized (PS) box cuts. Then, we performed the proximal tibial refreshing cuts using a cutting jig connected to an intramedullary rod kept loose in the metaphysis. Tibial cut orientation included the planned supplemental bone resection and/or metallic augments to modify

TABLE 1 | Estimated angular correction given by apposing a tibial component with a unilateral augment to a uniformly flat bone surface.

Tibia size #	Tibia width (mm)	Augment thickness (mm)	Angular correction (degrees)
1	61	5	5.8
2	64	5	5.5
3	67	5	5.3
4	70	5	5.1
5	74	5	4.8
6	77	5	4.6
7	80	5	4.4
8	85	5	4.2
1	61	10	11.5
2	64	10	11.0
3	67	10	10.5
4	70	10	10.0
5	74	10	9.5
6	77	10	9.1
7	80	10	8.8
8	85	10	8.3

TABLE 2 | Estimated angular correction given by apposing a femoral component with a unilateral augment to a uniformly flat bone surface.

Femur size #	Femur width (mm)	Augment thickness (mm)	Angular correction (degrees)
1	59	5	5.8
2	62	5	5.5
3	65	5	5.3
4	68	5	5.1
5	71	5	4.8
6	74	5	4.6
7	77	5	4.5
8	80	5	4.3
1	59	10	11.5
2	62	10	11.0
3	65	10	10.5
4	68	10	10.0
5	71	10	9.6
6	74	10	9.2
7	77	10	8.9
8	80	10	8.5
1	59	15	17.0
2	62	15	16.2
3	65	15	15.5
4	68	15	14.9
5	71	15	14.2
6	74	15	13.7
7	77	15	13.2
8	80	15	12.7

Distal augments are available in 5, 10, and 15 mm sizes. Posterior augments are available in 5 and 10 mm sizes only.

TABLE 3 | Encountered problems specific to mechanically aligned primary arthroplasties revised with the rKA protocol and their solution.

Problem	Diagnosis	Plausible solution
Coronal malalignment of the femoral component	1) AP standing long leg x-ray 2) Preoperative x-rays 3) Contralateral knee anatomy	1) Medial distal femoral augment to correct excessive varisation from native anatomy common in MA. 2) Lateral distal femoral augment to correct excessive valgisation from native anatomy
Coronal malalignment of the tibial component	1) AP standing long leg x-ray 2) Preoperative x-rays 3) Contralateral knee anatomy	1) Lateral tibial augment to correct excessive valgisation from native anatomy common in MA 2) Medial tibial augment to correct excessive varisation from native anatomy.
Femoral axial malalignment	1) CT-Scan of the TKA	1) Posterior medial femoral augment to correct systematic external rotation in MA 2) Posterior lateral augment to correct excessive internal rotation from native anatomy.
Anterior overstuffing of the femoral component	1) Lateral x-ray of the knee 2) CT-Scan of the TKA	1) Medial and lateral posterior augments to posteriorize the femur 2) Larger medial femoral augment than lateral to correct excessive external rotation

the mPTA when required while keeping the tibial slope neutral (**Table 1**).

With trial implants in place, the collateral ligaments' laxities in 10° of flexion are assessed to determine the polyethylene thickness and serve as an indicator for achieving a planned coronal alignment (goal is 1–2 mm of medial and 2–3 mm of lateral joint opening). Next, the medial and lateral flexion gaps are assessed (goal is 2–3 mm of medial and 3–4 mm of lateral joint opening). If present, hyperlaxity is addressed by increasing the femoral size, using posterior augments. In cases of significant mediolateral imbalances (>4 mm difference) or gross flexion instability with the larger femoral component compatible with the selected tibial size, a varus-valgus constrained liner (TS) was used. Such imbalances were present in cases with longstanding soft tissue changes: ligament stretching or contractures where complete capsulectomy and debridement was required to obtain satisfactory ROM. Lastly, the patella was left intact if well tracking or revised if resurfaced with malposition or under resection.

RESULTS

Indications for performing knee revision are presented in **Table 4**. All interventions included both femoral and tibial components revision, except for one case where only the femoral component was revised for aseptic loosening. Cemented stems were used for both the femur and tibia in 28 (65%) cases, for the femur alone in 13 (30%) cases, and no stems in two cases. The

TABLE 4 | Indications for revision (there were revisions with more than one factor leading to revision indication).

Indication	*N*
Aseptic component loosening	
Femoral component	7
Tibial component	6
Both components	–
Component malpositioning	
Femoral component	
Coronal	Valgus: 3 Varus: 7
Axial	Internal rotation: 4 External rotation: 1
Sagittal	Flexion: 1
Tibial component	
Coronal	Valgus: 2 Varus: 3
Axial	Internal rotation: 2 External rotation: 10
Sagittal	Flexion: 4
Anterior overstuffing	
Femoral component anteriorized	2
Patella under resection	2
Sizing error	
Femoral component	Oversized: 3; undersized: 2
Tibial component	Oversized: 1; undersized: 1
Joint line	Distalized: 3 Proximalized: 1
Osteolysis	
Femoral side	2
Tibial side	2
Both sides	4
Pain as one of the main factors	23
Ligamentous instability	10
Polyethylene wear	2
Septic failure	3
Patellar instability	2
Stiffness	12

TABLE 5 | Stem length details.

Stem length	Femur *N* (%)	Tibial *N* (%)
No stem	3 (7%)	5 (11.6%)
Stubby/bullet tip	0	12 (27.9%)
50 mm	35 (81.4%)	25 (58.1%)
100 mm	5 (11.6%)	1 (2.3%)

TABLE 6 | Radiographic measurements (negative value represents varus and positive represents valgus).

Radiographic measurements	Pre-revision	Post-revision	*P*-value
aHKA mean (min–max, ±SD)	−1.8 (−19–7, ±4.4)	−0.8 (−5–4, ±2.1)	0.172
mDFA mean (min–max, ±SD)	0.4 (−8–8, ±3.2)	1.7 (−2–5, ±1.6)	0.678
mPTA mean (min–max, ±SD)	−2.2 (−11–2, ±2.4)	−2.5 (−5–1, ±1.4)	0.518

aHKA, arithmetic mechanical hip-knee-ankle angle (mDFA + mPTA); mDFA, mechanical distal femoral angle; mPTA, mechanical proximal tibial angle; SD, standard deviation.

stem lengths are presented in **Table 5**. Thirty-nine (91%) cases required femoral side augments, one case required augments in both femoral and tibial components, and three cases required no augments. A PS tibial insert was used in 31 (72%) cases, while 12 (28%) cases required a more constrained TS insert. The patella was resurfaced during the primary surgery in 39 (91%) cases, kept as is in 20 (47%) cases, and revised in 19 (44%) cases. Four (9%) patella were not resurfaced in any surgery. Mean surgical time was 102 min (66–156, ±18). Mean intraoperative blood loss was 236 ml (50–600, ±121).

After a mean post-revision follow-up of 4 years (0.9–7.7, ±2), no patient was lost to follow-up, and there was only one case of reoperation. This case is a female aged 67 years at the time of her index primary TKA in 2012. We performed a revision surgery in 2014 for instability. After the revision, she complained of persisting femorotibial instability. In 2016, we performed a simple polyethylene exchange from a PS to a TS insert. At the final follow-up at 78 months, this patient had a WOMAC score of 61 and a ROM of 0–130°.

There was a total of four adverse events requiring conservative treatment. First, there were two postoperative periprosthetic fractures due to trauma (one undisplaced metaphyseal femoral fracture and one transverse patellar fracture) treated conservatively and healed uneventfully. One patient developed ipsilateral thromboembolic disease and was treated with anticoagulants. Finally, one patient developed a wound complication (localized superficial wound infection) and was treated with antibiotics alone.

At the last follow-up, the mean WOMAC score was 34.4 (0–80, ±21.7). There were 14 (32.6%) patients who complained of persisting knee pain despite knee revision. These patients had a mean WOMAC score of 36.5 (3–71, ±20.5). In most cases, the pain level was reported as improved compared to the pre-revision level and could not be attributed to any specific cause. Two of these patients experienced mild pain associated with unresolved relapsing knee effusion. In one patient, the pain was attributed to a painful neuroma of the infrapatellar branch of the saphenous nerve. Finally, in one patient, the pain was thought to be of neuropathic origin, and the patient was referred to the pain clinic for further treatment.

There were no radiolucencies or osteolysis noted on radiographic evaluation. Pre- and post-revision radiographic measurements are provided in **Table 6**.

Case Examples

To illustrate the type of cases included in the present cohort, three cases examples are presented.

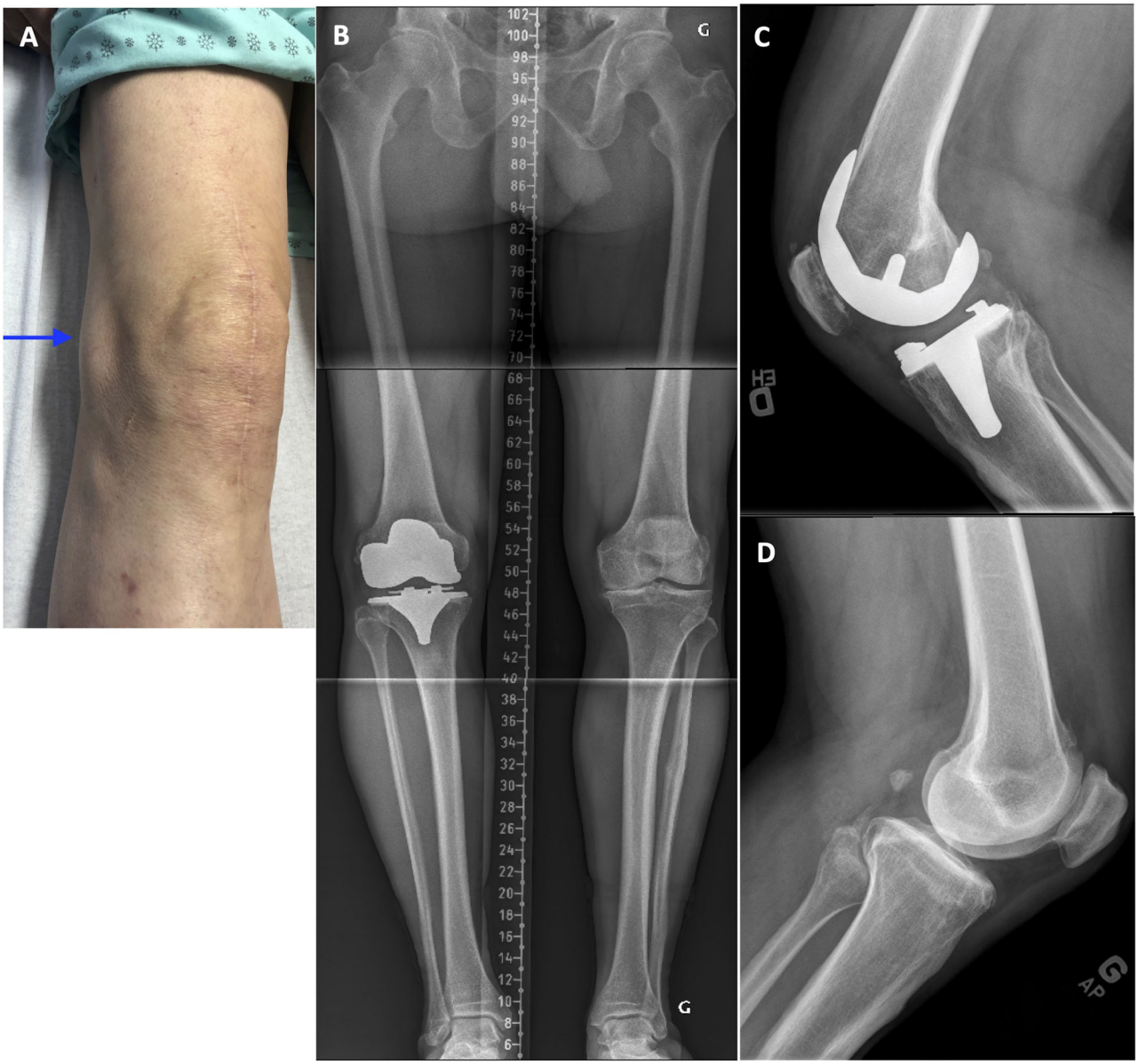

FIGURE 3 | (A) Right knee clinical examination where swelling of the biceps tendon is observed. **(B)** Pre-revision long leg standing X-Ray reveals a right TKA implant with mDFA of 4° varus and a mPTA of 1.5° varus (5.5° varus aHKA). On the intact left side, the mDFA is 3.0° valgus and mPTA 3.5° varus (aHKA of 0.5° varus). **(C)** right knee lateral view where the implant posterior tibial slope is 6.5°. **(D)** Left knee lateral view where the native tibial slope is 2.0° posterior.

Case 1

A 61-year-old male with a painful and unstable right TKA 2 years after the surgery. At clinical examination, important MCL laxity was observed along with a biceps femoris tendinitis (see **Figure 3A** and **Supplementary Video 1**). Compared to the intact contralateral lower limb, the prosthetic knee was implanted with increased femoral varus (+7.0°), decreased tibial varus (–2.0°), and increased posterior tibial slope (+4.5°, **Figures 3B–D**). During revision surgery and after implant removal (no bone loss), to correct the mDFA by 7°, a 5-mm distal medial femoral augment was used in combination with a lateral distal condyle bone resection of 2 mm. Tibial bone surface was refreshed, by removing 4 mm of anterior bone (none posteriorly, reducing the slope) and 2 mm medially to adjust varus/valgus orientation. With trial implants in place, the observed laxities (MCL 1–2 mm and LCL 3–4 mm) at 10° of flexion confirmed that we achieved our goals. As diaphyseal stem fixation would prevent the restoration of the patient's joint orientations, on both femoral and tibial sides, 12 × 50-mm cemented stems were used. A standard PS insert was selected (**Figures 4A–C**). At 18 months follow-up, the patient reported to be pain-free with a WOMAC score of 15 and a ROM of 0–125°.

Case 2

A 75-year-old female was unsatisfied with the clinical results of her left TKA, 5 years after the surgery. There was a mid-flexion instability at clinical examination with a medial opening of 5 mm at 45° of flexion and a total ROM of 0–90°. On radiographic examination (**Figures 5A–D**), there was an oversized tibia (lateral overhang), a lateral patellar retinaculum calcification, and, compared to the intact contralateral lower limb, the prosthetic knee was implanted with increased femoral varus (+4.0°), decreased tibial varus (–5.5°), and increased tibial posterior slope (+6°). During revision surgery and after implant removal, to correct the mDFA by 5° and lower the elevated joint line, a 10-mm distal medial femoral augment was used in combination with a 5-mm augment on the lateral side after a 2-mm refreshing cut. Posterior augments (5 mm) were used medially and laterally. The tibial bone surface was cut by removing 5 mm of anterior bone (none posteriorly, reducing the slope) and 5 mm medially to adjust varus/valgus orientation. With trial implants in place, the observed laxities (MCL 2 mm and LCL 3 mm) at 10° of flexion confirmed that we achieved our goals. With the patient's bone anatomy, a 50 × 12-mm femoral stem and a short tibial stubby were cemented. A standard PS insert (13 mm) was selected (**Figures 6A,B**). At 53 months follow-up, the patient reported no pain and significantly improved with a WOMAC score of 13 and a ROM of 0–115°.

Case 3

A 76-year-old male with a painful left TKA 4 years after the surgery. At clinical examination, the knee had a flexion contracture of 15° and reached 90° of flexion. There was profound medial femoral and patellar pain upon palpation. On radiographic examination, compared to the intact contralateral lower limb, the right operated side was implanted with increased femoral valgus (+2°), decreased tibial varus (−2.0°), and reduced tibial posterior slope (−9.5°, **Figures 7A–D**). In addition, the unresurfaced patella was subluxed and severely worn. Posterior femoral offset was estimated to be 5–7 mm shorter, and the femoral implant translated anteriorly. After implant removal, in addition to a refreshing cut, a supplemental 2-mm resection on the distal lateral condyle was performed to correct the mDFA by 2°. To maintain the joint line, 5-mm distal augments were used on both condyles. To compensate for the posterior femoral condyles' asymmetry of the implant in place (Genesis femur from Smith and Nephew has a thicker medial condyle), and to increase posterior femoral offset, we used a 10-mm posterior augment on the medial side and a 5-mm augment on the lateral side. Tibial bone surface was cut by removing 5 mm of anterior bone (none posteriorly, reducing the slope) and 2 mm medially to adjust varus/valgus orientation. With trial implants in place, the MCL laxity was 5 mm larger than LCL at 10° of flexion. This difference was hypothesized to be secondary to long-term tension on the MCL and subsequent stretching. In such a situation, we preferred to use a semi-constrained implant (**Figures 8A–C**). At 16 months follow-up, the patient reported having minimal pain and a ROM of 0–125°.

DISCUSSION

The most important finding of the present study was that rKA principles can be safely used in revision TKA in the short- to mid-term, thus supporting our hypothesis. At a mean 4 years' follow-up, only one (2.3%) subject in our study required a reoperation for a polyethylene exchange.

Most revision TKA cases included in this study had unsuccessful clinical results of the primary joint replacement (persisting pain, stiffness, instability, etc.). To improve patients' function and satisfaction, the rKA protocol was used for revision TKA. In contrast to the studies listed in **Table 7** where TS inserts were used almost systematically, the rKA protocol allowed most of our cases to be balanced with a standard PS insert (72%) and we obtained one of the lowest reoperation rates.

The PROMs of revision knee arthroplasty using rKA in our study showed a WOMAC score of 34.4 (0–80, ±21.7) at the last follow-up. We also found that 14 (33%) patients reported persisting anterior knee pain after their revision surgery, even though we did not use a pain scale to quantify this finding. PROMs and satisfaction rates differ between primary and revision TKAs, with revision surgeries showing less improvement (4, 22). It is very difficult to evaluate the functional results of patients with revision TKA because of the high heterogeneity of the causes of failure. The primary operation has a substantial influence on the postoperative outcome of the revision. Baker et al. (4), analyzing data from the National Joint Registry for England and Wales (NJR) found the highest improvements in PROMs and satisfaction in cases where aseptic loosening was the cause and the lowest improvements when stiffness was the cause for revision. Greidanus et al. (22) studied 60 TKA revision surgeries and found a total WOMAC score of 30.9 at 2 years after surgery. Kasmire et al. (23) followed 175 patients who underwent revision TKA for aseptic failure and reported a total WOMAC score of 28.1 at 2 years' follow-up. Notably, there is a paucity of literature regarding WOMAC scores for revision TKA at more than 2 years, and even though our scores do not show a superiority over the MA technique, we can assume that our WOMAC results would be at least comparable to projecting the results of the previous studies to a longer follow-up.

Radiographic analysis in the present study showed no radiolucencies or signs of loose components. Therefore, standing coronal alignment was changed from 1.8° to 0.8° of aHKA varus to recreate the native knee anatomy set within the limits of rKA protocol. Our findings suggest that rKA used in revision TKA does not preclude good outcomes for revision arthroplasty.

This study and the proposed rKA technique for revision TKA are not without limitations. First, to be eligible for a revision with the rKA protocol, a patient must be eligible to be revised with a short-cemented stem. If a longer stem with diaphyseal fixation is required, the longer stem may not be compatible with the patient's anatomy and its restoration. Therefore, it is plausible that some of the more complicated revision cases with severe

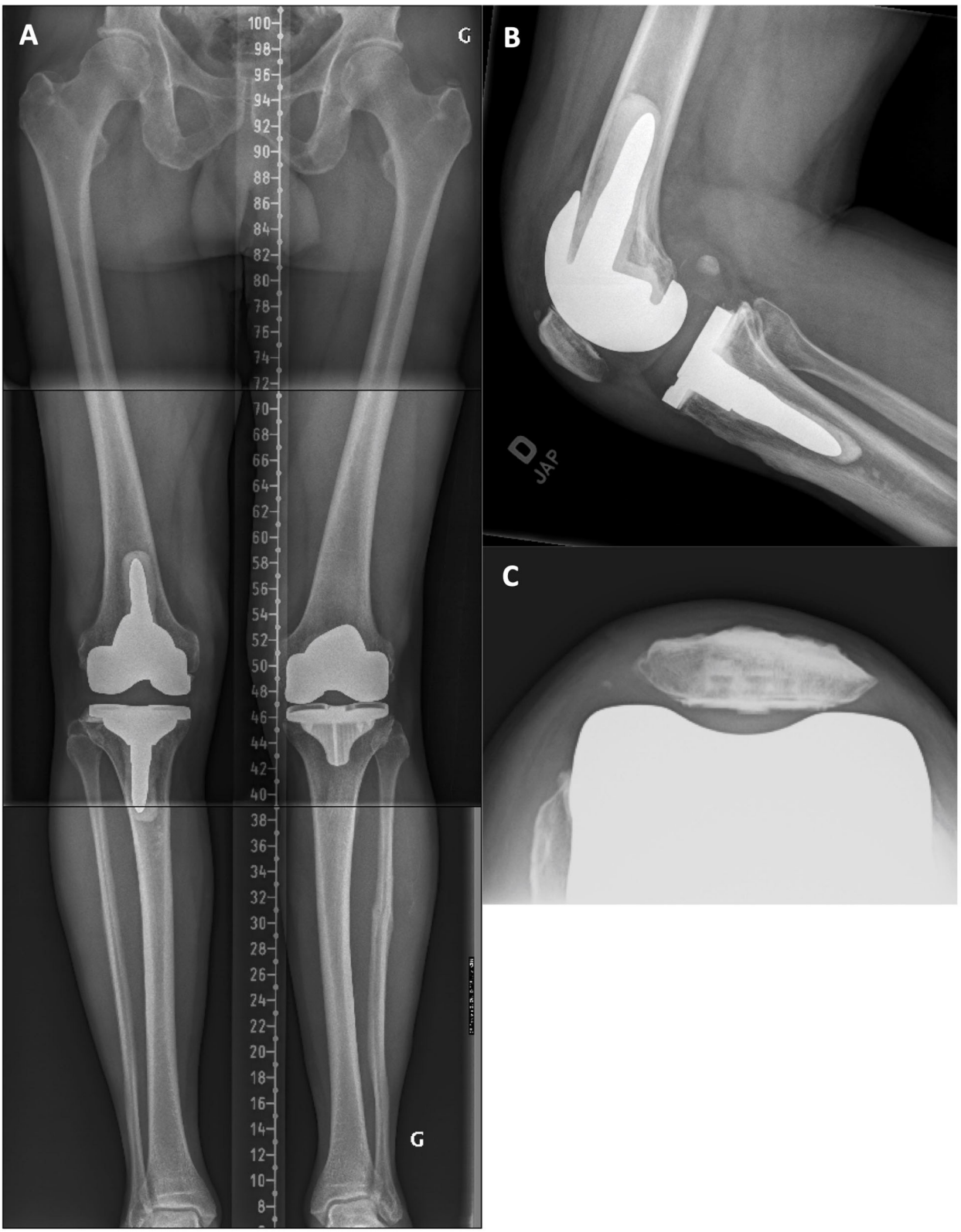

FIGURE 4 | (A) Post-revision standing long-leg X-ray of the right lower limb where the implant mDFA has been modified to 3.0° valgus and the mPTA at 4.0° varus (1.0° varus aHKA). As expected, the 50 mm cemented stems are not aligned with the tibial and femoral bone diaphysis and comes in contact with the lateral cortex on the tibial side. **(B)** Right knee lateral view where the implant posterior tibial slope has been corrected to 2.0°. **(C)** Right patella skyline view showing a well-centered implant.

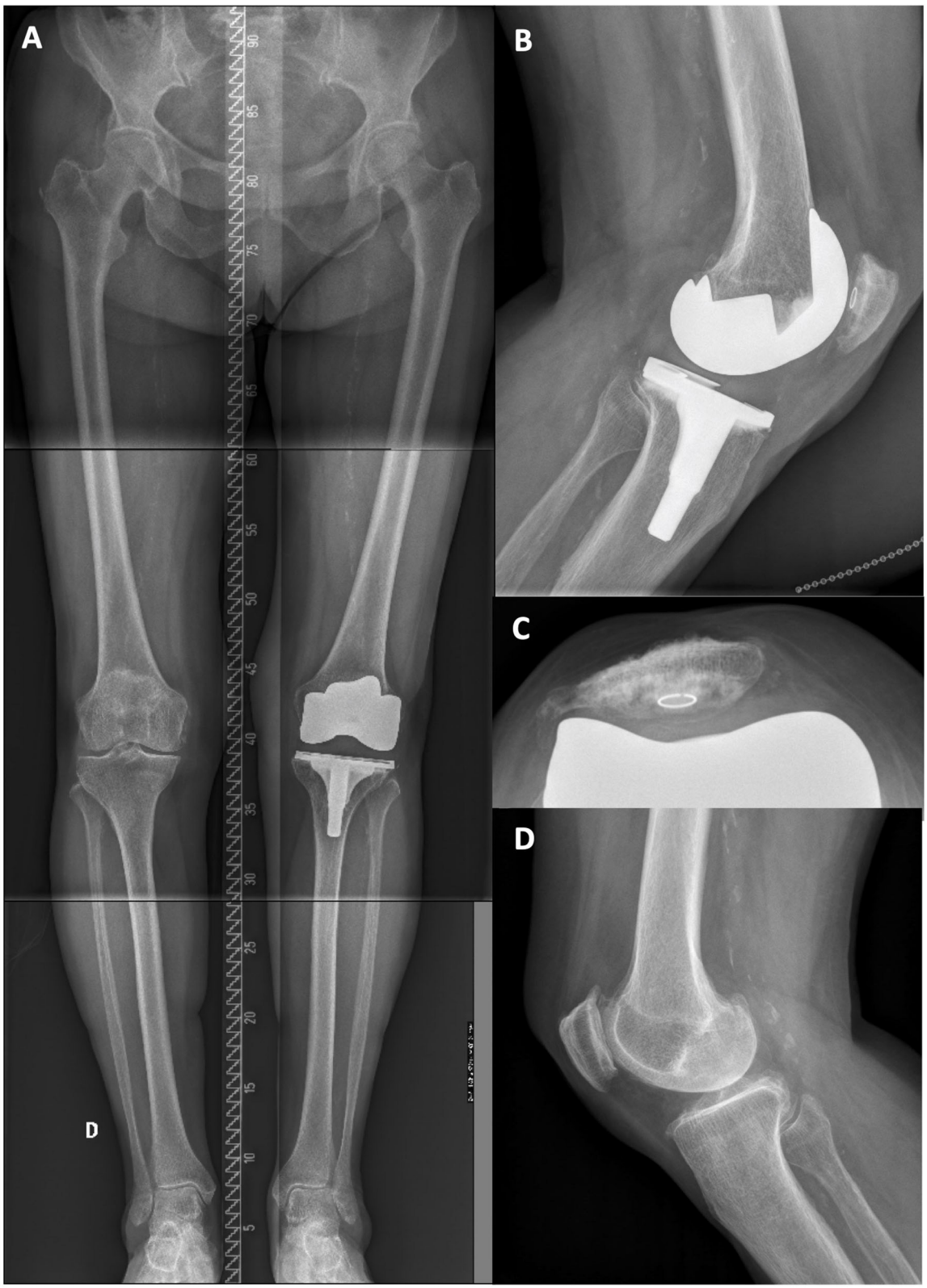

FIGURE 5 | (A) Pre-revision long leg standing X-Ray reveals a left implant mDFA of 2° varus and an mPTA of 2° valgus (0° varus aHKA). On the intact right side, the mDFA is 2.0° valgus and mPTA 3.5° varus (aHKA of 1.5° varus). **(B)** Left knee lateral view where the implant posterior tibial slope is 12.0°. **(C)** Left patella skyline view showing a lateral patellar retinaculum calcification and a well-centered resurfaced patella. **(D)** Right knee lateral view where the native tibial slope is 6.0° posterior.

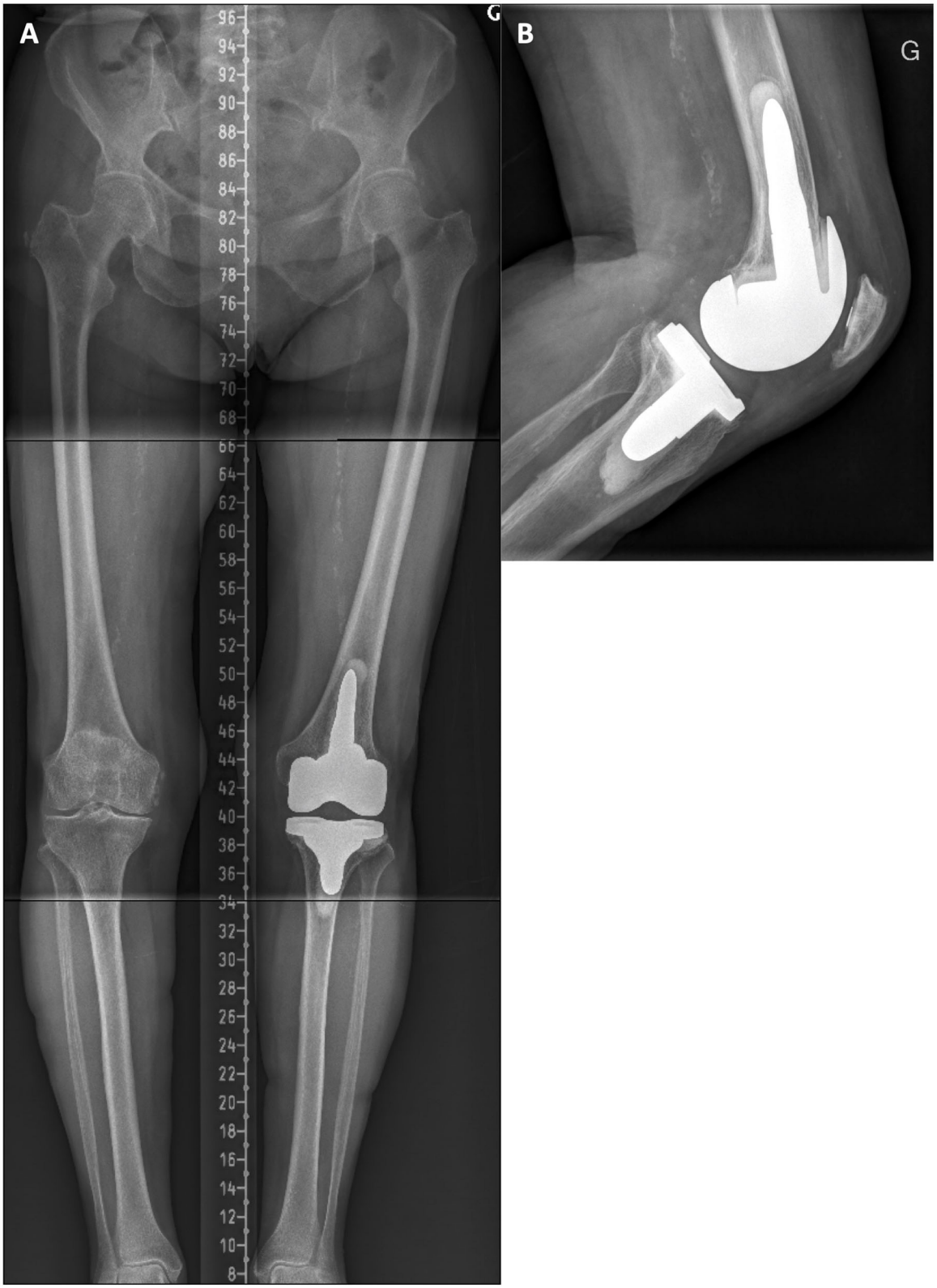

FIGURE 6 | (A) Post-revision standing long-leg X-ray of the left lower limb where the implant mDFA has been modified to 2.0° valgus and the mPTA at 3.0° varus (1.0° varus aHKA). As expected, the femoral cemented stems is not aligned with the femoral bone diaphysis. On the tibial side, to restore patient's alignment, only a stubby stem could be used and comes in contact with the lateral cortex. **(B)** Left knee lateral view where the implant posterior tibial slope has been reduced to 3.0°. Because manufacturer recommendations for this implant is a neutral slope, we did not aim at patient's contra-lateral side value of 6°.

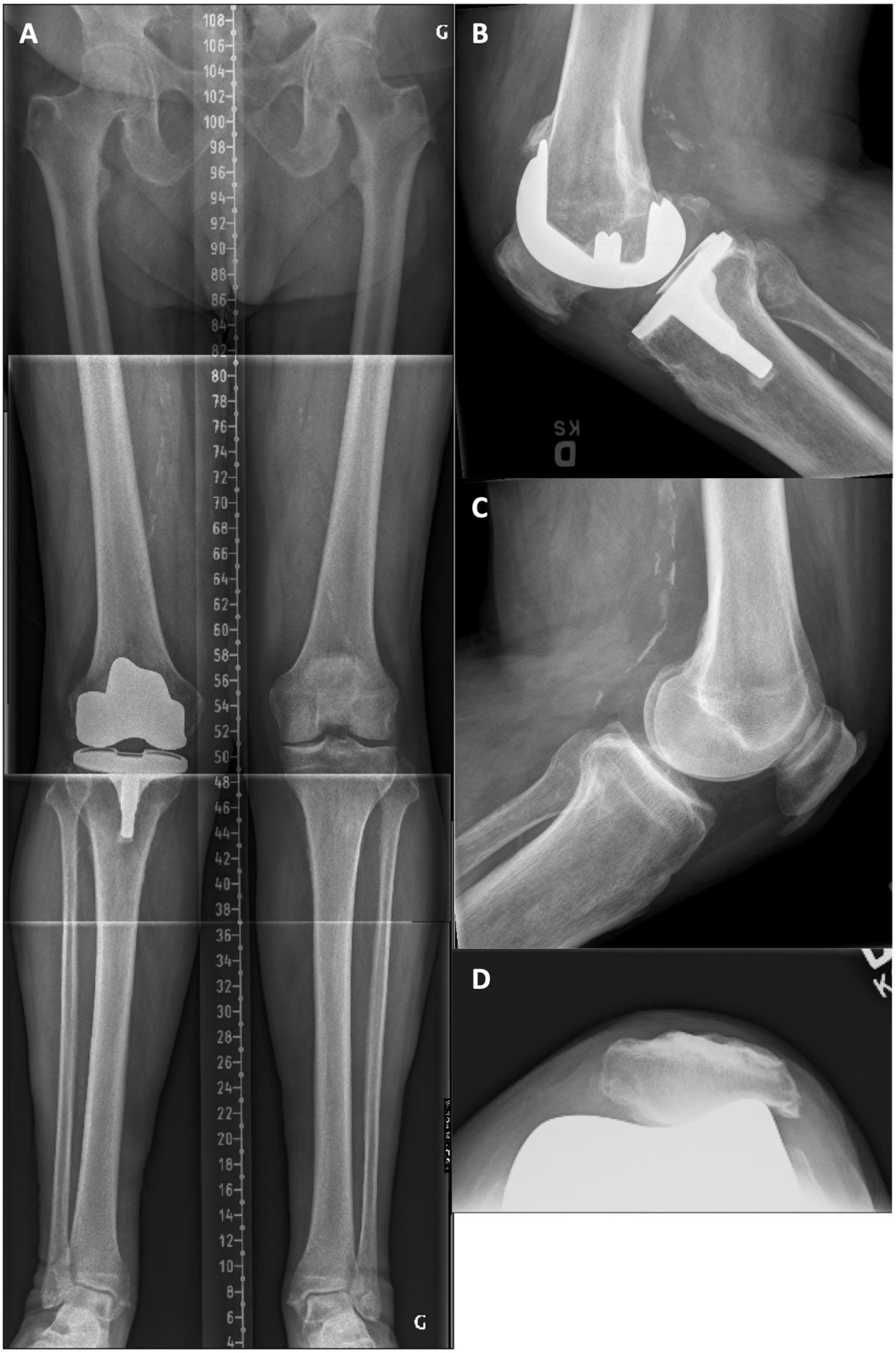

FIGURE 7 | (A) Pre-revision long leg standing X-Ray reveals a right implant mDFA of 4° valgus and an mPTA of 1.5° valgus (5.5° valgus aHKA). On the intact left side, the mDFA is 2.0° valgus and mPTA 0.5° varus (aHKA of 1.5° valgus). **(B)** Right knee lateral view where the implant tibial slope is 1.5° anterior. **(C)** Left knee lateral view where the native tibial slope is 8.0° posterior. **(D)** Right knee skyline view showing a subluxed and worn patella.

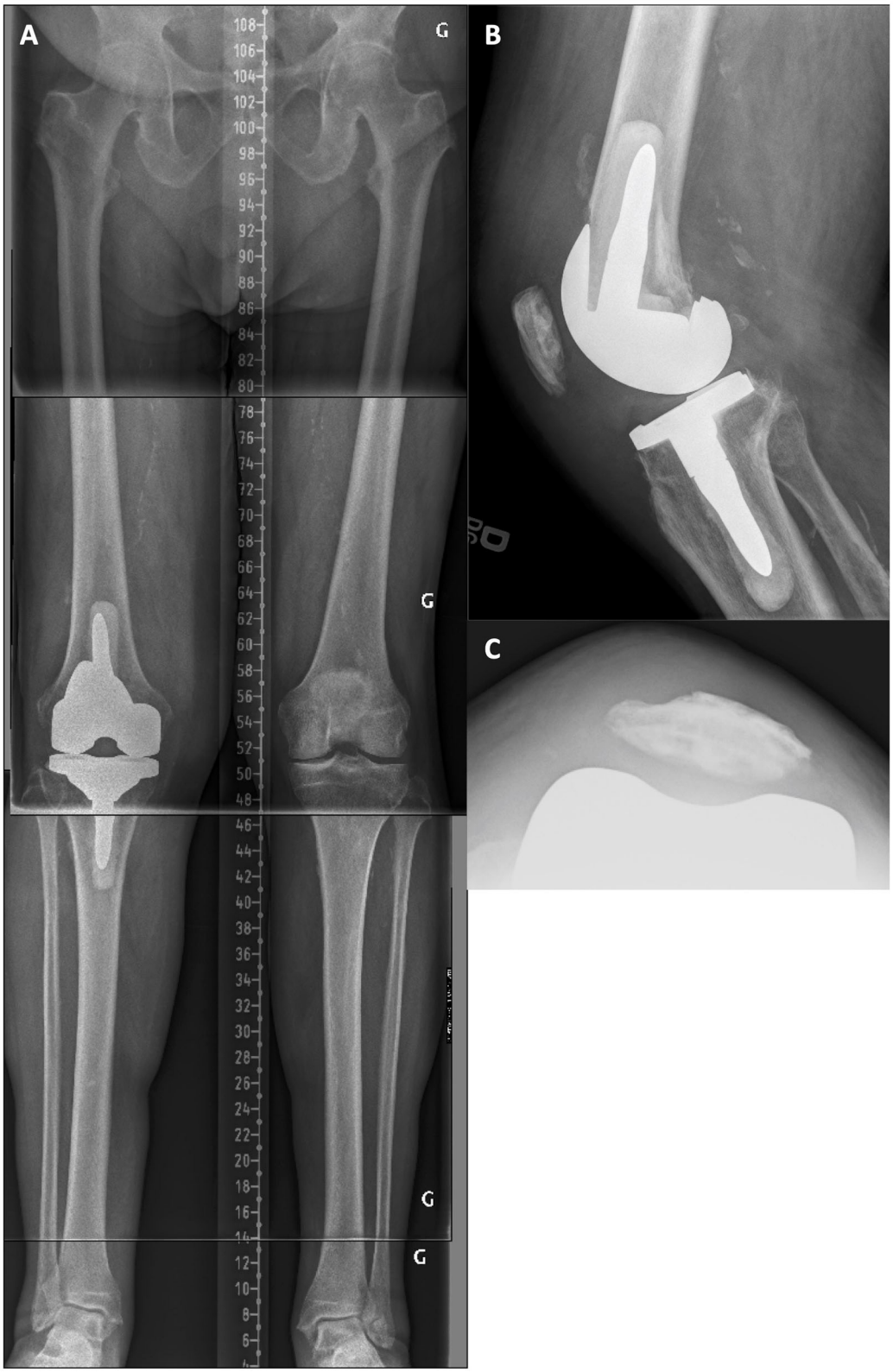

FIGURE 8 | (A) Post-revision standing long-leg X-ray of the right lower limb where the implant mDFA has been modified to 1.0° valgus and the mPTA at 0.5° varus (0.5° valgus aHKA). **(B)** Right knee lateral view where the implant tibial slope has been shifted from 1.5° anterior to 2.0° posterior. The femoral implant has also been translated posteriorly to be flush with the anterior cortex. **(C)** Right knee skyline view showing a well-centered resurfaced patella.

TABLE 7 | Results of studies reporting their outcomes with the Triathlon TS Knee System (Triathlon Total Knee System; Stryker Orthopedics, Mahwah, NJ) for revision TKA.

References	N TKAs/ mean FU in years	Indication for revision	Type of PE insert	Component fixation	Rerevisions	PROMs preoperatively mean (range, ±SD)	PROMs at final follow-up mean (range, ±SD)	Radiological analysis
Gwam et al. (19)	93/4	NR, septic failures were excluded	TS	NR	4 aseptic loosening 2 septic failures	NR	KSS: 86 (38–100) Functional KSS: 52 (15–90)	Excluding the revised cases, there were no progressive radiolucencies or osteolysis noted
Hamilton et al. (10)	53/2	NR, septic failures were excluded	TS	Fully cemented	None	OKS: 19.1 (±7.41)	OKS: 36.4 (±8.2)	NR
Stevens et al. (20)	100/7.4	85 aseptic reasons 15 septic reasons	TS	Fully cemented	6 septic failures 3 instability 1 infected periprosthetic fracture 2 reoperations for additional patellar resurfacing	NR	OKS: 27 (0–46, ±11.9) FJS: 32.3 (0–100, 30.4) SF-12 PCS: 40.6 (23.9–67.1 ±17.6) SF-12 MCS: 48.3 (23.9–69.1, ±15.5)	Excluding the revised cases, nine postoperative radiographs demonstrated non-progressive radiographic lucent lines with no evidence of loosening. One radiograph demonstrated progression of radiographic lucent lines and lysis
Limberg et al. (21)	416/4	122 instability 105 aseptic loosening 97 septic failure 92 other	TS	Fully cemented	23 septic failures 17 instability 10 aseptic loosening 1 arthrofibrosis 1 periprosthetic fracture 1 patella fracture	KSS: 46	KSS: 81	NR
Present study (2021)	43/4	40 aseptic reasons 3 septic reasons	31 PS 12 TS	Fully cemented	1 instability	NR	WOMAC: 34.4 (0–80, ±21.7)	No progressive radiolucencies or osteolysis noted

KSS, Knee Society Score; OKS, Oxford Knee Score; FJS, Functional Joint Score; SF-12 PCS, Physical Component Summary; SF-12 MCS, Mental Component Summary; SD, standard deviation; NR, Not reported.

bone loss or instability requiring hinge implant, for example (22/85 cases), were excluded from this study. This might explain our lower rerevision rate compared to other studies. Second, our study is limited by its small sample size (43 revision TKAs carried out by only one surgeon) and this might contribute to overlooking the increased risk for aseptic loosening and recurrent infection after revision surgery. However, it is a continuous series, and we believe that our cohort is representative of an academic center revision practice. Second, our study has a short mean follow-up (4 years), and longer follow-up studies are warranted to evaluate the long-term safety of this technique. Third, many patients that participated in our study were referred to us from different institutions and data regarding the primary surgery were not available to us. Therefore, because of the retrospective nature of this study, we could not measure the improvement in PROMs from primary surgery.

We believe that this study, being the first of its kind, will spark the interest in the orthopedic community to use rKA for revision TKA, especially in the cases of early, non-wear-related unsuccessful MA TKAs. It is agreed that using precision tools like navigation or robot is the future way to go to perform such procedures. Navigation in the setting of rKA revisions has been used by the authors (PAV, MOK). While this technology helps to make accurate refresh cuts, the actual design of the cutting block made for primary TKA makes it difficult to stabilize in cases with significant metaphyseal bone loss. It also does not allow the surgeon to perform step cuts. In the near future, robotic surgery may prove to be an appealing option to facilitate rKA knee revisions once the appropriate software is available.

Last, there is limited scientific evidence to define the acceptable lower limb alignment and joint line tilt limits and related implants orientations. Such evidence, supporting the universal use of KA in extreme anatomies, may allow removing rKA boundaries. Nevertheless, in the meanwhile, we believe that rKA is a safe and favorable new technique for TKA revision.

CONCLUSION

Although current revision TKA implants are not ideal for revision TKA performed with rKA; it is an appealing alternative to MA in the mid-term, especially in the cases of early, non-wear-related unsuccessful MA TKAs.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Comité d'éthique de la recherche CIUSSS de l'Est-de-l'Île-de-Montréal. The patients/participants provided their written informed consent to participate in this study. All patients consent for inclusion of their case.

AUTHOR CONTRIBUTIONS

LK, GBR, SM, M-OK, and JB collected the data and wrote the manuscript. JB carried out the statistical analysis. P-AV was involved in the experimentation and surgery performance and performed the surgeries, designed the study, reviewed the article, and was responsible for manuscript submission. All authors have approved the final article.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fsurg.2021.721379/full#supplementary-material

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SYSTEMATIC REVIEW
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Clinical and Radiological Changes of Ankle in Knee Osteoarthritis With Varus After Total Knee Arthroplasty: A Systematic Review

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Background: Arthritis with severe varus deformity remains a challenge in total knee arthroplasty (TKA). Until recently, surgeons aimed at a neutral lower limb alignment when performing a TKA. However, the impact of TKA on the ankle joint has been ignored. Therefore, we conducted a systematic review to assess the clinical and radiological changes in the ankle joint after TKA on knees with severe varus deformity.

Methods: A systematic search was conducted in four English (PubMed, Embase, Cochrane Library, and Web of Science) and four Chinese (CBM, VIP, CNKI, and Wan Fang Database) databases. Screening of literature and extraction of data were independently performed by two researchers. The modified methodological index for non-randomized studies (MINORS) was used to assess the quality.

Results: A total of eight studies were eligible, namely, four prospective and four retrospective studies. TKA resulted in a negative clinical effect in the ankle joint in patients with ankle osteoarthritis. Seven studies reported changes in the mechanical tibiofemoral angle, and four studies reported radiological changes in the hindfoot. The mean score of the MINORS was 9.8 out of eight (9–11).

Conclusion: As a result of the correction of the knee osteoarthritis with severe varus deformity following mechanically aligned TKA, the radiological malalignment of the ankle joint was improved. However, some patients experience increased ankle pain after undergoing TKA, especially, if there was a residual knee varus deformity, a stiff hindfoot with varus deformity, or ankle arthritis.

Keywords: systematic review, ankle, knee osteoarthritis, varus knee, total knee arthroplasty

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INTRODUCTION

Concomitant ankle osteoarthritis (OA) is frequently found in patients who undergo TKA, which is a classic surgery for elderly patients, who have experienced knee osteoarthritis (KOA), with multiple joint degenerative changes (1–3). Furthermore, malalignment of the knee joint caused by KOA could induce ankle tilt that would further aggravate ankle OA (4). Nonetheless, a few patients experienced increased or newly developed ankle pain after TKA (5). Surgeons lack a comprehensive consideration of the ankle condition of the patient when performing TKA.

Most of the patients with knee arthritis who undergo TKA have varying degrees of knee joint deformity, which may be associated with hindfoot deformity (6–8). Previous studies reported an association between varus alignment of the knee joint and valgus alignment of the hindfoot in patients with KOA (7, 8). Because the mild deformity of the knee joint can be compensated by the subtalar joint (8), the knee joint alignment modification after TKA can affect the hindfoot alignment. Previous studies have demonstrated that improvements in the hindfoot alignment have been observed in patients who experience OA after TKA (7, 9, 10). However, hindfoot valgus may show little improvement and persist after TKA (7, 9).

Patients with a hindfoot deformity present a particular challenge when undergoing TKA. Clarifying the relationship between hindfoot alignment and TKA is useful to change the current state. Thus, this systematic review attempted to assess prospective and retrospective cohort studies to determine the relationship between the radiological changes and clinical symptoms of the ankle joint following acute correction of the lower alignment using TKA for severe varus knee.

METHODS

Literature Search

A systematic search was conducted in four English (PubMed, Embase, Cochrane Library, and Web of Science) and four Chinese (CBM, VIP, CNKI, and Wan Fang Database) databases from inception to December 2020 for relevant non-randomized controlled trials (nRCTs). The search was based on the following search terms: ("Arthroplasty, Replacement, Knee" OR "Total knee arthroplasty" OR "Knee replacement" OR "TKA") AND ("varus knee") AND ("ankle alignment" OR "ankle deformity" OR "hindfoot alignment" OR "hindfoot deformity"). Additional records were obtained by screening the references. Detailed inclusion and exclusion criteria were formulated to review the results of the search by two reviewers (Feng ZH W and Ma M); the abstract was screened first before reading the full text.

Literature Inclusion and Exclusion

The inclusion criteria were as follows: (1) nRCT, prospective or retrospective studies, and case control studies; (2) patients who underwent primary TKA as research participants; (3) with mechanical tibiofemoral angle (MTA), hindfoot alignment angle (HA), American Orthopedic Foot and Ankle Score (AOFAS), talar tilt (Tt), medial ankle joint space (MAJS), and medial ankle clear space (MACS) as indicators of the postoperative results; and (4) all retained studies should have the same hip knee ankle (HKA) goal, i.e., neutral mechanical alignment (MA). If not, the study should be excluded. The exclusion criteria were as follows: (1) diagnosis of a disease other than primary KOA; (2) KOA with valgus malalignment or rheumatoid arthritis; (3) history of femoral or tibial fractures in the past; (4) incomplete or missing research data; and (5) research data from animal experiments or theoretical analysis. Repeated publications, letters, case reports, comments, conference abstracts, or books were also excluded.

Data Extraction

We performed data extraction of all the included documents with predesigned tables, and all the studies were independently retrieved and assessed by two reviewers (ZH W Feng and M Ma). The extracted data should include the following: (1) title, first author, publication time, study design, clinical indicators, and radiological indicators; (2) patient characteristics such as number of patients, age, sex, number of patients who underwent TKA, and follow-up time; and (3) study details such as clinical results, radiological results, and conclusions. The extracted information was cross-checked to ensure accuracy. When there were disagreements, the decision was made by a third person.

Quality Assessment

The methodological quality of nRCTs was assessed using the modified MINORS (11). Eight questions for the nRCTs were used to score the relevant aspects of each study: a clear research purpose (I), continuous follow-up of patients (II), prospective research (III), suitable research purpose (IV), unbiased assessment of the research outcome (V), an appropriate follow-up period for the study (VI), the lost-to-follow-up rate was $< 5\%$ (VII), and perform a prospective calculation of the sample size (VIII).

The score criteria are as follows: not reported scored as 0, reported but inadequate scored as 1, and reported and adequate scored as 2. The MINORS score was assessed separately by the two reviewers (ZH W Feng and M Ma). Then, the categories were determined according to the study by Ekhtiari et al. (12): "0–4 points" were categorized as very low; "5–8 points" as low; "9–12 points" as good; and "13–16 points" as excellent.

RESULTS

Study Selection

A total of 733 studies were included in this study. After removing 277 duplicates, the titles, abstracts, and full articles were screened, and 425 studies were further excluded. A total of eight eligible articles were considered for further analysis. The results of the study selection process are presented in **Figure 1**.

Study Characteristics

A total of 913 patients and 1,157 knees were included in the eligible studies. All included studies were observational studies, and their publication years ranged from 2012 to 2019. The follow-up duration was extended from 6 months to 3 years. **Tables 1**, **2** show the characteristics of the included study.

Quality Assessment

We used the MINORS criteria to assess the methodological quality of the nRCTs. The categories were determined according to the research of Ekhtiari et al. (12). The quality evaluation of the included research literature is shown in **Table 3**.

Research Details

After removing duplicate studies and applying the inclusion and exclusion criteria, eight studies were eligible for further analysis (**Figure 1**). The eligible studies included a total of 913 patients

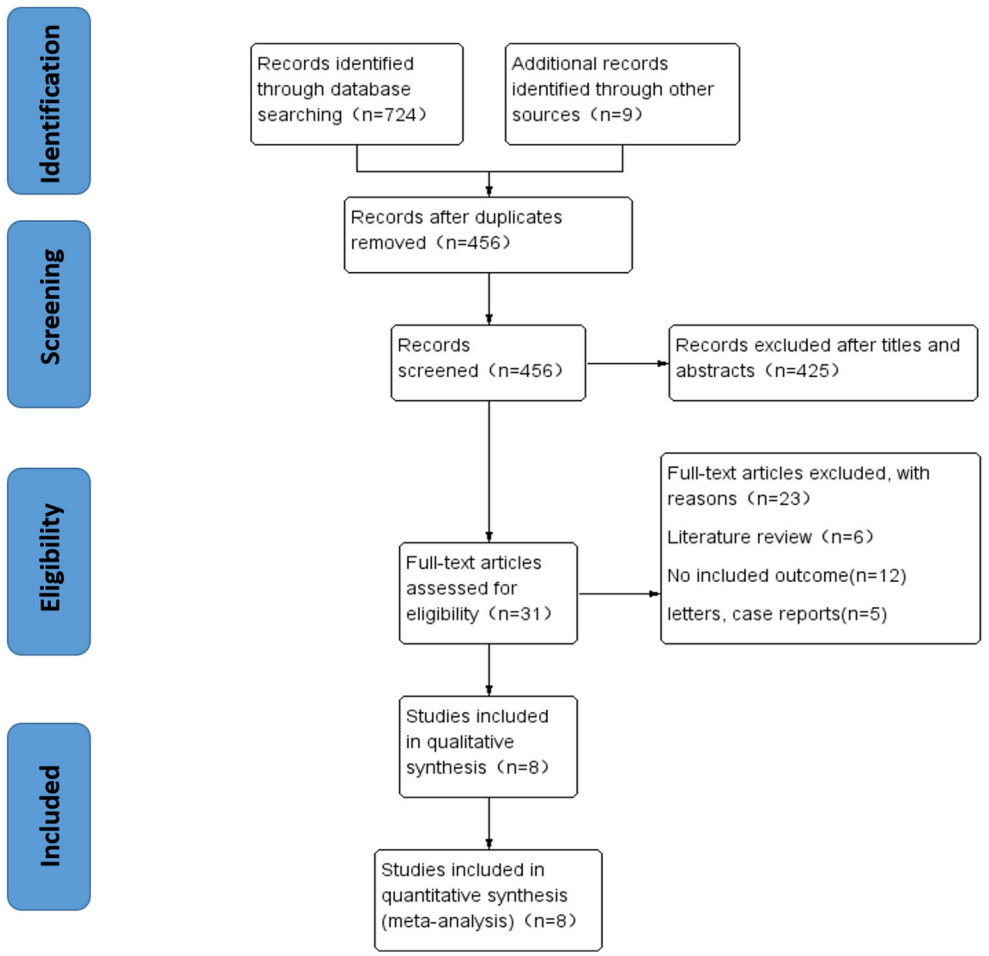

FIGURE 1 | Flowchart for the identification of eligible studies.

TABLE 1 | Study details.

References	Country	Design	Cohort description	Total number (people/knee)	Mean age (year)	Male (M/F)	Follow-up	Outcomes
Cho et al. (13)	South Korea	Pc	Varus < 10° KOA, Varus ≥ 10° KOA	117/195	69.1 ± 6.1	N/R	2 years	①②
Okamoto et al. (5)	Japan	Rc	Varus ≤ 6° KOA, Varus > 6° KOA	75/80	72.5 (range, 58–85)	8/67	2 years	①③④
Chang et al. (14)	South Korea	Rc	Varus KOA + Ankle OA, Varus KOA + NO Ankle OA	56/99	70 ± 6.8	6/50	2 years	①②④⑤⑥
Gursu et al. (15)	Turkey	Rc	Varus > 10° KOA	78/80	67 (range, 54–78)	18/60	3 years	①④⑥
Jeong et al. (16)	South Korea	Pc	Varus KOA	331/375	68.3 ± 7.8	23/308	6 months	①②④
Palanisami et al. (17)	India	Pc	Varus > 10° KOA	91/121	63.4 ± 7.6	29/62	1 year	①②③
Lee et al. (18)	South Korea	Rc	Varus + valgus KOA	110/142	65.8	N/R	3 years	④⑤⑥
Kim et al. (19)	South Korea	Pc	Varus KOA	55/ 65	N/R	N/R	2 years	①②③④⑤⑥

PC, prospective cohort; RC, retrospective cohort; N/R, not reported; ①, MTA or the angle formed between the mechanical axis of the femur and the mechanical axis of the tibia; ②, HA or the angle between the diaphyseal axis of the tibia and the longitudinal axis of the calcaneus; ③, AOFAS or the American Orthopedic Foot and Ankle Score; ④, Tt or the angle between the distal tibial surface and the upper talus; ⑤, MAJS or the distance between the medial of the talar dome and the distal tibial surface; ⑥, MACS or the distance between the medial articular surface of the talus and the medial malleolus articular surface.

TABLE 2 | Study details.

References	Clinical indicator		Radiographic indicator		Correlation	Conclusion
	Knee	Ankle	Knee	Ankle		
Cho et al. (13)	N/R	N/R	Significant difference of MTA after TKA ($p < 0.001$)	Significant difference of HA after TKA ($p < 0.001$)	Correlation between MTA and HA before and after TKA ($p < 0.05$).	The hindfoot valgus deformity in patients with knee varus deformity does not require to be corrected before TKA.
Okamoto et al. (5)	Significant difference of KSS, KSFS after TKA ($p < 0.05$)	Significant difference of AOFAS after TKA ($p < 0.05$)	Significant difference of MTA after TKA ($p < 0.001$)	Significant difference of Tt after TKA ($p < 0.05$)	Correlation between MTA and Tt before and after TKA ($p < 0.05$).	Patients with severe knee deformity would experience persistent hindfoot pain and valgus alignment after TKA.
Chang et al. (14)	N/R	Patients with ankle OA had increased ankle pain and worse clinical outcomes after TKA ($p < 0.05$).	Significant difference of MTA after TKA ($p < 0.001$)	Significant difference t of Tt, MAJS, and MACS after TKA ($p < 0.05$)	Correlation between MTA and Tt, MAJS, and MACS before and after TKA ($p < 0.05$).	The ankle OA is related to the increased ankle pain after TKA and adversely affects the clinical outcomes.
Gursu et al. (15)	N/R	N/R	Significant difference of MTA after TKA ($p < 0.001$)	Significant difference of Tt and MACS after TKA ($p < 0.05$)	N/R	The correction of severe knee varus deformity following TKA would lead to ankle malalignment.
Jeong et al. (16)	N/R	N/R	Significant difference of MTA after TKA ($p < 0.001$)	Significant difference t of HA and Tt after TKA ($p < 0.001$)	Correlation between MTA and HA, Tt before and after TKA ($p < 0.05$).	The correction of knee varus deformity after TKA would lead to compensatory changes, which occurred at the ankle and the subtalar joints.
Palanisami et al. (17)	Significant difference of OKS after TKA ($p < 0.001$)	Significant difference of AOFAS after TKA ($p < 0.001$)	Significant difference of MTA after TKA ($p < 0.001$)	Significant difference of HA after TKA ($p < 0.001$)	Correlation between MTA and HA before and after TKA ($p < 0.05$).	The knee and hindfoot alignment in patients with knee varus deformity can be restored by TKA.
Lee et al. (18)	N/R	N/R	Significant difference of MTA after TKA ($p < 0.001$)	Significant difference of Tt, MAJS, and MACS after TKA ($p < 0.05$)	Correlation between MTA and Tt, MAJS, and MACS before and after TKA ($p < 0.05$).	The correction of knee varus deformity after TKA would lead to radiographically progressed ankle arthritis.
Kim et al. (19)	N/R	Significant difference of AOFAS and VAS after TKA ($p < 0.01$)	Significant difference of MTA after TKA ($p < 0.001$)	Significant difference of Tt, HA after TKA ($p < 0.05$)	Correlation between MTA and Tt, HA before and after TKA ($p < 0.05$).	The correction of knee varus deformity after TKA would lead to more serious ankle pain.

N/R, not reported; KSS, Knee Society Score; KSFS, Knee Society Functional Score; VAS, visual analog scale; OKS, Oxford Knee Score; MTA, mechanical tibiofemoral angle; HA, hindfoot alignment angle; AOFAS, American Orthopedic Foot and Ankle Score; Tt, talar tilt; MAJS, medial ankle joint space; MACS, medial ankle clear space.

TABLE 3 | MINORS score.

References	I	II	III	IV	V	VI	VII	VIII	Total score
Cho et al. (13)	2	1	1	2	1	2	1	1	11
Okamoto et al. (5)	2	1	0	2	1	2	1	1	10
Chang et al. (14)	2	1	0	2	1	2	0	1	9
Gursu et al. (15)	2	1	0	2	1	2	0	1	9
Jeong et al. (16)	2	1	1	2	1	1	0	1	9
Palanisami et al. (17)	2	1	1	2	1	2	1	1	11
Lee et al. (18)	2	1	0	2	1	2	0	1	9
Kim et al. (19)	2	1	1	2	1	2	1	1	11

I–VIII, question; MINORS score, not reported scored as 0, reported but inadequate scored as 1, reported and adequate scored as 2.

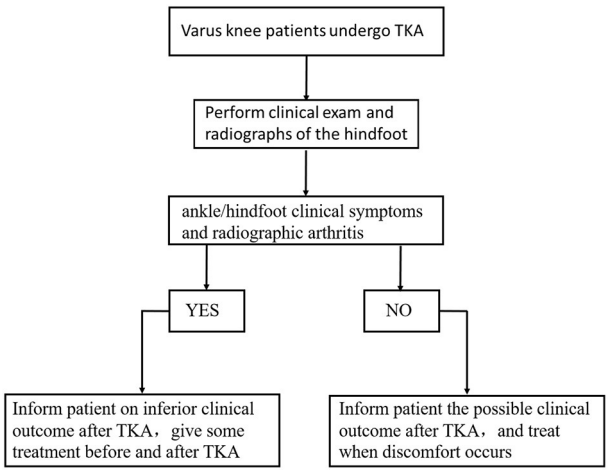

FIGURE 2 | Flowchart in patients undergoing TKA.

and 1,157 knees, which included four prospective cohort studies (13, 16, 17, 19) and four retrospective studies (5, 14, 15, 18). Seven studies (5, 13–17, 19) only studied the varus KOA, and one study (18) investigated both varus and valgus KOA. The characteristics of the eligible studies were extracted by two researchers (**Table 1**).

All the clinical and radiological outcomes of the knee and hindfoot after TKA are shown in **Table 2**. Four studies (5, 14, 17, 19) have reported the specific clinical outcomes of the knee and hindfoot after TKA. Okamoto et al. (5) reported that patients with hindfoot deformity after TKA would have a significant improvement in Knee Society Score, Knee Society Functional Score, and AOFAS. Chang et al. (14) reported that patients with ankle OA experienced increased ankle pain and poor clinical prognosis after TKA. Meanwhile, Palanisami et al. (17) reported that the Oxford Knee Score and AOFAS of patients with foot deformities after TKA significantly improved. Kim et al. (19) also reported that a persistent ankle varus deformity could be attributed to increased ankle pain after TKA.

Seven studies (5, 13–17, 19) compared the change in MTA pre- and postoperative, which found significant postoperative improvement of MTA after TKA. Five studies (13, 14, 16, 17, 19) included a radiological analysis of HA before and after TKA, and found significant improvement in hindfoot deformity. Cho et al. (13) also found that there was a weak negative correlation between the preoperative HA and MTA (-0.484, $p < 0.001$), and a very weak correlation between the postoperative MTA and postoperative HA at 6 weeks (-0.147, $p = 0.040$). Six studies (5, 14–16, 18, 19) included a radiological analysis of pre- and postoperative Tt, which found significant improvement. Lee et al. (18) found that the incidence of ankle arthritis would obviously increase when the preoperative Tt was closer to the ankle medial or when the angle of correction was greater after TKA. Lastly, three studies (14, 18, 19) included a radiological analysis of MAJS and MACS pre- and postoperatively, which showed a significant difference.

DISCUSSION

Traditionally, obtaining a neutral lower limb alignment after a TKA was perceived as the ideal goal (20–23). However, since very few individuals have such anatomy, it implies a significant modification for most. Freeman et al. (24) first introduced the concept of right-angled femoral and tibial bone cuts in TKA-MA. Subsequently, Scuderi et al. (25), raised the importance of balancing the resulting medial–lateral and flexion–extension joint gaps. MA technique *gradually* became the gold standard in TKA. However, the recent studies found that MA-TKA generates disappointing efficacies (26, 27), probably due to MA-TKA produces a non-physiological prosthetic knee by changing the native anatomy, physiological ligament balance, and kinematics (28–31). Stephen Howell developed the kinematic alignment (KA) technique (28, 30). KA-TKA aims to generate a more physiological prosthetic knee joint by restoring the inherent knee joint anatomy and physiological soft tissue balance of the individual. Several studies have suggested that KA-TKA can accurately locate the position of the prosthesis (32), and also restore the native anatomy of the knee (32, 33) and physiological laxity (34, 35). The ultimate goal of TKA is to restore the anatomy and kinematics of native knees and provide a forgotten joint.

Recent studies have found that the alignment of the ankle joint and hindfoot could be affected by the malalignment of the lower limb (4, 5, 8, 36, 37). Moreover, the hindfoot deformity is closely associated with the lower limb alignment (38), and the clinical symptoms and radiographic outcome changes of the ankle joint and hindfoot in patients who underwent TKA would be influenced by changes in lower limb alignment (5). Chang et al. (14) found that there was less radiographic alignment change in the ankle and hindfoot when patients had ankle OA and increased ankle pain after TKA; and patients with a stiff hindfoot who underwent TKA experienced increased ankle pain, probably because of the inability to reorient the ankle after TKA. Nevertheless, different findings have been reported by these

studies, but there have been no comprehensive reviews of this issue in the literature so far.

In this systematic review, we found that TKA may affect the clinical and radiological outcomes of patients with hindfoot deformity before TKA. In addition, the HA before TKA had a weak negative correlation with MTA (13). Clinically, four studies (5, 14, 17, 19) detected an obvious improvement in AOFAS at the hindfoot after TKA. However, increased ankle pain after TKA has also been reported in the patients with ankle OA or persistent knee deformity (14, 19). When patients have a residual deformity and pain of the hindfoot 6 weeks after TKA, they must receive active treatment because further improvement cannot be expected (13). Furthermore, five studies (13, 14, 16, 17, 19) reported an obvious radiological improvement in hindfoot alignment after TKA. Kim et al. (19) also reported a relationship between residual varus deformity and ankle pain after TKA.

Figure 2 shows the flowchart for the general treatment of patients with knee varus and ankle stiffness before and after TKA. Before TKA, the clinicians should perform clinical and radiological examinations of the ankle/hindfoot. If the patient has clinical or imaging problems with the ankle/hindfoot, the clinicians should inform the patient about the results and provide some treatment before and after TKA. If the patient does not have ankle/hindfoot problems before TKA, the clinician should tell them about possible problems after TKA. Patients should be informed and treated when discomfort occurs.

This study has several limitations. First, eligible papers according to the search criteria used were not identified completely. Second, the eligible studies found for this systematic review had a relatively small number and a relatively high heterogeneous group, which could not be studied by meta-analysis. Third, the follow-up time in two studies (16, 17) was <2 years, which limited the ability to draw a long-term conclusion.

In conclusion, an improvement in the clinical function and radiological alignment of the hindfoot can be achieved following TKA. However, when patients had concomitant ankle OA with hindfoot stiffness, there is an increased ankle pain and a worse clinical outcome after TKA.

Therefore, the comprehensive preoperative evaluation of surgeons of the ankles of patients who complain of pain pre- and postoperatively and the correction of alignment during TKA should be given careful attention.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

AUTHOR CONTRIBUTIONS

ZF and MM worked on literature search, study review, and manuscript draft. YW, CY, and ZL prepared the tables and figures. YX worked on manuscript review, process supervision, and draft revision. All authors have read and approved the final manuscript.

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Fluid Homeostasis May Predict the Prognosis of Non-infectious Fever After Total Knee Arthroplasty Within 7-Day: A Retrospective Cohort Study

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Background: In the perioperative management of Total Knee Arthroplasty (TKA), postoperative fever has always been a concern. Current research focuses on infectious fever, and there is no relevant research on the occurrence of non-infectious fever (NIF) and its risk factors. Hence, the aim of this study was to clarify the risk factors for NIF after TKA, and construct an easy-to-use nomogram.

Methods: A retrospective cohort study was conducted. Consecutive patients undergoing primary unilateral TKA were divided into the non-infectious fever group and the control group. Clinicopathological characters were collected from electronic medical records. Univariate Logistic regression was used to analyze the related independent risk factors. The optimal threshold for each selected factor and combined index was determined when the Youden index achieved the highest value. And the predictive nomogram was developed by these independent factors.

Results: Ultimately, 146 patients were included in this study. Of them, 57 (39.04%) patients experienced NIF. Results of the univariable logistic regression analysis indicated that intraoperative blood loss (OR, 1.002; 95% CI, 1.000–1.0004), postoperative drainage fluid volume (OR, 1.003; 95% CI, 1.001–1.006) and frequency of blood transfusion ($n = 1$; OR, 0.227; 95% CI, 0.068–0.757) were independent risk factors of NIF occurrence. The predictive nomogram that incorporated the above independent risk factors was developed, and it yielded an areas under the curves (AUC) of 0.731 (95% CI: 0.651–0.801; $P < 0.0001$) with 54.39% sensitivity and 82.02% specificity.

Conclusions: Non-infectious fever after TKA prolongs the time of antibiotic use and hospital stay. Our results demonstrated that the nomogram may facilitate to predict the individualized risk of NIF occurrence within 7-day by intraoperative blood loss, postoperative drainage fluid volume and frequency of blood transfusion.

Keywords: total knee arthroplasty, risk factors, nomogram, fluid homeostasis, non-infectious fever

INTRODUCTION

Total Knee Arthroplasty (TKA) can improve joint mobility, correct deformities and restore joint function, and is recognized as the best treatment option for end-stage osteoarthritis (OA) (1–3). With the improvement of the quality of life for OA patients, the demand for knee replacement has greatly increased (4). In the perioperative management of this surgery, postoperative fever has always been a concern (5, 6). Infectious fever (IF) has been paid much more attention by scholars whereas non-infectious fever (NIF) has much less (7). In fact, non-infectious fever, majority of the fever after arthroplasty, is common in clinical practice (8). Non-infectious fever usually refers to the negative bacterial culture of blood, urine, sputum and joint cavity puncture fluid accompanied by fever symptoms (9). Limited studies have found that non-infectious factors such as tissue damage, drug and blood transfusion reactions, anemia, and deep vein thrombosis can all stimulate the body's release of inflammatory mediators and increase body temperature, but the primary and secondary relations of various factors is still unclear (10). Moreover, there are currently no reliable markers to predict the prognosis of NIF.

Clinically, patients with postoperative fever may prompt expensive invasive tests to determine whether it is an infection, but studies have shown that 76–98% of patients have negative test results (11). It can be seen that non-infectious fever is the main body of fever after TKA, and current research focuses on infectious fever, and there is no relevant research on the occurrence of non-infectious fever and its risk factors. By analyzing the risk factors of non-infectious fever after TKA, the perioperative management plan for elective surgery can be optimized, the occurrence of postoperative fever can be reduced, and the patient's prognosis can be improved.

Connecting with the practical situation, this paper probes into the easily monitored risk factors, which could affect fluid balance and blood volume, like intraoperative blood loss, blood transfusion and postoperative drainage fluid volume. These factors correlated significantly with fluid homeostasis of the organism, a key factor in maintaining thermoregulatory capacity (12, 13).

Therefore, the clinical data of patients undergoing primary unilateral knee replacement in our hospital were collected retrospectively in this study, aiming to clarify the risk factors for non-infectious fever of primary unilateral TKA, and constructed an easy-to-use nomogram for the risk of occurrence.

METHODS

Participants

From July 2018 to December 2019, 183 patients undergoing knee replacement were admitted to the Department of Orthopadics and Traumatology of the First Affiliated Hospital of Zhejiang Chinese Medical University.

Inclusion criteria included: (1) Diagnosed as knee osteoarthritis; (2) Using artificial knee joint replacement or total knee replacement; (3) First unilateral surgery; (4) Postoperative chest radiograph, hematuria, articular cavity puncture and other examinations showed no obvious signs of infection. *Exclusion criteria* included: (1) Patients undergoing unicondylar replacement surgery; (2) Severe perioperative complications, such as myocardial infarction, stroke, diffuse intravascular coagulation disorder, shock or pulmonary embolism, etc.; (3) Incomplete case data records.

Data Collection

Baseline Data and Drug Use Before TKA

Gender, age, diagnosis, past medical history (hypertension, diabetes, hyperlipidemia, cerebrovascular disease, etc.), preoperative chest radiograph, blood routine, urine routine and medication use (antibiotics, non-steroidal anti-inflammatory analgesics).

Operation Record

Surgeon, operation time, operation duration, prosthesis company, intraoperative blood loss, and blood transfusion.

Stay of Hospital, Postoperative Complications, and Related Parameters

Total length of hospital stay, postoperative complications (arrhythmia, myocardial infarction, stroke, diffuse intravascular coagulopathy, shock or pulmonary embolism, etc.), postoperative drainage fluid volume, postoperative body temperature and duration of antibiotic use.

From the day after the operation to the 7th day, the nurse used an infrared tympanic thermometer to collect and record the patient's body temperature. The temperature is measured at least 4 times a day (6:00, 10:00, 14:00, 18:00). In addition, this study defines non-infectious fever as: the body temperature measured at any point within 7-days after surgery is equal to or higher than 38.0°C, and negative chest x-ray, urine culture, blood culture, or other interventions included joint aspiration, Doppler ultrasound, or chest computed tomography (14).

The study was approved by the Ethics Committee of the First Affiliated Hospital of Zhejiang Chinese Medical University (Ethical approval ID: 2018-KL-018-01).

Statistics

Data were analyzed using Statistical Package for Social Sciences (SPSS Windows version. 21.0; SPSS Inc., Chicago, IL., USA) R statistical software (version 3.3.3, https://www.r-project.org). Combined with the normal test chart, Kolmogorov-Smirnov (K-S) results are used to determine whether the measurement data obey a normal distribution. Normally distributed measurement data is represented by the Mean ± Standard Deviation (M ± SD), and skewed distribution measurement data is represented by the Mean (25 percentile, 75 percentile), that is, M (P25, P75). For comparison between groups, independent-sample *t*-test and Mann-Whitney U test were used for measurement data according to whether they obey normal distribution, and chi-square test was used for count data. For the variables with statistical significance, the two-class single-factor Logistic regression was used to analyze the related independent risk factors. Receiver operating characteristic (ROC) curves, including the area under the areas under the curves (AUC) and its 95% confidence

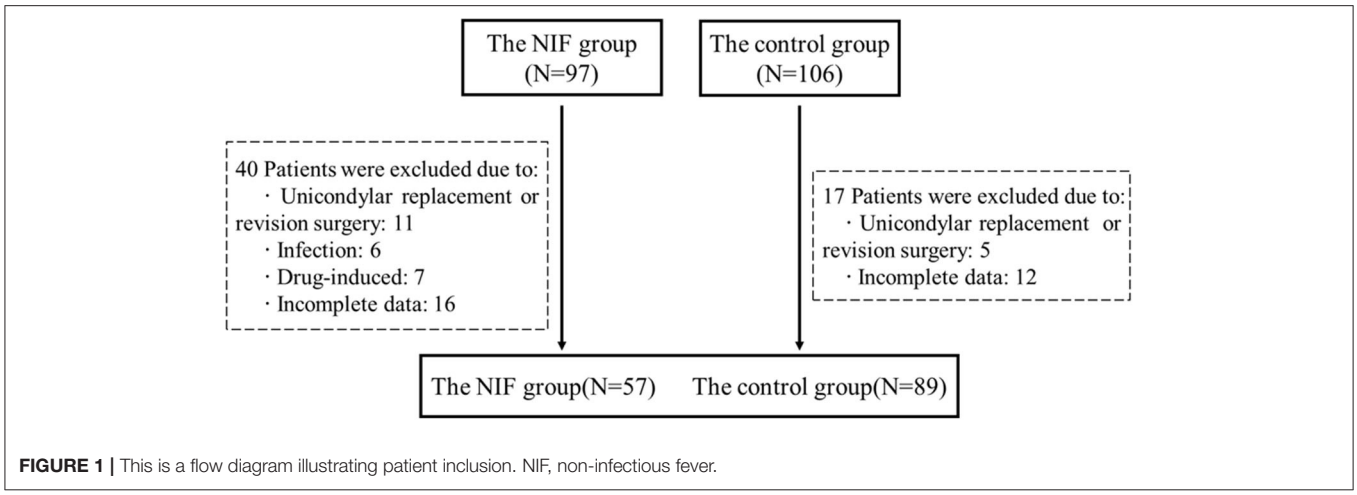

FIGURE 1 | This is a flow diagram illustrating patient inclusion. NIF, non-infectious fever.

TABLE 1 | Comparison of relative factors between the non-infectious fever group and the control group after total knee arthroplasty.

Characteristic	The non-infectious fever group (*N* = 57)	The control group (*N* = 89)	Statistics	*P*-value
Gender (male/female)	9/48	23/66	2.052	0.152
Age	66.36 ± 8.64	66.93 ± 9.09	−0.373	0.710
Hypertension	30	44	0.142	0.707
Diabetes	9	16	0.117	0.732
Operation duration (min)	193.95 ± 45.264	196.01 ± 41.678	−0.282	0.778
Intraoperative blood loss (ml)	363.33 (200, 500)	270.78 (150, 400)	−2.780	*0.005**
Postoperative drainage fluid volume (ml)	259.73 (100, 280)	151.30 (80, 170)	−4.822	*0.001**
Blood transfusion	32 (56.14%)	37 (30.33%)	2.958	0.085
Frequency of blood transfusion (≥2)	12 (21.05%)	5 (5.61%)	8.046	*0.005**
Duration of antibiotic use (day)	8.87 (4, 9)	5.52 (4, 7.5)	−2.429	*0.015**
Total length of hospital stay (day)	26.12 ± 9.517	23.34 ± 6.635	2.075	*0.04**

**Significant at α level P < 0.05.*

interval (95% CI), were analyzed to evaluate the performance of prognostic prediction. The optimal threshold for each selected factor and combined index was determined when the Youden index achieved the highest value (15). Based on the differences, the optimal model was selected, and then parameter estimates of this model were then used for constructing a nomogram using the "rms" package (16). Statistical significance was set at $\alpha = 0.05$.

RESULTS

Verified the 203 selected participants, 16 patients underwent knee unicondylar replacement or revision surgery, 13 patients had postoperative fever caused by specific drugs for osteoporosis or infection, and 28 patients had incomplete data. Finally, 146 patients were included in this study (**Figure 1**).

Clinical Characteristics of Study Subjects

Demographics are available in **Table 1** and are summarized here. The mean age of participants was 66.71 ± 8.89 years (range, 44–81 years); the majority of participants were female (78.08%, 114/146) and male (21.91%, 32/146); 57 (39.04%) patients experienced NIF. According to the presence or absence of the primary endpoint, the patients were categorized into the non-infectious fever group (57 patients) and the control group (89 patients). There was no difference in the demographic characteristics between the two groups for age, gender or comorbidities.

Intraoperative blood loss, postoperative drainage fluid volume, frequency of blood transfusion, duration of antibiotic use and total length of hospital in the control were significantly different from those in the NIF group, however, blood transfusion and operation duration were similar.

Risk Factors of NIF Occurrence

Then, we performed further univariable logistic analysis using the factors with a $P < 0.05$ in the comparison between groups. Results of the univariable logistic regression analysis indicated that intraoperative blood loss (OR, 1.002; 95% CI, 1.000–1.0004), postoperative drainage fluid volume (OR, 1.003; 95% CI, 1.001–1.006) and frequency of blood transfusion ($n = 1$; OR, 0.227;

TABLE 2 | Univariate logistic regression analysis of risk factors.

Covariates	*P*-value	OR	95%CI		OR(95%CI) plot
			Lower	Upper	
Intercept	0.336	0.503			
Intraoperative blood loss	0.030*	1.002	1.000	1.004	
Postoperative drainage volume	0.014*	1.003	1.001	1.006	
Frequency of blood transfusion	0.021*				
i 1	0.016*	0.227	0.068	0.757	
≥2	0.300	0.505	0.139	1.838	

*95% CI, 95% confidence interval. *P < 0.05.*

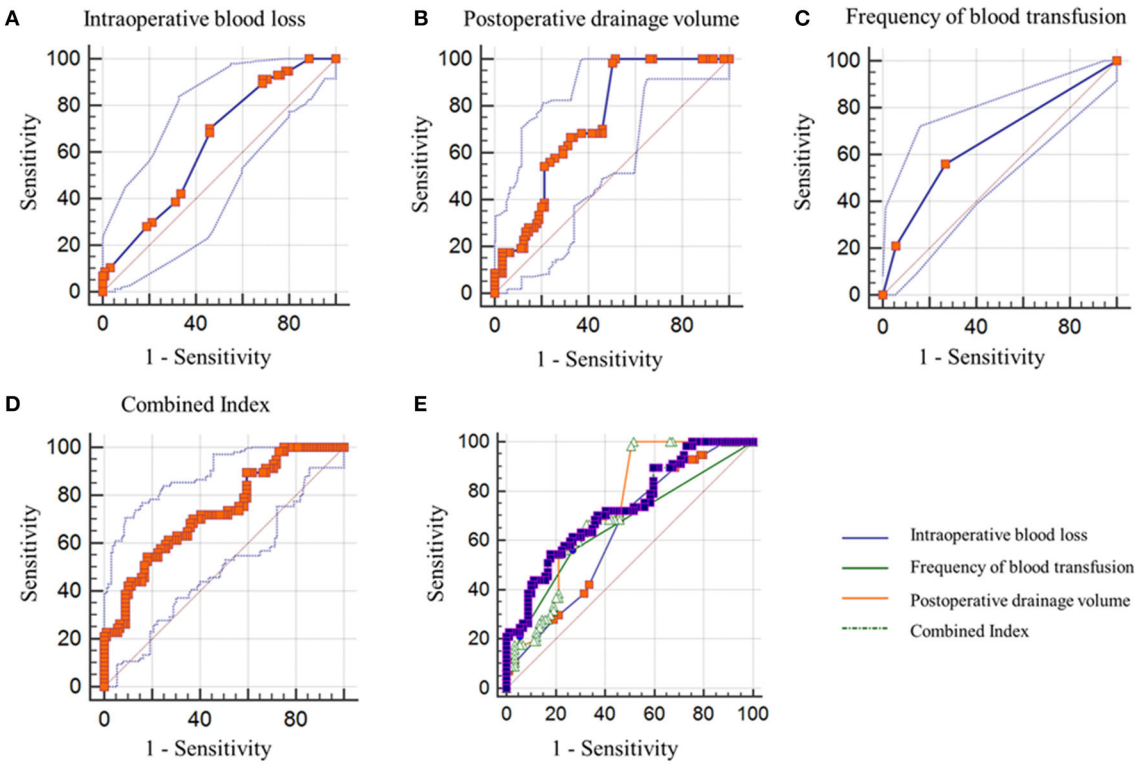

FIGURE 2 | ROC curve analysis using the intraoperative blood loss **(A)**, postoperative drainage fluid volume **(B)**, frequency of blood transfusion **(C)**, and Combined Index **(D)** for predicting the 7-day endpoint. Combined Index was chosen as the optimal model **(E)**. ROC, receiver operating characteristic.

95% CI, 0.068–0.757) were independent risk factors of NIF occurrence, and display the results with a forest map (**Table 2**).

Predictive Performance of the Intraoperative Blood Loss, Postoperative Drainage Fluid Volume, Frequency of Blood Transfusion and Combined Index

ROC curve analysis was used to analyze the predictive performance of the intraoperative blood loss, postoperative drainage fluid volume, frequency of blood transfusion and Combined Index (**Figure 2**). The optimal cut-offs and corresponding sensitivity and specificity are listed in **Table 3**. As expected, Combined Index yielded an AUC of 0.731 (95% CI: 0.651–0.801; $P < 0.0001$) with 54.39% sensitivity and 82.02% specificity, suggesting that the prognostic model had good sensitivity and specificity in predicting patients 7-day endpoint.

Nomogram Construction

The predictive nomogram that incorporated the above independent risk factors was developed and is depicted in **Figure 3**. For the Clinical medical and nursing staff, the plot was available to locate a patient's intraoperative blood loss, postoperative drainage fluid volume and frequency of blood transfusion in each axis; to draw a line straight

TABLE 3 | Predictive performance of the intraoperative blood loss, postoperative drainage fluid volume, frequency of blood transfusion and Combined Index.

Variables	Cut-off	AUC (95% CI)	Sensitivity	Specificity	*P*-value
Intraoperative blood loss	0.2411	0.635 (0.551–0.713)	70.18%	53.93%	*0.0028**
Postoperative drainage fluid volume	0.4831	0.736 (0.657–0.806)	100%	48.31%	*<0.0001**
Frequency of blood transfusion	0.2917	0.658 (0.576–0.735)	56.14%	73.03%	*0.0001**
Combined Index	0.3641	0.731 (0.651–0.801)	54.39%	82.02%	*<0.0001**

*AUC, areas under the curves; 95% CI, 95% confidence interval. *P < 0.05.*

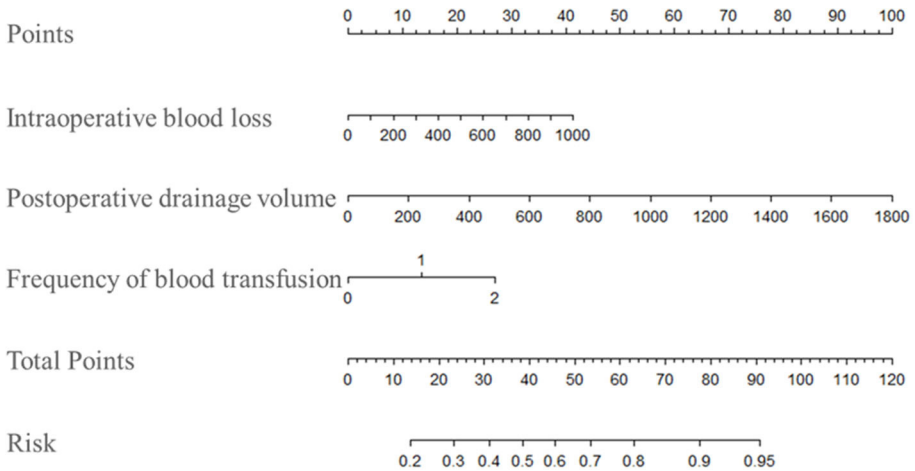

FIGURE 3 | Nomogram plot of NIF probabilities within 7-day was demonstrated. NIF, non-infectious fever.

upward to the point axis and sum up the total points; and then to draw a line straight downward to determine the patient's risk for non-infectious fever of primary unilateral TKA. For example, a patient with a 600 ml intraoperative blood loss (25 points), 800 ml postoperative drainage fluid volume (45 points) and one time blood transfusion (15 points) underwent primary unilateral TKA, his total occurrence points were 75, with an approximated 7-day non-infectious fever occurrence probability of 88%. The ROC curve depicted in **Figure 2D** shows that derived nomogram performed well when compared to the actual results (AUC = 0.731).

DISCUSSION

To the best of our knowledge, this is the first study to explore the occurrent risk factors and construct an easy-to-use nomogram for NIF. This study retrospectively analyzed 146 patients after TKA, 57 patients developed non-infectious fever after surgery, the incidence was 39.04%, which was in line with the previous literature reports of 40%-50% (10). And the study clarified the harm of fever to patients, including prolonging the hospital stay of patients after TKA and the duration of antibiotic use. In addition, clinical observation found that non-infectious fever can cause panic in patients, affect doctors' clinical judgment or other interventions may have been performed.

Compared with non-infectious fever, transient postoperative hyperthermia has self-healing tendency, will not repeat, and is easy to be controlled by preventive antibiotics, However, non-infective fever is characterized by persistent POF and negative CXR, UC, and BC.

In the present study 11 related factors were included, results of the univariable logistic regression analysis indicated that intraoperative blood loss, postoperative drainage fluid volume and frequency of blood transfusion were independent risk factors of NIF occurrence. This result is similar to the results of Lu et al. (17), Kennedy et al. (18), Ishii et al. (19), and the incidence of fever after TKA is relatively high in cases of body fluid imbalance. However, Pan et al. found that reducing allogeneic blood transfusion may help prevent fever complications, especially in large orthopedic surgery (20). In addition, the amount of fluid drained after surgery is usually related to local vascular damage, wound exudation and metal stimulation. Andres et al. found that the bleeding and exudation of the surgically injured area will stimulate local inflammation, promote tumor necrosis factor, interleukin and other cytokines in the body, promote the production of endogenous heat sources, and cause the patient's body temperature to rise (21).

In addition, the entire research cycle is controlled within 2 years, and operation duration between the two groups were similar, which reduces the variable differences between the two groups to a certain extent and improves the reliability of the

research results. However, there are several drawbacks to this study. First, as a retrospective design, our study has a certain selection bias; Second, as a single-center study, the number of included cases is small; Third, the included factors are still not comprehensive enough, and the relevant parameters of medical records, such as various inspection and laboratory results, are not fully included. Therefore, its clinical value requires further verification.

CONCLUSION

To sum up, non-infectious fever after TKA prolongs the time of antibiotic use and hospital stay, which seriously affects the medical cost after surgery. We developed a nomogram to predict the individualized risk of NIF occurrence by intraoperative blood loss, postoperative drainage fluid volume and frequency of blood transfusion. This nomogram was well-fitted. Our well-fitted nomogram suggests that physicians should pay attention to fluid balance and weigh blood transfusion decisions, which is of great significance to reduce non-infectious fever after TKA.

DATA AVAILABILITY STATEMENT

The data used to support the findings of this study are available from the corresponding author upon request.

ETHICS STATEMENT

The study was approved by the Ethics Committee of the First Affiliated Hospital of Zhejiang Chinese Medical University. Written informed consent from patients/participants was not required for this study in line with national and institutional requirements.

AUTHOR CONTRIBUTIONS

MX and XH: conception and design. MX and PT: administrative support. TX and PT: provision of study materials or patients. NX, MY, and YP: collection and assembly of data. NX, XT, and LX: data analysis and interpretation. All authors manuscript writing and final approval of manuscript.

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Preliminary Study on Immediate Postoperative CT Images and Values of the Modular Polyetheretherketone Based Total Knee Arthroplasty: An Observational First-in-Human Trial

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Background: Total knee arthroplasty (TKA) is now frequently performed and is highly successful. However, patient satisfaction after TKA is often difficult to achieve. Because of the presence of metallic prosthetic knee joints, there is a lack of imaging tools that can accurately assess the patient's postoperative prosthetic position, soft tissue impingement, and periprosthetic bone density after TKA. We conducted a clinical trial of the world's first totally modular polyetheretherketone (PEEK) TKA and determined the bone density values in the stress concentration area around the prosthesis based on postoperative computed tomography data to reconstruct a three-dimensional model of the PEEK prosthetic knee joint after implantation. Based on the model, the overhang of the prosthesis was measured at various locations on the prosthesis.

Methods: All patients who underwent PEEK-based TKA were postoperatively assessed with radiography and computed tomography (CT). Hounsfield units (HUs) for the different components of the quantitative CT assessment were measured separately.

Results: Ten patients (nine female and one male) aged 59–74 (mean 66.9, median 67) years were included. The HU values were as follows: PEEK prosthesis mean 182.95, standard deviation (SD) 4.90, coefficient of variation (CV) 2.68; polyethylene mean −89.41, SD 4.14, CV −4.63; lateral femoral osteochondral mean 192.19, SD 55.05, CV 28.64; lateral tibial osteochondral mean 122.94, SD 62.14, CV 42.86; medial femoral osteophyte mean 180.76, SD 43.48, CV 24.05; and medial tibial osteophyte mean 282.59, SD 69.28, CV 24.52. Analysis of the data at 1, 3, and 6 months showed that the mean PE ($p = 0.598$) and PEEK ($p = 0.916$) measurements did not change with the time of measurement. There was a decrease in bone mineral density in the lateral tibia at 3 months ($p = 0.044$). Otherwise, there was no significant change in bone density in other regions ($p = 0.124$–0.803). There was no overhang in all femoral prostheses, whereas there were two cases of overhang in tibial prostheses. Overhang measurements do not differ significantly across time points. The overhang measurements were not significantly different at all time points ($p = 0.186$–0.967).

Conclusion: PEEK knee joint prosthesis has excellent CT compatibility. The change in periprosthetic bone volume during the follow-up period can be determined using the HU value after CT scan, while the prosthesis position can be assessed. This assessment may potentially guide future improvements in knee prosthesis alignment techniques and artificial knee prosthesis designs.

Keywords: arthroplasty, polyetheretherketone, computed tomography, bone density, prosthetic overhang

INTRODUCTION

Total knee arthroplasty (TKA) is one of the most successful orthopedic procedures for patients with end-stage arthritis, offering the opportunity to restore joint motion and improve the quality of life of older patients with knee osteoarthritis, severe rheumatoid arthritis, and tumors (1, 2). Traditional implants for total knee replacement primarily comprise titanium or cobalt-chromium alloys, forming the femoral and tibial components (1). Despite the decades-long history of success with metallic prostheses, there are still material defects that require improvement. For example, adverse reactions due to metal allergy have been reported after TKA in some patients (3–5).

The prevalence of contact allergy to nickel, cobalt and chromium in the population has been estimated at 13% (20% in women), 2.4%, and 1.1%, respectively (6–8). Eben et al. suggested that complications related to metal allergy are often underestimated, which reaches 29.6% (7). Complications associated with allergy to metal implants include dermatitis, poor wound healing, infection-like reactions, oozing, pain, and loosening (9). Although the mechanism by which metal allergy leads to TKA failure is unclear (10), there is consensus among surgeons to avoid postoperative discomfort, such as joint swelling, skin pruritus, and decreased range of motion (ROM), due to metal allergies.

Conversely, the stress-masking effect of the long-term fixation of metal prostheses cannot be avoided with bone cement fixation, which theoretically leads to the loss of bone volume around the prosthesis, resulting in periprosthetic bone resorption, pathological fractures, and loosening (2). The PEEK implant has a significantly lower stress-shielding effect compared to metal and the strain after implantation is not significantly different compared to intact bone (11). Bone loss due to metal implants is also considered a common side effect of frequent knee replacements (12–14). According to Wolff's law, this would be of great significance in avoiding loss of bone around the prosthesis. The imaging assessment of postoperative periprosthetic infection and aseptic loosening is hindered by the large metallic artifacts in imaging tests such as computed tomography (CT) and magnetic resonance imaging, which greatly limits the early diagnosis of infection and loosening after TKA. It is also difficult to accurately analyze the match of the prosthesis-osteointegration interface, prosthesis boundary, and osteotomy surface boundary after metal prosthesis placement, which may affect the development of high-performance artificial knee joint replacement technology.

Polyetheretherketone (PEEK), which has an elastic modulus more similar to bone than to metals (15, 16), better biocompatibility, and enables osteogenesis around the implant (17), has been used in intervertebral lumbar cages, screws, and cranial patches in orthopedic surgery (18). Moreover, research on PEEK as an artificial knee material has also progressed (19). A clinical trial of PEEK afemoral components and all-polyethylene tibial components has been reported recently (20), but there has been no clinical study about the totally modular PEEK knee joint prosthesis until now.

Our previous animal experiments demonstrated that cemented PEEK-on-highly cross-linked polyethylene (HXLPE) artificial knee joints have good biosafety in goat models (21). PEEK weight-bearing surfaces have better prevention of periprosthetic and contralateral cartilage degeneration than CoCrMo (cobalt-chromium-molybdenum alloy, vitallium) weight-bearing surface microprostheses (22). Bone density examination after PEEK artificial joint implantation showed an early periprosthetic femoral transient mild decrease, whereas no change was observed around the tibial prosthesis (21).

In 2016, Suzhou SinoMed Biomaterials Co., Ltd., China, in collaboration with Solvay, USA, developed the PEEK Knee system. Based on the positive results of the overall bio-completeness, *in-vitro* mechanical strength, and simulated wear experiments of the PEEK Knee system, we provided the PEEK artificial knee joint to 10 patients after obtaining ethical approval from the Shanghai Jiao Tong University School of Medicine, Renji Hospital Ethics Committee (KY2021-025). We performed X-ray, CT, and measurement studies on early prosthesis position, peripheral bone density, cement fixation status, and prosthesis-bone border matching after PEEK implantation to provide reliable methods and basic data for further quantitative imaging analyses for postoperative follow-up.

MATERIALS AND METHODS

The current trial was registered at ClinicalTrials.gov (NCT04927104) in June 2021. We conducted a one-arm parallel clinical exploratory study in adult patients undergoing PEEK TKA from June 2021 to July 2021 at a single center. Written consent for participation in the study was obtained from each patient.

Abbreviations: 3D, three-dimensional; BMD, bone mineral density; BMI, body mass index; CT, computed tomography; CV, coefficient of variation; HU, Hounsfield unit; HXLPE, highly cross-linked polyethylene; MRI, magnetic resonance imaging; PEEK, polyetheretherketone; ROI, region-of-interest; ROM, range of motion; SD, standard deviation; TKA, total knee arthroplasty.

FIGURE 1 | The complete knee prosthesis consists of the PEEK femoral component, PEEK tibial component, and an all-polyethylene bearing. PEEK, polyetheretherketone.

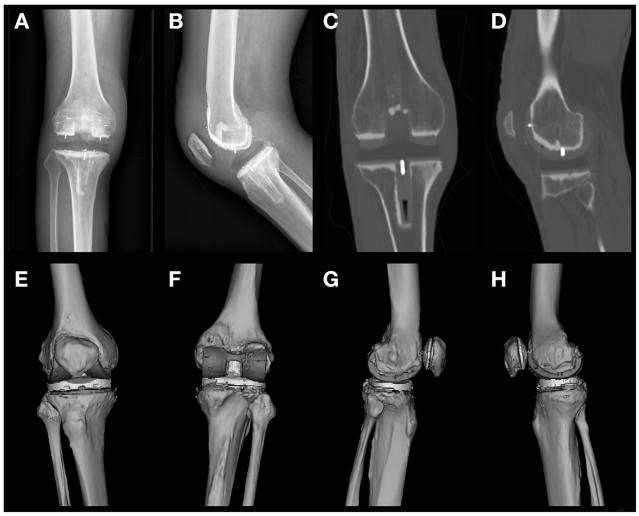

FIGURE 2 | Postoperative X-rays of frontal and lateral views of patient 1 **(A,B)**, images of postoperative CT coronal intermediate and lateral condyle central layers **(C,D)**, and a preview of the 3D reconstructed model **(E–H)** are shown. CT level selection: coronal, sagittal, and axial positions consistent with the joint force lines. The most central metal line was selected according to the position of the central tibial plateau prosthesis and the central lateral femoral condyle. The most central position of the metal wire was selected as the intercept plane **(C)**. Mimics reconstruction software was used to arrange the viewing angles in the order of anterior, posterior, lateral, and medial positions **(E–H)**.

Study Patients

All patients meeting the inclusion criteria were assessed for eligibility by three trained study coordinators. The inclusion criteria were as follows: (1) those aged 55–74 years; (2) patients who were skeletally mature; (3) patients with indications for TKA; and (4) patients whose diseased knee had not undergone TKA surgery. The exclusion criteria were as follows: (1) neuromuscular insufficiency that might have led to postoperative knee instability or gait abnormalities; (2) patients with bilateral knee disease who were expected to require bilateral knee replacement during the study (i.e., within the following 12 months); (3) alcohol or substance abusers; (4) those with a body mass index (BMI) of >35 kg/m^2; (5) patients with severe diabetes mellitus (fasting glucose $>$ 10 mmol/L); (6) pregnant or lactating women; and (7) those with other comorbidities that would have limited their participation in the study, prevented compliance with follow-up, or affected the scientific validity and integrity of the study. Ten patients were included in the first trial, in accordance with the inclusion criteria and clinical study design.

The 10 patients had a mean age of 66.9 (59–74) years, median age of 67 years, mean weight of 62.4 (53–89) kg, median weight of 60 kg, mean height of 158.4 cm, median height of 158.5 (148–175) cm, mean BMI of 24.87 (17.31–33.50) kg/m^2, and median BMI of 24.72 kg/m^2 (**Supplementary Table 1**).

Manufacturing the PEEK Prosthesis

The PEEK artificial knee joint consists of four parts: the femoral condyle (PEEK), tibial tray (PEEK), bearing (HXLPE), and patellar component (HXLPE). The femoral condyle and tibial tray were injection-molded from Solvay PEEK pellets and irradiated for sterilization. The bearing and patellar component were processed from Quadrant highly cross-linked polyethylene material and sterilized using ethylene oxide. The PEEK components and HXLPE bearing (Zeniva PEEK ZA-500, Chirulen HXLPE 1020X) were provided by Suzhou SinoMed Biomaterials Co. Ltd. (**Figure 1**).

Surgical Procedures

All procedures were performed under general anesthesia by the senior author. The surgical technique was the same for all the knee joints. All procedures were performed using an ∼15-cm-long anterior skin incision at the midline of the knee.

Every patella underwent surface replacement, which was essentially guaranteed to be similar in thickness to the preoperative patella. An intramedullary femoral guide and an extramedullary tibial guide were used to adjust the force lines. The size and rotation of the components and bearing were selected using a joint spacer and tensor, respectively. All components were cemented. During each procedure, the surgeon routinely measured the fit of the prosthesis relative to the osteotomy margin after bone removal. The intraoperative C-arm X-ray machine revealed a good prosthesis position.

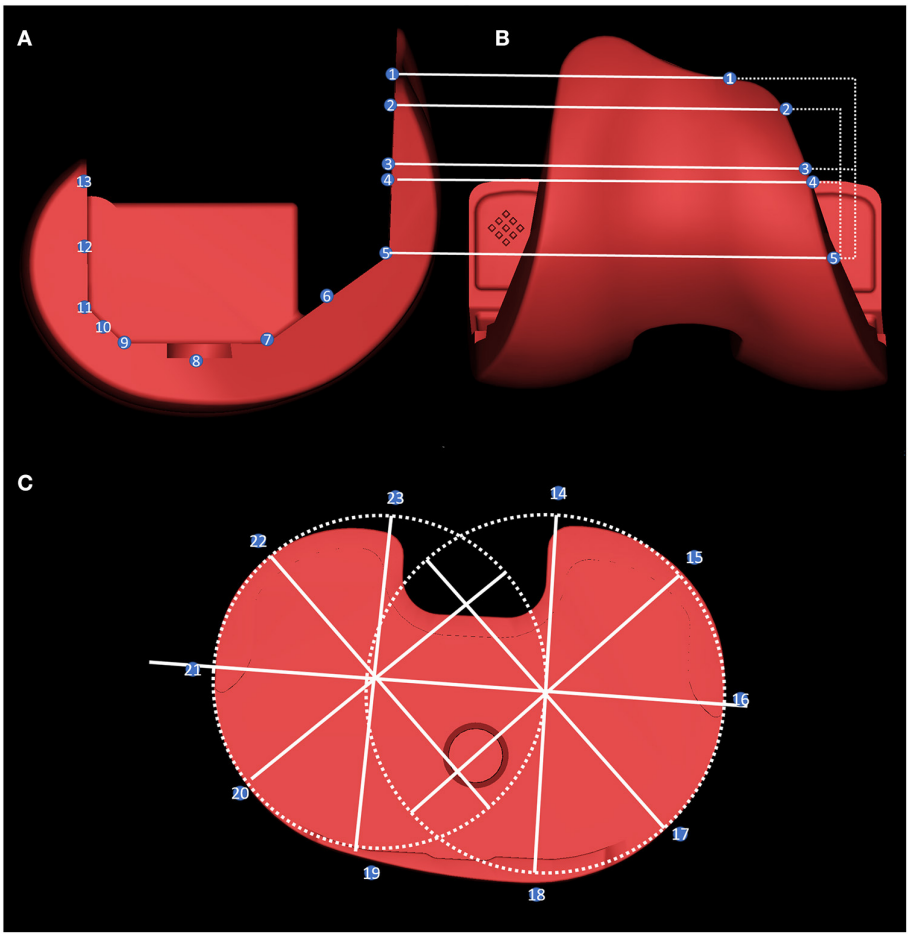

FIGURE 3 | The overhang measurement method. The femoral side was measured by taking the five planes of the prosthesis, the midpoint of each plane, and the length of the prosthesis and the bone-implant bed on the horizontal line of the inner and outer edges of points 1–13 **(A,B)**. For tibial overhang measurement: two external tangential circles were made at the interior and lateral edge of the prosthesis, and the difference between the length of the prosthesis and the bone-implant bed was measured every 45° on these radii at points 14–23 **(C)**.

Radiographic Evaluation

Patients underwent preoperative radiography, CT, and X-ray postoperatively. The specific imaging systems used were the DigitalDiagnost (Philips, Amsterdam, Netherlands) for X-rays and uCT 780 (United Imaging Healthcare, Shanghai, China) and Optima CT680 series (GE Healthcare, Chicago, IL) for CT. We performed detailed imaging evaluations on 10 cases measured at 1 month, 10 cases at 3 months, and seven cases at 6 months.

The three-dimensional (3D) model reconstruction was based on different window widths for different tissues according to the data obtained from CT observation by Mimics version 21.0.0.406 (Materialise, Leuven, Belgium). The specific parameters were as follows: PEEK material, 120–220 Hounsfield unit (HU); bone and bone cement, 220–2,000 HU; and HXLPE,−100-−60 HU. The sketch obtained was the 3D reconstruction model shown in **Figure 2** and **Supplementary Figures 1**–**9**.

Tiny particles that are not reconstructed from bone tissue, metal and cement were defined as noise. The location of these noises is often outside the bone tissue and joint prosthesis, so their removal does not affect the measurement of the prosthesis position. The stereolithography file prosthesis models obtained from the manufacturer were directly matched and superposed for the assembly of the models used in **Figures 3**, **4**, in a manner similar to that previously reported (23).

The methods for measuring the HU values of the PEEK prosthetic stem, HXLPE bearing, and osteophyte are shown in **Figure 5**. We measured density data at 1, 3, and 6 months. Weasis Medical Viewer was used to measure the HU values of the HXLPE bearing and the PEEK tibial prosthetic stem in a postoperative CT coronal view of the selected area. The region-of-interest (ROI) was encircled using the circle tool while ensuring that no non-tissue of interest was involved, and the software automatically generated the average HU values in the area.

According to the results of previous pre-experiments (21), the HU values of these two areas are relatively stable and not easily disturbed by metallic artifacts or bone cement. The lateral and medial condyles were selected in the sagittal superior sagittal position (the midpoint of the metal positioning line), and the

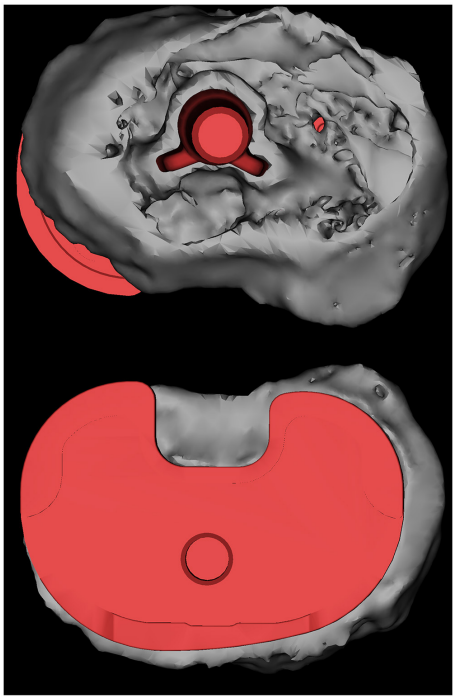

FIGURE 4 | The results of the 3D reconstruction of a patient are shown, with the HXLPE bearing, patella and patellar prosthesis, femoral stem, and a part of the tibial stem and fibula removed. The prosthesis was superposed by the corresponding type of prosthesis, and the placement of the prosthesis was determined by matching the results of the previous 3D reconstruction. A tibial plateau prosthesis with a posteromedial overhang is shown. HXLPE, highly cross-linked polyethylene.

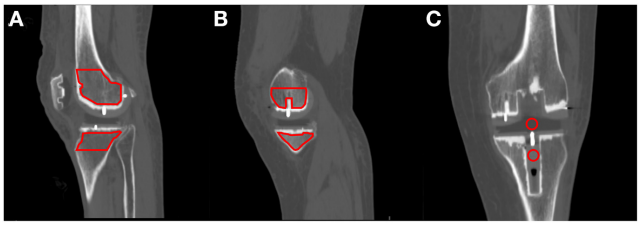

FIGURE 5 | The CT density measurement method. In the sagittal position, the lateral and medial condyles were selected centrally (midpoint of the metal alignment line), and the cancellous area was encircled using the Weasis polygon tool **(A,B)**. The HU values of the HXLPE bearing and the PEEK tibial prosthesis stem (stem) were selected in the coronal position **(C)**. The ROI is distributed up to the highest area of the femoral prosthesis to the joint line a, and the lowest area of the tibial plateau is visible on CT to the joint line. CT, computed tomography; HU, Hounsfield unit; HXLPE, highly cross-linked polyethylene; PEEK, polyetheretherketone; ROI, region-of-interest.

osteophyte area of the polygon tool was used to circle the area from the highest to the joint line of the femoral prosthesis and the area from the lowest to the joint line visible on the medial tibial plateau. The software automatically generated the HU values within the area.

The method of measuring the overhang of each component of the prosthesis is shown in **Figure 3**. Before measurement, the prosthesis within the reconstructed model was replaced with an engineered prosthesis model to obtain more accurate edge measurements. **Figure 4** shows a schematic diagram of the femoral and tibial overhang measurement methods. The overhang was measured on the femoral side by taking the five plane turning points of the prosthesis, the midpoint of each plane, and the position of the inner and outer edges of the upper edge of the prosthesis.

The length of the prosthesis and bone-implant bed on the horizontal line was measured on the condyles of the femur, where points 1, 2, 5, 7, 9, 11, and 13 were the locations of the turning points of the union surfaces of each facet prosthesis (**Figure 3A**). Moreover, points 3, 4, 6, 8, 10, and 12 were the locations of the midpoints between each turning point of the prosthesis on the anterior femoral condyles. Point 3 was the midpoint of points 1 and 5, while point 4 was the midpoint of points 2 and 5.

When measuring the lateral tibial overhang, the circles tangential to the lateral edges of the two platforms were drawn on the medial and lateral platforms. The centers of the two circles were connected as the transverse axis of the prosthesis. Moreover, a radius was drawn at the center of the two circles at 45°, and the length of the prosthesis and the bone-implant bed was measured on these radii at points 14–23 (**Figure 3B**). The bone exceeding the prosthesis was recorded as positive, and the opposite was recorded as negative. The specific measurements are listed in **Supplementary Tables 2**, **3**.

Statistical Analysis

Grayscale data were read using Weasis version 3.7.1, and the length data of the overhang on each radial were read using Mimics. All data were retained to two decimal places. The means, standard deviations (SD), medians, and variability were calculated using SPSS version 26 (IBM Corp., Armonk, NY).

To minimize observational bias, two independent investigators repeated all imaging measurements at 2-week intervals. Intraclass correlation coefficients were used to assess intra- and interobserver reliabilities for all measurements. In this study, the intraclass correlation coefficient values for all measurements indicated intra- and interobserver reliabilities >0.8. Therefore, the mean values can be used for analysis.

RESULTS

Radiographs

Postoperative radiographs showed that all bone fragments were cleared, and the joint space was rebalanced. Both the PEEK and HXLPE components showed low radiograph signals in the entire prosthetic knee system. Because of the low contrast, it was relatively difficult to distinguish the prosthesis from the soft tissue on the X-rays. However, the bonding of the cement between the articular prosthesis and the implant bed surface can be demonstrated because of the radiopaque nature of the bone cement. The knee prosthesis has a metal wire for positioning, which was clearly visible on radiographs

and facilitated its intraoperative fluoroscopic examination (**Figures 2A,B**). Misalignment of the metal wires often indicates dislocation of the prosthesis (24).

CT

CT with a window level of 350 HU and a window width of 2,000 HU allowed for clearer visualization of the prosthetic component. Most structures around the knee, including the PEEK and polyethylene components, as well as the femoral and tibial cement sleeves, could be reasonably well-visualized. We recommend that subsequent investigators look at the PEEK prosthetic knee system after implantation in this window width (**Figures 2C,D**).

The PEEK prosthesis value was 182.95 [SD 4.90, coefficient of variation (CV) 2.68] HU, the mean HXLPE value was −89.41 (SD 4.14, CV −4.63) HU, the lateral femoral osteochondral mean was 192.19 (SD 55.05, CV 28.64) HU, the lateral tibial osteochondral mean was 122.94 (SD 62.14, CV 42.86) HU, the medial femoral osteophyte mean was 180.76 (SD 43.48, CV 24.05) HU, and the medial tibial osteophyte mean was 282.59 (SD 69.28, CV 24.52) HU. After our initial exploration, we found that the range of variation in HU values for both HXLPE and PEEK materials in CT testing was in a relatively small range, as described in **Supplementary Figure 10**.

Without the interference of metal artifacts and bone cement, the HU values of PEEK and HXLPE on CT had low inter-patient variability and were comparable, whereas the osteophyte density was more labile. The mean, SD, and variability of 1 month post operation data for all patients are presented in **Table 1**. The 3 and 6 months post operation bone density data are presented in **Supplementary Tables 2**, **3**. In **Supplementary Table 4**, the results of the ANOVA analysis show that there was no significant difference in the overall CT HU value measurements of PE, PEEK, and bone density data we measured from 1 to 6 months, but there was a statistically significant difference in the decrease in bone density of the lateral tibial plateau by 3 months ($p = 0.044$), and there is no longer a significant difference in bone density between 6 and 3 months postoperatively (**Figure 6**, **Supplementary Figures 11A–F**). We are only able to provide partial 6-month follow-up information because the time for follow-up is not yet available. We also found that bone density decreased at 3 months and slightly rebounded at 6 months in all regions, except for the medial femoral BMD, which increased at 6 months, but none of them were statistically different. These results indicated that the CT HU values of the prosthesis components could be used as a reference in subsequent examinations to assess the patient's postoperative acute bone loss.

TABLE 1 | Results of HU measurements for HXLPE, PEEK, and cancellous bone (1 month post operation).

No.	PE	T PEEK	L F	L T	M F	M T
1	−95.50	177.90	176.90	174.50	174.60	421.40
2	−91.50	185.20	214.90	117.50	139.50	252.10
3	−92.50	180.40	167.60	110.40	112.50	168.50
4	−92.30	176.10	169.70	132.70	166.40	227.60
5	−92.30	177.20	252.30	176.80	192.60	301.60
6	−86.10	190.60	256.10	139.00	270.90	310.80
7	−81.80	187.00	276.00	147.20	222.40	342.70
8	−87.70	183.20	164.10	72.10	164.10	292.60
9	−83.90	184.20	129.00	93.40	190.30	270.00
10	−90.50	187.70	115.30	65.80	174.30	238.60
Average	−89.41	182.95	192.19	122.94	180.76	282.59
SD	4.14	4.90	55.05	38.60	43.48	69.28
C.V.	−4.63	2.68	28.64	31.40	24.05	24.52

*HU values for HXLPE, PEEK, lateral femur, lateral tibia, medial femur, and medial tibial cancellous bone were measured on CT. The measurement method is shown in **Figure 3**. HU, Hounsfield unit; HXLPE, highly cross-linked polyethylene; PEEK, polyetheretherketone; F, femoral; T, tibial; SD, standard deviation; CV, coefficient of variation; CT, computed tomography.*

3D Model Reconstruction

The 3D reconstruction model provides a broad view of the frontal, posterior, lateral, and medial aspects of the model. The 3D model provides a cursory view of the prosthetic alignment and generally shows the position of the implant and the match between the prosthetic components. The model reconstruction showed that the components of the prosthetic knee system were well-mounted and accurately aligned with the HXLPE bearing in place and the patella and patellar prosthesis in place (**Figures 2E–H**).

Overhang Measurement

The specific measurement method for the overhang of the prostheses has been described in detail in Section Radiographic Evaluation. Before the measurement, the prosthesis within the reconstruction model was replaced by an engineering prosthesis model to obtain more accurate edge measurements.

The overhang was measured on the femoral side by taking the length of the prosthesis and bone-implant bed on the horizontal line of the five plane turning points of the prosthesis, the midpoint of each plane, and the position of the inner and outer lateral edges of the upper edge of the prosthesis (25). Greater than 3 mm on the femoral side and 1.5 mm on the tibial side were defined as overhang, and vice versa as underhang (25, 26). The specific measurement for 1, 3, and 6 months post operation results are shown in **Supplementary Tables 5–10**. The results of the ANOVA analysis showed that there were no explicit that differences in the measurements at 1, 3, and 6 months, and the results are shown in **Supplementary Table 11** ($p > 0.05$). For reasons previously stated, only partial measurements at 6 months are available.

We did not observe any overhang on the femur bone-implant interface. Two cases of overhang were observed on the tibia bone-implant interface in which case 3 had an overhang in both the medial posterior and lateral posterior angles (2.72 and 2.26 mm, respectively), whereas case 7 had a 4.04-mm overhang in the medial posterior angle. **Figure 4** shows a 3D model of a patient with significant overhang at the medial posterior tibial plateau, which was obtained from the postoperative CT image reconstruction of case 7.

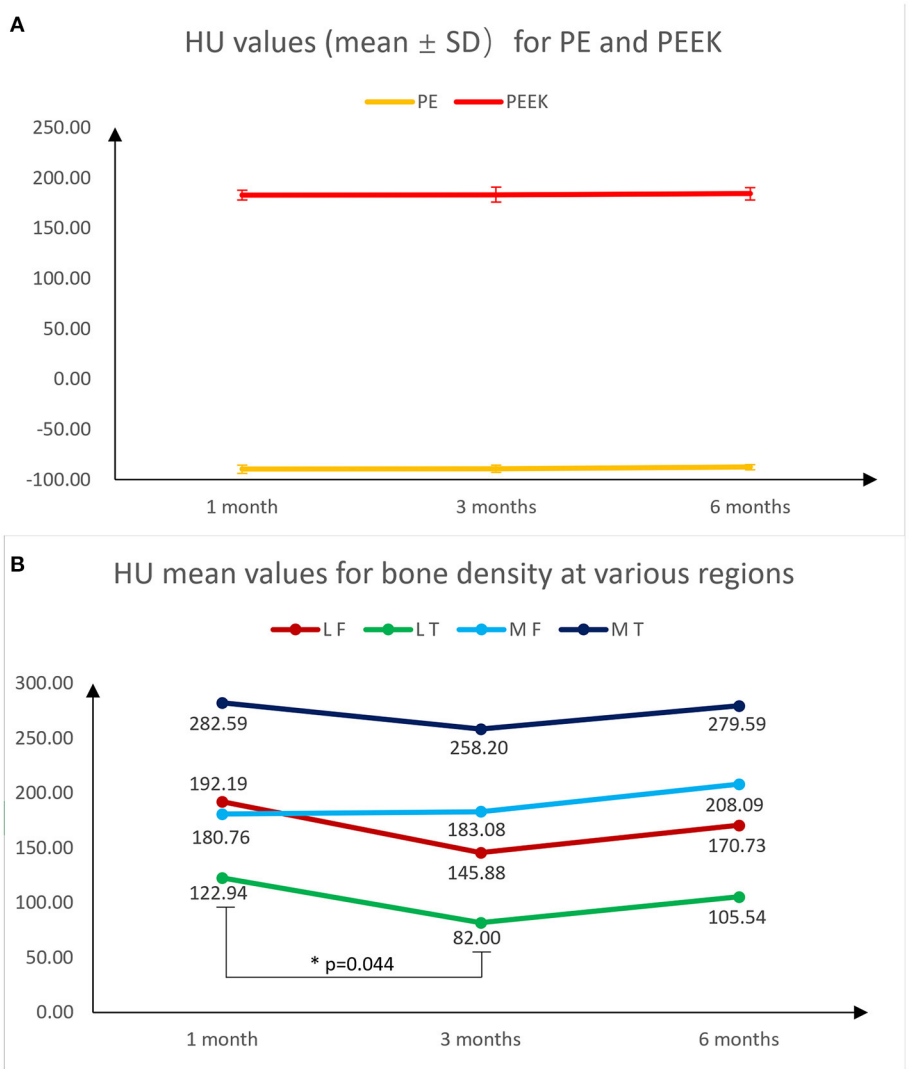

FIGURE 6 | Fold plots of the change in HU values of PE, PEEK, lateral femur, lateral tibia, medial femur and medial tibia measured using CT at 1, 3, and 6 months postoperatively, which reflect the trend of density change in the measured area. Among them, the mean and standard deviation of HU values for PE and PEEK were almost unchanged **(A)**. Except for the medial femur, which did not decrease at 3 months, there was a trend of decreasing bone density at 3 months in the remaining regions, with a statistically significant decrease in the medial tibia. All regions showed a rebound in bone density at 6 months **(B)**.

DISCUSSION

Admittedly, as a very early report of a new technology, this study has some limitations. We included only a small number of participants and no subgroup analyses were performed, such as differences in sex, age and BMI. The density of cement and bone on CT images were similar, making it difficult to distinguish between bone volume and overhang after model reconstruction. During densitometry, the density of the PEEK prosthesis close to the cemented area was prone to shift. As the first clinical trial of a fully assembled PEEK artificial knee prosthesis, the short follow-up period prevented us from evaluating imaging and other aspects of the patient's mid- to late-stage condition. However, our results demonstrate the importance of CT for the postoperative assessment of PEEK prosthetic knees.

As a copolymer compound, in contrast to metals, the biomaterial PEEK has a range of properties superior to those of metals, including reduced allergenicity, lighter weight (27), greater fatigue and chemical resistance (28). The average amount of bone removed in a total knee arthroplasty is about 155 g, while the weight of a metal knee prosthesis with bone cement is about 430 g, so the weight gain of the knee joint after implantation of a metal joint is very significant (29). According to the data provided by the manufacturer, the weight of our prosthesis with bone cement is ∼120 g. Attempts to use polymers for joint prostheses began in the 1980's, with Moore et al. first pioneering attempts to use polyacetal (Delrin) for femoral prostheses (30). However, due to the poor sterilization tolerance of Delrin and its poor fixation stability to bone, research on polyacetal prostheses has since declined. The leaching of formaldehyde is also a hindrance

to its promotion for long-term application *in vivo* (31). The structure of PEEK as a polyetheretherketone gives it excellent chemical resistance, making it extremely inactive and inherently resistant to chemical, thermal, and post-irradiation degradation. Radiation stability data shows that PEEK components can be effectively sterilized by gamma irradiation in air (28). Smooth PEEK prostheses are weakly osseointegrated and require surface modification for osteoinduction to enhance osseointegration, making biofixation of pure PEEK prostheses more difficult to achieve (32). Our choice of a cemented prosthesis in this experiment circumvents this problem and maintains consistency with conventional knee prosthesis fixation methods. Carbon fiber-reinforced PEEK has also been a hot topic of research in the past, but research in this area is slowly declining due to the higher polyethylene wear and still-higher modulus of elasticity associated with carbon fibers (33). We conducted the first-in-human trial of the world's first totally modular PEEK TKA and performed X-ray, CT, and measurement studies on early prosthesis position, peripheral bone density, cement fixation status, and prosthesis-bone border matching after PEEK implantation.

Subjective patient satisfaction after TKA is often lower than orthopedic surgeons' satisfaction with the imaging assessment, and prosthetic overhang and soft-tissue impingement have been suggested as potential causes of postoperative pain and decreased ROM (25, 34, 35). Previous studies have reported that the overhang in knee replacement prostheses may lead to surrounding soft-tissue compression, resulting in pain and poor functional recovery in the medium to long term postoperatively (25, 36–38). Simultaneously, underhang may be associated with tibial osteolysis and prosthesis sinking (39). Current techniques are limited in measuring the impingement site because metal prostheses produce artifacts in CT examinations. Moreover, most overhang measurements after prosthesis fitting are mostly performed in a two-dimensional plane (39), which undoubtedly produces errors in 3D examinations. The projections of both metal and bone are compressed in a finite number of two planes, and that the change in projection due to rotation causes many times many times loosening may be underestimated (39). Our study is the first to use unprocessed raw data for femoral and tibial overhang measurements due to the use of a PEEK prosthetic system without metal CT artifacts.

Mahoney et al. suggested that a >3-mm overhang at any one or more locations of the lateral femoral prosthesis increased the probability of postoperative pain by 90% after 2 years postoperatively (25). Moreover, we set overhangs of >3 mm as a risk factor in our study. However, no >3-mm overhang was observed in this study. No significant overhang was found on the femoral side (≤1.69 mm). On average, the femoral and tibial prostheses were slightly smaller than the osteotomy plane in the measurement direction, with an average overhang of 1.28 and 1.32 mm on the femoral and tibial sides, respectively. The tibial overhang generally occurs at the posterior corner of the tibial osteotomy surface, and the average overhang is 2.4 mm according to the ideal position (26). However, in this study, two patients had overhangs (2.72 and 4.04 mm), and the prosthesis was clearly outside of the osteotomy plane in the 3D model. Moreover, we observed that the underhang was relatively common on the femoral (up to 9.14 mm) and tibial (up to 7.15 mm) sides at the posterior lateral tibial angle. The femoral side had at least one measurement point of underhang in seven cases and more than three measurement points of underhang in four cases, with the largest degree of underhang occurring at point 4 in case 7 at 9.14 mm. The presence of underhang in conventional prostheses correlates with the degree of bone resorption in the corresponding tibia (39, 40), and the use of PEEK prostheses may reduce the occurrence of this phenomenon. These results may guide prosthetic fitting techniques and prosthesis design to reduce soft-tissue impingement and improve postoperative satisfaction in patients who had undergone TKA.

As an another issue of concern, although periprosthetic bone and stress-masking effects do not affect short-term patient satisfaction after TKA, they are a concern in the long term. Long-term osteoporosis not only affects prosthesis longevity but may also increase the risk of periprosthetic fractures (41). Biological fixation has been proposed as an alternative to cemented fixation to reduce osteoporosis following long-term periprosthetic fixation. Conversely, bone density around metal prostheses is difficult to measure, making it impossible to quantitatively analyze the relationship between periprosthetic bone density and late prosthetic failure. Although dual-energy radiography can measure whole-body bone density, it does not represent actual bone density changes in the prosthesis area. A more established method of measuring bone density in specific areas is based on quantitative CT (42, 43). In the past, this method could not be used in patients after TKA because of metal artifacts, but the PEEK prosthesis solves this problem. In this study, the HU values of PEEK, HXLPE, and cancellous bone in the stress concentration area were measured on CT scans. The density values of PEEK and HXLPE were very stable on CT (mean: −89.41 and 182.95 HU, CV −4.63 and 2.68%, respectively) and could be used as a reference value to quantify the bone loss of patients during mid- and long-term postoperative examinations (44), a quantitative localization that is not possible with conventional metal prostheses.

To avoid errors between CT examinations, we sought data that could be used as a reference value on CT images. We found that both PEEK prosthesis and HXLPE bearing maintained low variability between CT examinations. Moreover, we may consider setting parameters to normalize the bone mineral density (BMD) using the grayscale values of PEEK or HXLPE in the future, thus avoiding errors in the examination that may mislead the trend in BMD. Such a method would be useful for the prevention, diagnosis, treatment, and intervention of postoperative osteoporosis in artificial joints, preventing prosthetic loosening and periprosthetic fractures.

In conclusion, the first clinical application of the totally modular PEEK prosthetic joint is a milestone in developing a full-polymer total knee replacement system, offering a better option for patients with metal allergies. The method of local precision assessment may theoretically improve the level and accuracy of imaging assessment of patients after TKA. However, the long-term clinical performance and patient satisfaction of all-polymer joints after implantation in humans still require longer follow-up.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Shanghai Jiao Tong University School of Medicine, Renji Hospital Ethics Committee (KY2021-025). Written informed consent was obtained from individual or guardian participants. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

YW primarily contributed to the study conception and design. ZC, XQ, and YZ performed material preparation, data collection, and analysis. ZC wrote the first draft of the manuscript. All authors commented on previous versions of the manuscript and read and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fsurg.2022.809699/full#supplementary-material

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Combination of Synovial Fluid IL-4 and Polymorphonuclear Cell Percentage Improves the Diagnostic Accuracy of Chronic Periprosthetic Joint Infection

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Background: Synovial fluid biomarkers have been found to improve the diagnosis of chronic periprosthetic joint infection (PJI); however, no "gold standard" exists yet. Interleukin-4 (IL-4) and polymorphonuclear cell (neutrophil) count in the synovial fluid are crucial in mediating local inflammation during bacterial infections and could be valuable biomarkers for PJI.

Methods: This prospective study was conducted to investigate the diagnostic potential of synovial fluid IL-4 (SF-IL4) and polymorphonuclear cell percentage (SF-PMN%) for chronic PJI. A total of 110 patients who underwent revision arthroplasty between January 2019 and October 2020 were enrolled, and 11 patients were excluded. Of 99 patients, 43 were classified as having PJI and 56 as having aseptic failures according to the 2013 Musculoskeletal Infections Society criteria. In all patients, SF-IL4, SF-PMN%, serum C-reactive protein (CRP), and serum erythrocyte sedimentation rate (ESR) were quantified preoperatively. The diagnostic value for each biomarker was analyzed, and optimal cutoff values were calculated.

Results: The patient demographics did not significantly vary. The area under the curve of SF-IL4 and SF-PMN% was 0.97 and 0.89, respectively, higher than that for serum ESR (0.72) and serum CRP (0.83). The combination of SF-IL4 and SF-PMN% provided higher specificity (97.0%) and accuracy (96.0%) when the cut-off values were 1.7 pg/mL and 75%, respectively.

Conclusion: SF-IL4 is a valuable biomarker for chronic PJI detection, and the combination of SF-IL4 and SF-PMN% improved the diagnostic value of chronic PJI, and further studies are needed until its clinical application.

Keywords: synovial fluid, interleukin 4, polymorphonuclear cell percentage, chronic periprosthetic joint infection, diagnosis

INTRODUCTION

Periprosthetic joint infection (PJI) is a catastrophic complication after joint replacement surgery. Total knee arthroplasty (TKA) and total hip arthroplasty (THA) have low incidence rates of 0.3–2.4% and 0.8–2%, respectively (1, 2); however, PJI is the most common cause of revision for failed TKA and the third most common cause for revision for failed THA (3, 4). The cost of treatment of a PJI is three to four times higher than that for primary surgery (5). It is important to preoperatively distinguish between PJI and aseptic failure because it will determine the course of antibiotic therapy and surgical strategies.

Currently, there is no "gold standard" for PJI diagnosis (6). The diagnostic standards for PJI have been refined over the past decades (7–9). Serum C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are highly sensitive markers of PJI, but their lack of specificity limits their diagnostic accuracy (10–12). In recent years, the use of synovial fluid (SF) biomarkers to diagnose PJI has attracted attention because of their low cost, ease of interpretation, and high accuracy (13, 14). Neutrophils are the first cells to produce a defensive response to bacterial infections; therefore, they are suitable candidates to achieve high sensitivity and specificity for PJI detection (15). SF-PMN% has been the basic indicator of SF analysis, but the cut-off value is still controversial (14, 16). Therefore, more valuable biomarkers to detect chronic PJI are needed.

IL-4 is involved in acute and chronic bacterial defense inflammatory responses, but the diagnostic value for chronic PJI is not yet known. IL-4 promotes immunoglobulin isotype switching and regulates the function of macrophages mainly via the Stat6 pathway (17). Serum IL-4 level is upregulated in bacterial infection-induced systemic inflammatory response syndrome and can be a good predictor of infection-related mortality risk (18). Serum IL-4 can be used as an immunological marker for diagnosing active tuberculosis and for monitoring the efficacy of antituberculosis therapy (19). Local administration or expression of IL-4 enhanced the pulmonary clearance of *Pseudomonas aeruginosa in vivo* and decreased mortality following infection (20). In joint aspiration, IL-4 was first secreted by synovial mast cells and then by T helper 2 (Th2) cells (21). Previous studies have demonstrated that the level of IL-4 is elevated in the SF during bacterial infection (6, 22). Therefore, we hypothesized that SF-IL4 may be used as a useful biomarker for chronic PJI detection.

This study was conducted to (1) explore and set an optimal cut-off value for serum CRP, ESR, SF-IL4, and SF-PMN% for chronic PJI diagnosis and (2) improve the diagnostic efficiency of chronic PJI by combining SF-IL4 with other biomarkers.

Abbreviations: PJI, periprosthetic joint infection; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; SF-IL4, synovial fluid interleukin 4; SF-PMN%, synovial fluid polymorphonuclear cell neutrophil percentage; PPV, positive predictive value; NPV, negative predictive value; +LR, positive likelihood ratio; -LR, negative likelihood ratio; DOR, diagnostic odds ratio; ROC, receiver operating characteristic; AUC, area under the curve.

TABLE 1 | The Musculoskeletal society 2013 criteria for defining periprosthetic joint infection.

Periprosthetic joint infection is present if one of two major criteria or three of five minor criteria exists	
Major criteria	1. A sinus tract communicating with the joint; or 2. Two positive periprosthetic cultures with phenotypical identical organisms
Minor criteria	1. Elevated serum C-reactive protein (CRP) AND erythrocyte sedimentation rate (ESR); or 2. Elevated synovial fluid white blood cell (WBC) count OR ++ change on leukocyte esterase strip; or 3. Elevated synovial fluid polymorphonuclear neutrophil percentage (PMN%); or 4. Positive histological analysis of periprosthetic tissue; or 5. A single positive culture

MATERIALS AND METHODS

This prospective study protocol was approved by the institutional ethics board of the First Affiliated Hospital of Chongqing Medical University. Informed consent was obtained from every patient. Patients who underwent revision TKA or THA between January 2019 and October 2020 were enrolled in this study. Patients were divided into chronic PJI group and aseptic failure group based on the 2013 Musculoskeletal Infections Society criteria (2013 MSIS) (**Table 1**) (8). Chronic PJI was defined as the occurrence of PJI symptoms more than 6 weeks after the primary implantation (23, 24). Aseptic failures included aseptic loosening, wear, instability, dislocation, adverse local tissue reactions, and metal allergic reactions (9). To rule out interference with other possible preconditions associated with elevated inflammatory factors, patients with (1) infections of other organs, including pneumonia and urinary tract infection, (2) active rheumatoid arthritis, ankylosing spondylitis, and gouty arthritis, or (3) malignant tumors were excluded.

Data on patient demographics (age, gender, preoperative diagnosis [PJI or aseptic failure and joint involved: hip or knee]) and the survival time of primary implantation were collected. Before revision surgery, peripheral venous blood (3 mL) was withdrawn to test serum ESR and CRP levels. SF (3–4 mL) was sampled for analyzing SF-IL4, SF-PMN%, and culture (48-h routine culture and 14-day prolonged culture; at least three intraoperative tissues were cultured). All biochemical assays were performed at the biochemistry laboratory of the biology technical platform in our institution.

Statistical Analysis

Data were analyzed using SPSS 26.0 (IBM Corporation, TX). Continuous data with a non-normal distribution are presented as the median and interquartile range (IQR). Mann-Whitney U test was used to analyze the statistical significance, and the chi-square test was used to compare the sensitivity and specificity of laboratory test data and categorical data (age, gender, joint involved). $P<0.05$ (two-tailed) was considered to indicate a statistically significant difference. Receiver operating characteristic (ROC) curves and the area under the curve

TABLE 2 | Demographic data for the study population.

Characteristic	Chronic PJI (*N* = 43)	Aseptic failure (*N* = 56)	*P*-value
Age (year)	70.58 ± 5.26	68.98 ± 6.05	0.17*
Gender			
Male	22 (51.2%)	27 (48.2%)	0.77*
Female	21 (48.8%)	29 (51.8%)	
Joint type			
Hip	17 (39.5%)	31 (55.4%)	0.12*
Knee	26 (60.5%)	25 (44.6%)	
BMI (kg/m^2)	22.74 ± 3.91	23.21 ± 4.66	0.59 #
Survival time of implantation (month)	67.91 ± 29.06	76.82 ± 21.55	0.08#

**Chi-square test, #independent Student's t-test; PJI, periprosthetic joint infection.*

TABLE 3 | Analysis of single markers in patients with chronic PJI and aseptic failure.

Marker		Chronic PJI (*N* = 43)	Aseptic failure (*N* = 56)	*P*-value
ESR (mm/h)	Range	7.20–120.00	2.00–58.00	
	Median	35.00	22.00	0.001#
	P25, P75	22.00; 50.00	17.50; 32.00	
	Mean ± SD	42.10 ± 26.23	24.38 ± 12.80	
CRP (mg/L)	Range	5.80–91.20	1.25–28.00	
	Median	21.40	6.75	<0.001#
	P25, P75	13.20; 33.40	3.29; 16.00	
	Mean ± SD	27.31 ± 20.02	9.81 ± 7.75	
SF-IL4 (pg/mL)	Range	1.20–14.10	0.09–2.88	
	Median	3.30	1.10	<0.001#
	P25, P75	2.20; 9.7	0.55; 1.28	
	Mean ± SD	5.57 ± 4.37	1.00 ± 0.53	
SF-PMN%	Range	60.32–96.65	23–89.20	
	Median	87.58	56.95	<0.001#
	P25, P75	83.50, 90.50	53.40, 56.95	
	Mean ± SD	86.15 ± 7.31	59.30 ± 15.53	

SD, standard deviation; #Mann-Whitney U test.

(AUC) were calculated using MedCalc 19.0.7 (Ostend, Belgium). The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were estimated for tested markers. The optimal cut-off value for each maker was computed using the maximized Youden index (sensitivity+specificity-1) method. A higher diagnostic odds ratio (DOR) indicated better discriminatory strength (25).

RESULTS

Baseline Data of the Two Groups Did Not Significantly Differ

Of the 110 patients initially enrolled, six patients were excluded due to "dry aspiration," four patients with active rheumatoid arthritis, and one patient with acute PJI. Finally, 99 patients were included in the study, with 43 (43.4%) in the chronic PJI group and 56 (56.6%) in the aseptic failure group. The baseline characteristics of the two groups were similar (**Table 2**) with no significant difference in the demographics ($P > 0.05$).

SF-IL4 Had Higher Diagnostic Power Than Serum ESR and CRP Levels

As shown in **Table 3**, the median value of serum ESR (35.00 mm/h [7.20–120.00 mm/h]) was higher in the chronic PJI group than in the aseptic failure group (22.0 mm/h [2.00–58.00 mm/h]; $P = 0.001$). Similarly, serum CRP level (21.4 mg/L [5.80–91.20 mg/L]) was higher in the chronic PJI group than in the aseptic failure group (6.75 mg/L [1.25–28.00]; $P < 0.001$). Results showed that the median level of SF-IL4 in the chronic PJI group is higher than that in the aseptic group (3.30 vs. 1.10 pg/mL, $P < 0.0001$). Finally, the median SF-PMN% was higher in the PJI group (87.58%) than in the aseptic failure group (56.95%), with statistical significance ($P < 0.001$).

ROC curves were used to measure the discriminatory strength of the indicators (**Figures 1A–D**). The AUC of SF-IL4 (0.97 [95% CI, 0.92–0.99]) was higher than that of serum ESR (0.72 [95% CI, 0.62–0.84]; $P = 0.0004$), serum CRP (0.83 [95% CI, 0.74–0.90]; $P < 0.0001$), and SF-PMN% 0.89 [95% CI, 0.82–0.95]; $P = 0.053$) (**Figure 1E**). The sensitivity, specificity, PPV, NPV, +LR, −LR, and DOR of these markers are in **Table 4**. The optimal cut-off value for SF-IL4 of 1.7 pg/mL achieved a sensitivity of 93.02% (95% CI, 80.9–98.5%), specificity of 94.64% (95% CI, 85.1–98.9%), and high PPV (93.0%), NPV (94.6%), and DOR (248).

Combination of SF-IL4 With SF-PMN% Had Improved Diagnostic Value for Chronic PJI

Next, we combined SF-IL4 with other biomarkers (**Table 5**). When the cut-off values of SF-IL4 and SF-PMN% were met at the same time, the specificity increased to 97% and accuracy increased to 96%, but the sensitivity decreased to 91% for chronic PJI diagnosis.

DISCUSSION

PJI is still a catastrophic complication of arthroplasty. Chronic PJI patients have poorer function score, lower quality of life, and significantly increased risk of short-term mortality (26–28). The diagnosis of chronic PJI relies on clinical symptoms, physical examination, biomarkers examination, and radiological examination. Because chronic PJI is a type of encapsulated and low-grade infection, it usually causes less extensive systemic inflammatory reactions, sometimes resulting in negative laboratory test results (29). Therefore, the diagnosis of chronic PJI is a challenge, especially without a "gold standard" (30).

SF interleukins play an important role in implant-associated infection. TNF-α, IL-1, and IL-6 are pro-inflammatory cytokines essential for initiating an inflammatory response to infection (31). IL-4 is an anti-inflammatory cytokine that participates in regulating chronic infection and immune processes (32).

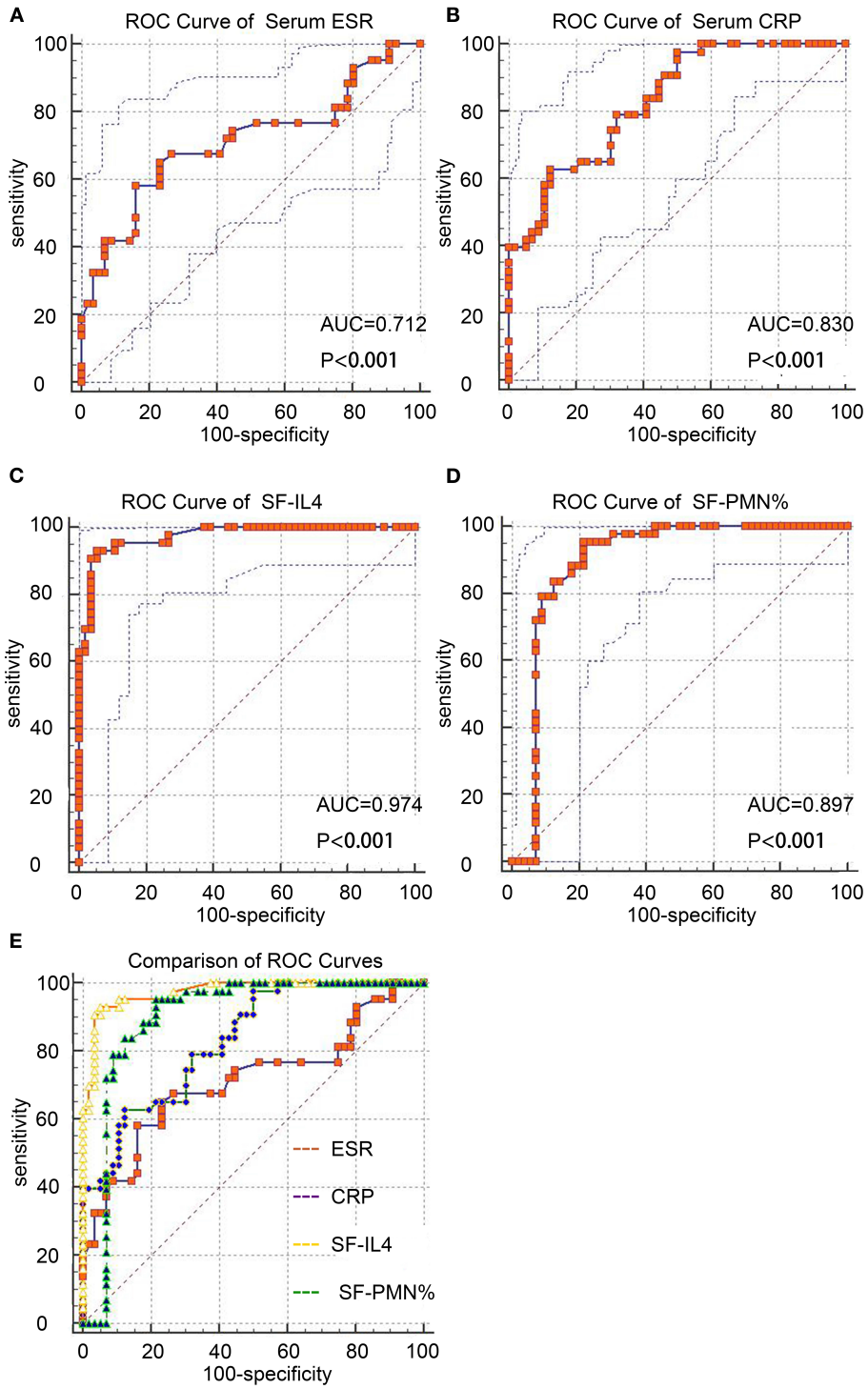

FIGURE 1 | ROC curves of the studied markers for chronic PJI diagnosis. **(A–D)** ROC curves of serum ESR, CRP, SF-IL4, and SF-PMN%. **(E)** Comparison of these four markers.

IL-4 regulates the ratio of Th1/Th2 lymphocyte subtypes in chronic infections (17). It can inhibit the development of biofilms in chronic infections of *Staphylococcus aureus* and promote spontaneous infection clearance (33). IL-4 induces the macrophage switch from the M1 to M2 phenotype, which inhibits osteoclast differentiation (34, 35), and promotes the

TABLE 4 | AUC, cut-off value, and diagnostic value of each marker for chronic PJI.

Test	CRP (mg/L)	ESR (mm/h)	CRP (mg/L)	ESR (mm/h)	SF-IL4 (pg/mL)	SF-PMN%
AUC (95% CI)			0.83 (0.74–0.90)	0.72 (0.62–0.84)	0.97 (0.92–0.99)	0.89 (0.82–0.95)
Cut-off level	10	30	18	34	1.7	75%
Sensitivity (95% CI)	81.4	67.4	62.79 (46.7–77.0)	58.14 (42.1–73.0)	93.02 (80.9–98.5)	95.35 (84.2–99.4)
Specificity (95% CI)	58.9	62.6	87.50 (75.9–94.8)	83.93 (71.7–92.4)	94.64 (85.1–98.9)	78.57 (65.6–88.4)
PPV	–	–	79.4 (65.0– 88.9)	73.5 (59.2–84.2)	93.0 (81.6–97.6)	77.4 (67.3–85.0)
NPV	–		75.4 (67.0– 82.10)	72.3 (64.3 –79.1)	94.6 (85.6–98.1)	95.7 (85.0–98.8)
+LR	–	–	5.02 (2.40– 10.40)	3.62 (1.9–6.9)	17.36 (5.8–52.4)	4.45 (2.7–7.4)
–LR	–	–	0.43 (0.3–0.6)	0.50 (0.3– 0.7)	0.07 (0.02–0.2)	0.06 (0.02–0.2)
DOR	–	–	11.67	7.24	248.00	74.17
Accuracy	58.6	50.5	72.7	68.7	92.9	84.8

AUC, area under the curve; PPV, positive predictive value; NPV, negative predictive value; +LR, positive likelihood ratio; –LR, negative likelihood ratio; DOR, diagnostic odds ratio.

TABLE 5 | Diagnostic value of different combinations of markers for chronic PJI diagnosis.

Combination	SF-IL4>1.7 pg/mL + CRP >18 mg/L	SF-IL4 >1.7 pg/mL + SF-PMN% >75%	CRP >18 mg/L + SF-IL4 >1.7 pg/mL+ SF-PMN% >75%
Sensitivity	0.88	0.91	0.53
Specificity	0.98	0.97	0.98
PPV	0.96	0.94	0.95
NPV	0.75	0.92	0.73
Accuracy	80.1%	96%	78.8%

PPV, positive predictive value; NPV, negative predictive value.

differentiation of B cells and plasma cells, participates in humoral immunity, and exhibits anti-infective properties (36, 37).

Similarly, SF-IL4 has shown promising potential for PJI diagnosis. Gollwitzer et al. reported that SF-IL4 has 93% sensitivity and 85% specificity in PJI, making it better than other serum markers and SF cytokines such as IL-1β and IL-6 (6). However, their study only enrolled patients with *S. aureus* infection, which is more virulent. Therefore, the cut-off value for SF-IL4 was 7.79 pg/mL in their study, much higher than our cut-off value (1.7 pg/mL). Fröschen et al. found that combining SF-IL2, SF-IL4, SF-IL5, SF-IL6, SF-IL12, and granulocyte-macrophage colony-stimulating factor can achieve 100% sensitivity and 88.9% specificity, but these are not universal values as it is expensive to quantify all these markers (38). Consistent with previous studies, we found that the median level of SF-IL4 in the chronic PJI group was 3.30 pg/mL. When the cut-off value was set as 1.7 pg/mL for SF-IL4, the highest sensitivity (93.02 [95% CI, 80.9–98.5%]), specificity (94.64% [95% CI, 85.1–98.9%]), and diagnostic accuracy (94.6% [95% CI, 85.1–98.9%]) were obtained compared with values for serum ESR, serum CRP, and SF-PMN%.

Synovial leukocyte analysis is the basis of the SF test, Synovial fluid leukocyte counts and differentiation ratios have been widely proposed and discussed as secondary diagnostic criteria for chronic PJI. Differences in thresholds exist between different institutions and counting methods. Leukocyte counts are more strongly affected by many factors, especially the use of antibiotics before joint aspiration (15, 39–41) and metallosis, while neutrophil percentages are more stable with infection An SF-PMN% more than 80% has been recommended for the diagnosis of chronic PJI (>6 weeks after surgery) in the 2013 MSIS consensus (8). Zahar et al. found that an SF-PMN% cut-off of 66.1% achieved a sensitivity of 80.6% and specificity of 83.3% for chronic PJI (42). Higuera et al. used an SF-PMN% cut-off of 80% and found the sensitivity and specificity of chronic hip PJI as 92.1 and 85.8%, respectively (16). In the present study, when the optimal cut-off value of SF-PMN% was 75%, the AUC of diagnosing chronic PJI was 0.89 (95% CI, 0.82–0.95), with higher sensitivity of 95.35% (95% CI, 84.2–99.4%) but relatively decreased specificity of 78.57% (95% CI, 65.6–88.4%), respectively.

The 2013 MSIS consensus recommends a CRP cut-off value of 10 mg/L, and at this cut-off, the sensitivity and specificity were 81.4 and 58.9%, respectively, and the diagnostic accuracy was only 58.6% in our study. When the cut-off value of serum ESR was 30 mm/h, the sensitivity, specificity, and accuracy were 67.4, 62.6, and 50.5%, respectively. The unacceptably low sensitivity was coupled with a high number of false negatives. When we set the cut-off values of serum CRP and ESR levels as 18 mg/L and 34 mm/h, respectively, the detection accuracy for chronic PJI improved to 72.7 and 68.7%, respectively.

No single test could provide 100% accuracy for PJI diagnosis. Therefore, a combination of different indicators, with different sensitivity and specificity values, should be used to confirm or rule out the infection under high clinical suspicion (43–46). We found that when the SF-IL4 is >1.7 pg/mL and the SF-PMN% was more than 75%, the specificity and accuracy improved to 97 and 96%, respectively, for chronic PJI diagnosis. However, the combined diagnosis had high specificity but reduced diagnostic sensitivity, which may lead to missed diagnoses in some patients.

This study had some limitations. First, we did not adopt the latest 2018 ICM modified PJI diagnostic criteria, which includes new markers such as serum D-dimer and a scoring system, which is validated to have a higher sensitivity of 97.7% and specificity of

99.5% (47); however, the application of D-dimer for PJI is still controversial (48, 49). Second, we excluded patients diagnosed with active inflammatory arthritis at the time of admission, including rheumatoid arthritis, ankylosing spondylitis, and gouty arthritis. As these patients usually have higher serum ESR, serum CRP, SF-WBC count, and SF-PMN%, the inclusion of this group of patients will affect the accuracy of our results (39), and excluding these patients limits the clinical application of our results due to the limited sample size. Therefore, multicenter studies with larger sample sizes are required to produce more reliable results.

CONCLUSION

When we set the cut-off value as 1.7 pg/mL, SF-IL4 achieved a higher sensitivity of 93.02 and specificity of 94.64% than serum ESR, serum CRP, and SF-PMN%. The combined measurement of SF-IL4 and SF-PMN% improved the specificity to 97% and the diagnostic accuracy for chronic PJI to 96%. However, the cut-off value of SF-IL4 for chronic PJI detection is not yet consensual, requiring more research data to support our conclusion.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Institutional Ethics Board of the First Affiliated Hospital of Chongqing Medical University (Ethics approved number: 20187101). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

NH and WH conceived and designed the study. JH, JW, and BZ analyzed and interpreted the data. JH drafted the article. NH and WH critically revised the paper. All of the authors approved the final submitted version.

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Comparing Revision Total Knee Arthroplasty Stems at a High-Volume Revision Center

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Introduction: Hybrid fixation and fully cemented fixation are commonly used in revision total knee arthroplasty (rTKA). These two techniques are typically done based on surgeon preference and one has not demonstrated superiority over the other. The purpose of this study was to examine if there was a difference in survivorship between the two different techniques.

Methods: A retrospective cohort study of all consecutive patients undergoing rTKA (CPT 27487) from January 1, 2011 to January 1, 2018 at a single academic center was performed. Patients were divided into cemented and hybrid rTKA groups with comparison of patient demographic, clinical and radiological outcomes, reoperation, change in post-operative hemoglobin (HgB), and length of stay (LOS).

Results: A total of 133 rTKA for 122 patients were identified: 30.1% in the cemented and 69.9% in the hybrid groups. There was no significant difference in age ($p = 0.491$), sex ($p = 0.250$), laterality ($p = 0.421$), or body mass index (BMI) ($p = 0.609$) between the two groups. Mean LOS (hybrid 4.13 days, cemented 3.65 days; $p = 0.356$) and change in Hgb (hybrid 2.95 mg/dL, cemented 2.62mg/dL; $p = 0.181$) were not statistically different between the groups. Mean follow up for the hybrid (25.4 months, range 2–114 months) and cemented (24.6 months, range 3–75.5 months) rTKA was not statistically significant ($p = 0.825$). Overall survival rates were 80.9% in the hybrid and 84.6% in the cemented groups ($p = 0.642$).

Conclusions: Hybrid and fully cemented rTKA techniques have similar survival rates at a minimum followup of 2 years. Additionally, in our cohort, age, gender, and BMI were not associated with failure in either group. Furthermore, we did not observe differences in LOS or change in hemoglobin suggesting early postoperative complications may not differ between cemented and hybrid stemmed groups. Continued long-term research is required for defining the best rTKA technique.

Keywords: stem fixation, revision total knee arthroplasty (rTKA), cemented stem, hybrid stem, press-fit stem

INTRODUCTION

Fixation techniques in revision total knee arthroplasty (rTKA) are still controversial. The main concerns in revision total knee arthroplasty (rTKA) arise from bone loss secondary to implant failure and subsequent removal. Revision stems have a history of success in addressing structural concerns when implant fixation is challenging (1–6). Traditionally, stems used for fixation during rTKA are either press-fit with cement in the metaphysis and under the implants in a hybrid technique or are fully cemented (7).

Cemented stems have been noted to have good initial stability with long-term fixation in stems as short as 30 mm (8–11). Additionally, cemented stems may accommodate canals of various deformities, especially in those with pronounced bone loss (12). It is also hypothesized that cemented stems may better seal off the canals and reduce postoperative blood loss. Some potential drawbacks include concern for stress shielding and an increase in bone loss if re-revision is needed (13, 14).

Alternatively, hybrid stems achieve primary fixation through their diaphyseal stem-bone fixation and secondarily with epiphyseal or metaphyseal cement. The stem position can dictate the position of the femoral and tibial components, thus potentially necessitating the use of offset stems. Press-fit stems used for hybrid fixation demonstrate improvements in pain and functional scores and long-term survival in some studies (6, 15–17). However, there are other studies reporting higher tibial stem tip pain, leading to lower knee scores and decreased patient satisfaction. Additionally, press-fit stems are associated with increased rates of periprosthetic fractures (18–21).

Despite long-term use in rTKA, high quality evidence comparing cemented stems to hybrid stems is scarce, making it difficult to differentiate between the two (1, 7, 22, 23). The consensus is that no significant differences exist between cemented and hybrid stems. Therefore, the primary objective of this study is to compare cemented and hybrid stems in rTKA, looking primarily at survivorship at final follow-up. The secondary objective will be to compare demographic factors that may be related to failure, in addition to blood loss and length of stay (LOS).

MATERIALS AND METHODS

This was a retrospective review of prospectively collected institutional data at an academic center with a large revision arthroplasty case load. All consecutive patients undergoing rTKA of both components (CPT 27487) between January 1, 2011 and January 1, 2018 were included. These included patients with cones, sleeves, unlinked constrained, and linked constrained components. Patients were excluded if they did not have both femoral and tibial components revised, did not have both femoral and tibial stem fixation, or the patient was lost to follow-up before 2 years. Medical records and radiographs were evaluated for all patients, and demographics including age, sex, body mass index (BMI), and laterality were recorded for each group.

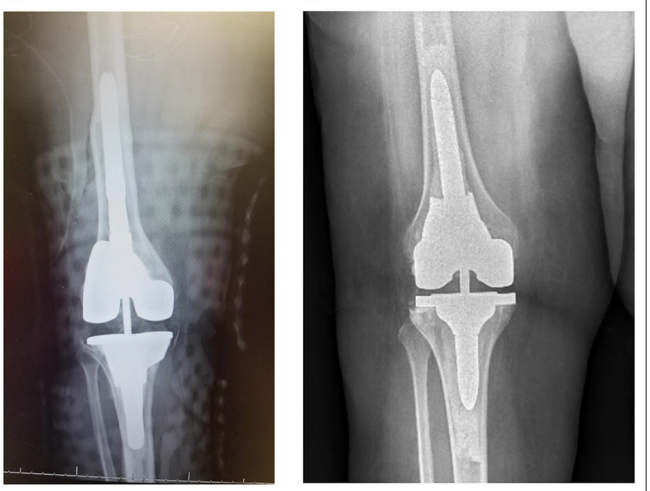

FIGURE 1 | (A) Depicts a hybrid RTKA fixation technique and **(B)** depicts the fully cemented RTKA technique. The hybrid technique has cement only in the metaphysis with cortical engaging stems within the diaphysis. In comparison, the fully cemented technique has cement fixation in both the diaphysis and the metaphysis.

The decision for fully cemented vs. hybrid fixation was determined by the senior surgeon. All the implants were pre-coated with cement prepared with a 4th generation technique to unitize the construct. After appropriate reaming, a cement plug for a 2-cm distal cement mantle was placed for the cemented fixation. The canals were then filled retrograde with cement and pressurized. For the hybrid fixation, diaphyseal reaming continued until the reamer outer diameter matched the inner diameter of the diaphysis. The diaphyseal stem was placed in a "line-to-line" method based on the size of the largest used reamer. Vacuum mixed cement was placed around the metaphyseal portions of the implants and pressurized into the metaphyseal bone, taking care to leave the canal open and free of cement. The hybrid implant was then inserted taking care to pressurize all epiphyseal and metaphyseal cement during implant impaction. Augments and constraints were used on a case-by-case basis when clinically indicated. In both fully cemented and hybrid fixation, the main goals of rTKA were joint line restoration, alignment according to the mechanical axis, a balanced knee, and a well tracking patella. Hybrid fixation and cemented fixation techniques were illustrated in **Figure 1**.

The primary objective was to assess the implant survivorship of cemented vs. hybrid stems. Failure was defined as any surgical re-operation on the rTKA, such as explant, amputation, polyethylene exchange, lysis of adhesions, fracture fixation, extensor mechanism reconstruction, and repeat rTKA. Time to failure between the fully cemented and hybrid rTKAs were compared via Kaplan-Meier plots. BMI, age, gender, and laterality were evaluated for possible correlations with early failures between the two techniques. Secondary endpoints of LOS and change in hemoglobin (HgB) (preoperative subtracted by post-operative nadir) were compared between the hybrid

and fully cemented rTKAs. The secondary objective was to compare change in Hgb and LOS between the two groups for possible correlations with early failures. Patients underwent routine postoperative clinical follow-up.

Statistical analysis was performed using Microsoft Excel (Microsoft Corporation; Redmond, WA). Student *t*-tests were utilized to compare continuous variables between the fully cemented and hybrid rTKAs. Categorical variables were compared between groups with a chi-squared test. A logrank test was used to examine whether survival of the rTKAs was statistically different between the groups. Patient BMI, age, gender, and laterality were compared with student *t*-tests and chi-squared tests between the fully cemented and hybrid fixation groups. Additionally, BMI, age gender, and laterality were compared within the fully cemented and hybrid fixation groups to identify any statistical correlation for failure with student *t*-tests and chi-squared tests. The secondary endpoints (LOS and change in HgB) were also analyzed between the fully cemented and hybrid fixation groups with student *t*-tests to identify any statistical correlation for failure. Statistical significance was set at $p < 0.05$.

RESULTS

A total of 188 rTKA under CPT were identified. Fifty-five knees were excluded, most commonly for being revisions without both femoral and tibial stems ($n = 23$), duplicate patients ($n = 12$), and falling outside the study time period ($n = 10$) (**Figure 2**). Of the 133 rTKAs, there were 40 fully cemented rTKAs (30.1%) and 93 hybrid rTKAs (69.9%).

The patient demographics of the 133 patients can be found in **Tables 1**, **2**. The overall survival rate was 81.8%.; Survival was 82.5% for the cemented cohort and 80.6% for the hybrid cohort which was not statistically significant ($p = 0.642$) (**Figure 3**). Descriptive information for the failed rTKAs is listed in **Table 3**. Age, sex, laterality, and BMI had no association with hybrid or cemented rTKA failure (**Table 2**). In both the fully cemented and hybrid cohorts, failed rTKAs had a significantly longer follow up than the surviving rTKAs (fully cemented $p = 0.014$; hybrid $p < 0.005$).

The overall mean LOS was 4.0 days (range: 0–15 days), with the mean LOS for the cemented and hybrid cohorts being 3.7 days (range: 0–15 days) and 4.1 days (range: 1–13 days) respectively ($p = 0.352$). The overall mean change in Hgb was 2.85 g/dL (range: 0–6.7 g/dL), with that for the cemented and hybrid cohorts being 2.62 g/dL (range: 0–4.7 g/dL) and 2.95 g/dL (range: 0–6.7 g/dL) respectively. Additionally, in the cemented cohort, the mean LOS was 3.1 days (range: 0–15 days) for stems which survived, compared to 5.4 days (range: 2–13 days) for those which failed ($p = 0.087$). In the hybrid cohort, the mean LOS was 4.3 days (range: 1–13 days) for stems which survived, compared to 3.6 days (range: 1–6 days) for those which failed ($p = 0.301$). In the cemented cohort, the mean change in HgB was 2.69 g/dL (range: 0.4–4.7 g/dL) for stems which survived, compared to 2.24 g/dL (range: 0.7–4.6 g/dL) for those which failed ($p = 0.373$). In the hybrid cohort, the mean change in HgB was 2.98 g/dL (range: 0.5–6.7 g/dL) for stems which survived, compared to 2.83 g/dL (range: 0.3–4.9 g/dL) for those which failed ($p = 0.700$).

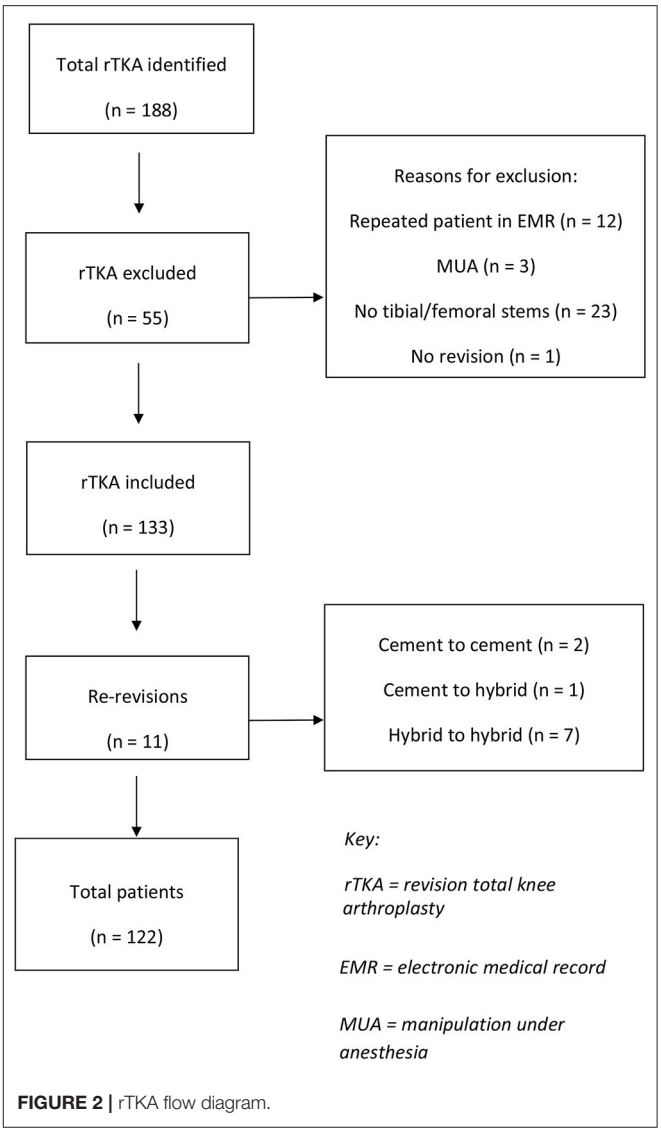

FIGURE 2 | rTKA flow diagram.

DISCUSSION

Choosing between cemented and hybrid stem fixation for revision TKA is a complex decision. One must consider patient bone quality, surgeon preference, and theoretical advantages of a particular fixation technique when choosing between the two techniques. (7, 22, 23) Current research suggests there are no significant differences in outcomes between the two fixation techniques (1, 23). The results of this study also identified no significant difference in implant survival at 2 year follow-up. Additionally, there was no significant difference in LOS or change in HgB between groups. These findings further support comparable surgical outcomes between cemented and hybrid stems.

TABLE 1 | Mean Patient demographics for fully cemented and hybrid cohorts.

	Overall	Cemented	Hybrid	
Age (years)	63.8 (range = 41–87)	63.8 (range = 45–85)	63.8 (range = 41–87)	$p = 0.491$
Sex (male)	47	13	34	$p = 0.653$
Laterality (right)	64	24	40	$p = 0.018$
BMI (kg/m^2)	33.4 (range = 20.9–62.2)	32.7 (range = 21.6–49.6)	33.8 (range = 20.9–62.2)	$p = 0.383$
Follow up (months)	25.8 (range = 2–114)	24.6 (range = 3–75.5)	25.4 (range = 2–114)	$p = 0.825$

BMI, body mass index.

TABLE 2 | Mean patient demographics for survival vs failure in cemented and hybrid cohorts.

	Cement survival	Cement failure		Hybrid survival	Hybrid failure	
Age (years)	64.2	61.7	$p = 0.491$	64.5	60.59	$p = 0.144$
Sex (male)	11	1	$p = 0.250$	28	7	$p = 0.819$
Laterality (right)	20	4	$p = 0.421$	34	6	$p = 0.351$
BMI (kg/m^2)	32.3	33.8	$p = 0.609$	33.7	33.5	$p = 0.918$
Follow up (months)	21.8	38.0	$p = 0.014$	21.3	42.0	$\mathbf{p = 0.005}$

BMI, body mass index. The bold values means statistically significant difference in follow up between hybrid stem survival and hybrid stem failure.

TABLE 3 | Description of Failed Hybrid rTKAs.

Patient	Indication for revision	Cause of revision failure	Age	Sex	Side	BMI (kg/m^2)	LOS (day)	HgB (g/dL)	Follow up (months)
1	Aseptic loosening	Infection	74	F	R	36.0	4	4.8	8.8
2	Infection	Fracture/catastrophic failure at stem junction at osteotomy site	49	M	L	29.8	2	0.9	37.5
3	Malalignment	Loosening/metallosis	62	F	R	30.0	2	3.9	53.5
4	Instability	Instability	63	F	L	26.2	1	1.6	57.5
5	Aseptic loosening	Aseptic loosening	59	F	L	38.2	4	1.9	114.0
6	Infection	Infection	55	F	R	45.1	3	1.7	58.0
7	Midflexion instability	Arthrofibrosis requiring poly exchange at outside hospital	72	F	L	36.9	4	0.7	24.5
8	Malrotation	Malrotation/patella maltracking	47	M	L	41.7	4	4.1	40.5
9	Instability	Infection	60	M	L	36.0	2	3.9	16.3
10	Femoral fracture	Infection	60	F	L	26.3	2	1.2	28.0
11	Infection	Infection	63	M	R	30.7	4	4.8	15.0
12	Infection	Infection	74	F	L	25.8	6	3.6	24.5
13	Infection w/extensor mechanism repair	Infection	75	M	R	33.5	5	3.7	23.5
14	Aseptic loosening of tibial component	Infection	69	F	L	32.9	5	n/a	85.5
15	Pain	Instability	41	F	L	32.3	3	3.3	52.0
16	Infection	Infection	48	M	R	42.2	4	0.3	27.3
17	Infection	Infection	59	M	L	26.4	6	4.9	47.8

BMI, body mass index (kg/m)^2; LOS, length of stay (days); HgB, hemoglobin (g/dL); F, female; M, male; R, right; L, left.

This study did not find any difference in survivorship between cemented and hybrid stems at short-term follow up, which is consistent with previously reported data. In 2017, Fleischman et al. analyzed 223 patients and found both techniques had a similar risk of mechanical failure when corrected for covariates (23). Further, a meta-analysis identified neither stem fixation technique to be superior in rates of failure, reoperation, infection, or aseptic loosening (1). Additionally, this study looked at

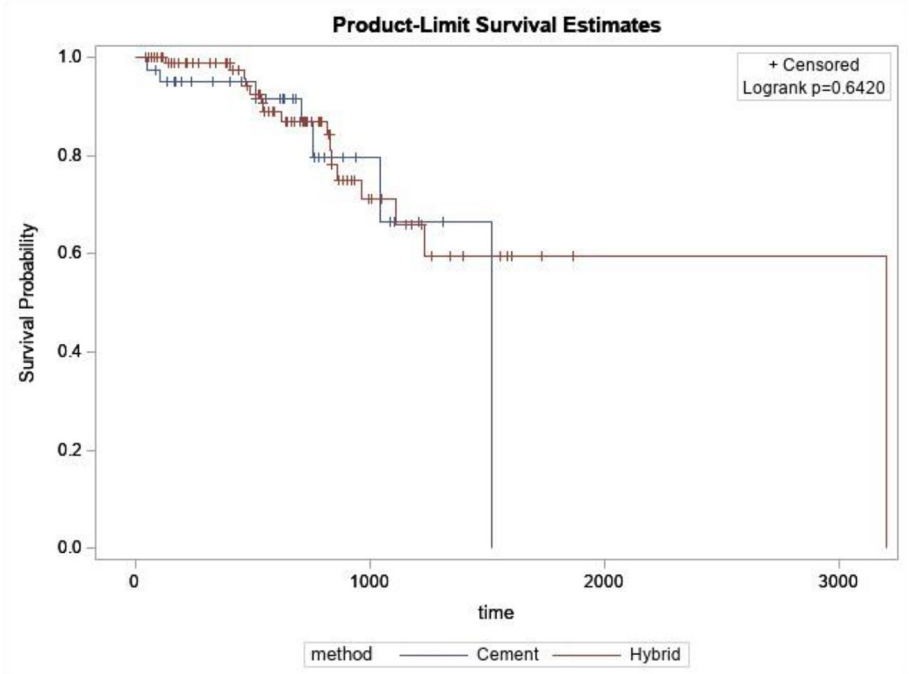

FIGURE 3 | Kaplan Meier survival curves after log-rank analysis.

changes in HgB and LOS as two possible perioperative indicators of early failure. We did not identify differences between the cemented and hybrid cohorts when analyzing the changes in HgB following surgery. While literature on changes in HgB in rTKA is scarce, a prior systematic review on blood loss in revision arthroplasty did not recognize stem fixation technique as a significant contributor to differences in blood loss (24). The mean LOS of 4 days was congruent with a prior study which reviewed 10,604 rTKA cases documented in the NSQIP database. This study identified increasing operative time as the main indicator of increased LOS (25). Further, our study did not find any patient characteristics that impacted implant survival.

The overall failure rate in this study was 18%, which was higher than reported in the literature. However, considering this study included both septic and aseptic revisions, and took place at a tertiary referral center with a complex patient population, we feel this failure rate to be comparable to similar studies that reported failure rates of 33–10% (23, 26, 27). While the bulk of the current literature has determined the two fixation techniques to be similar, there are studies that found the risk of radiographic loosening to be significantly less in a hybrid stem technique (26). However, this study also recognized the difficulty in eliminating selection bias, as it is likely the cemented cohort presented with worse bone quality, and thus, proved a more challenging operation with a lower chance of success.

There are several limitations to the study. Firstly, the study was a retrospective study done at a single institution with short-term follow-up. The design and non-randomized nature may have introduced some selection bias for the two groups. As a tertiary referral center, many of our patients travel from afar and do not follow up past 2 years unless there is an adverse outcome. Thus, we noticed decreasing compliance for continued follow up. Finally, while 133 rTKAs for inclusion is likely underpowered, this number is comparable to those reported in previous literature (26, 28). Subgroup analysis would have strengthened the paper, however, subgroup analysis with the number in our data set would have been small and unlikely to yield a clinically significant, even if statistically significant, result. While multiple implant companies were used in the study, comparison of all types of revision companies and the differences in component mechanisms such as stem size/diameter, polyethylene locking mechanisms, fixed bearing polyethylene, rotating platform, and mechanisms of linked and unlinked constraints, cones, and metaphyseal sleeves would have resulted in small cohorts where a clinically significant comparison would be underpowered. Continued research would be insightful in rTKA. Varus Valgus angle were not recorded as the amount of varus/valgus is depenendent on long leg films from hip to ankle, which was not present in most patients.

Our study has multiple strengths, notably the inclusion of all rTKAs. Many other studies exclude rTKAs that use cones, sleeves, or linked hinge devices. Thus, we believe that our data is more applicable clinically, as the application of metaphyseal fixation or linked constrained can change intraoperatively. Additionally, both septic and aseptic rTKA was included for analysis, while other studies exclude septic revisions (22, 27). Finally, we included multiply revised knees for analysis. Previous studies only analyzed primary to rTKA in terms of failure (22, 28); thus, our results are generalizable to the majority of orthopedic surgeons.

CONCLUSIONS

This study demonstrates that hybrid and fully cemented rTKA have similar overall survival rates in the short-term. When comparing these techniques, there was no association between patient characteristics and implant survival or failure. However, larger, prospective, ideally randomized studies are required to corroborate these findings. Practically, these studies should include rTKAs for any indication, including those with prior rTKA.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

All authors were involved in the conception and design of the study, data collection and analysis and interpretation, and preparation of manuscript.

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Combination of Fusiform Capsulectomy of the Posterior Capsule and Percutaneous Flexion Tendon Release in the Treatment of Fused Knee with Severe Flexion Contracture During Total Knee Arthroplasty—A Report of Six Cases

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Purpose: This clinical research aims to assess the safety and efficacy of a combination of fusiform capsulectomy of the posterior capsule and percutaneous flexion tendon release in the treatment of a fused knee with severe flexion contracture during total knee arthroplasty (TKA).

Methods: A retrospective analysis was performed in three patients (six knees) who had preoperative severe bony fused flexion contracture (>80°) prior to TKA and received a combination of fusiform capsulectomy of posterior capsule and percutaneous flexion tendon release during TKA between January 2016 and December 2019. The range of motion (ROM), knee functional score, postoperative complications, and radiographic results were evaluated.

Result: Three patients (six knees) were enrolled in this study. The mean duration of follow-up was 42.83 ± 15.77 months. The postoperative knee ROM was 100.0 (76.0, 102.75) ($p < 0.01$). The knee society score (KSS) clinical score increased from a preoperative 30.0 (25.0, 36.0) to a postoperative 64.0 (65.0, 78.0) ($p < 0.01$), and the KSS function score increased from a preoperative 0.0 (0.0, 30.0) to a postoperative 55.0 (40.0, 55.0) ($p < 0.01$). No implant loosening, infection, neurovascular complications, or revision were recorded in the cohort until the last follow-up.

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Conclusion: The technique of a combination of fusiform capsulectomy of the posterior capsule and percutaneous flexion tendon release is an effective and safe method during primary TKA for a fused knee with severe flexion contracture.

Keywords: total knee arthroplasty, fused knee with severe flexion contracture, fusiform capsulectomy of posterior capsule, percutaneous flexion tendon release, functional score

INTRODUCTION

Conversion of a severely fused knee to a total knee arthroplasty (TKA) is a challenging procedure with many complications. High incidence rates of various complications (53%–57%) have been reported, such as residual extensor lag and postoperative stiffness (1, 2). The routine techniques for correcting flexion contracture include excessive osteotomy and soft tissue release. However, excessive osteotomy usually cannot repair a severely fused knee in flexion effectively and restore stability without damaging the collateral ligaments and elevating the joint line (3). Posterior capsular release, combined with distal femur resection up to a maximum of 4 mm, has been proven to be effective in the treatment of flexion contracture, but only 5° correction has been achieved after medial soft tissue release and 2-mm additional osteotomy (3, 4). Residual flexion contracture will lead to an excessive requirement of quadriceps force in daily activities such as walking, which can cause aseptic loosening and unsatisfied clinical outcome. Previously, we had introduced a technique of fusiform capsulectomy of the posterior capsule to correct severe flexion contracture during primary TKA (5). In this study, for those with a fused knee with severe flexion contracture and that cannot be corrected by fusiform capsulectomy, we prescribe a combination of fusiform capsulectomy of the posterior capsule and percutaneous flexion tendon release and evaluate the clinical efficacy and safety.

MATERIALS AND METHODS

We retrospectively analyzed patients who had a fused knee with severe flexion contracture (>30°) and received a combination of fusiform capsulectomy of the posterior capsule and percutaneous flexion tendon release during primary TKA between January 2016 and December 2019. The inclusion criteria were as follows: (1) those whose preoperative fused knee with severe flexion contracture was more than 30°; (2) all surgeries were performed by one surgeon (C.W.); and (3) the follow-up period was more than 12 months. The exclusion criteria were as follows: (1) those who had missed providing necessary clinical data and (2) those who failed follow-up treatment regularly. This study was approved by our institutional review board (S2018-018-01), and written informed consent of all patients for data analysis was obtained retrospectively.

The preoperative and postoperative clinical evaluation were performed by two independent observers, including the preoperative and postoperative ranges of motion, knee society score (KSS) clinical score and KSS functional score, and perioperative and postoperative complications. The radiographs of the knee and lower extremities were used to determine the component position changes, limb alignment, and evidence of loosening or osteolysis.

Surgical Procedure

All patients had general anesthesia and pneumatic thigh tourniquets. Cemented knee prosthesis was adopted in all patients. The knees were exposed through the standardized medial parapatellar approach. After removing the osteophytes and releasing soft tissue routinely, the quadriceps oblique cutting technique would be used to expose the joint cavity. In the knee flexion position, the 10-mm standard osteotomy was performed in the distal femur, followed by opening the knee joint cavity through the "double knife method" at the height of the joint line. The first knife was at the joint line height of the knee flexion position, and the second knife was within 10 cm below the joint line. After completing the above operations, the spacer block was used to evaluate the extension gap. If the extension gap was significantly less than 20 mm, additional osteotomy in the distal femur was performed, and the osteotomy should not be more than 4 mm to avoid injury to the attachment of the medial and lateral collateral ligaments of the knee on the femoral side. If the extension gap was still not enough, the fusiform capsulectomy of posterior capsule would be performed. First, a spreader was used to open the flexion gap and mark the resection range in a 90° inflection of the knee. The resection margins were limited to the medial and lateral collateral ligaments, the posterior femoral condyles, and the tibial plateau to avoid injuring the popliteal vessels and the common peroneal nerve. Second, the posterior capsule was grasped with Kocher or forceps and the posterior capsule was resected with a lower output electrosurgical knife. The electrosurgical knife was controlled below 30 W, and the sleeve was used to limit the cutting depth within 2–3 mm. The fusiform capsulectomy of the posterior capsule should be completed until the fat or muscle tissue is found behind the posterior joint capsule. During the procedure of fusiform capsulectomy of the posterior capsule, the neurovascular bundle is generally not visible. This operation is very superficial, and only a part of the joint capsule is removed to release the knee joint. Once the fat behind the posterior joint capsule is found, great care must be taken. After the above procedures, the spacer block was used again to check the flexion and extension gap. Generally, the flexion contracture could be corrected by at least two-thirds for patients with ankylosing spondylitis (AS). According to the proper size and rotation of the distal femur and proximal tibia, the other procedures of osteotomy were performed. The tightest flexion tendon at the back of the knee joint was located

in extension position, following with percutaneous flexion tendons releasing behind the knee joint with a sharp knife. The released part was mainly the tendon of semitendinosus, semimembranosus, and biceps femoris, and the depth of release was controlled within 5 mm. Multiple parts of release were performed above and below the tendons as necessary until satisfactory straightening was achieved (**Figures 1**, **2**). Finally, the cemented knee prosthesis was implanted.

All patients were given 2.0 g of ceftriaxone intravenous antibiotics once a day for a postoperative period of 48 h and 100 mg of aspirin once a day postoperatively for 2 weeks. Among the patients included in the study, residual flexion contracture was corrected by wearing an extended plaster splint and pressing the weight of 10 pounds for 12 weeks. Contracture deformity was fixed at night by using a plaster splint in the maximum extended position. The weight was lifted above the knee during the day (5–10 kg) to improve the knee extension.

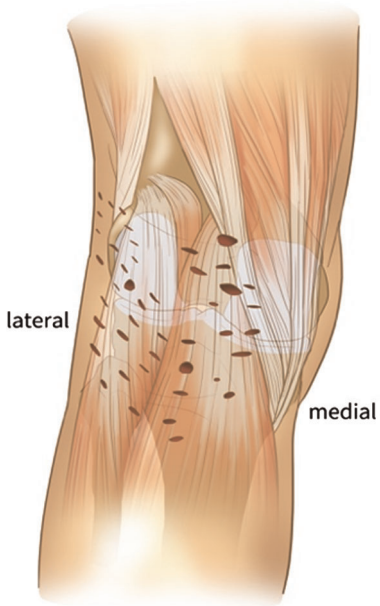

FIGURE 1 | Schematic diagram of the percutaneous flexion tendon release of a severe fused knee.

Statistical Analysis

Statistical analysis was performed with SPSS software 22.0 (SPSS, Chicago, IL, USA). Data were presented as means ± standard deviation or median with interquartile. The differences between the groups were assessed by using the paired *t*-test. A *p*-value of <0.05 (two-tailed) was considered significant.

RESULTS

From January 2016 and December 2019, we performed the technique of fusiform capsulectomy of the posterior capsule in three patients (six knees) during knee replacement. All of them were successfully followed up and enrolled in the study. Preoperative clinical information of three patients (six knees) is given in **Table 1**.

The prostheses in this study were PFC sigma (two knees) and TC3 (four knees) (DePuy, Warsaw, IN, USA). The average follow-up was 42.83 ± 15.77 months (range, 28–63 months). The exact pre- and postoperative range of motion (ROM) of every knee at every time point is given in **Table 2** and **Table S1**. In the last follow-up, the postoperative knee ROM was 100.0 (76.0, 102.75) ($p < 0.01$). The KSS clinical score increased from a preoperative 30.0 (25.0, 36.0) to a postoperative 64.0 (65.0, 78.0) ($p < 0.01$), and the KSS function score increased from a preoperative 0.0 (0.0, 30.0) to a postoperative 55.0 (40.0, 55.0) ($p < 0.01$) (**Table 2**).

Typical Case

Male, AS, and bilateral TKA preoperative bony flexion contracture angles were 95° in both knees (**Figure 3**). A combination of fusiform capsulectomy of the posterior capsule and percutaneous flexion tendon release was used. Plaster

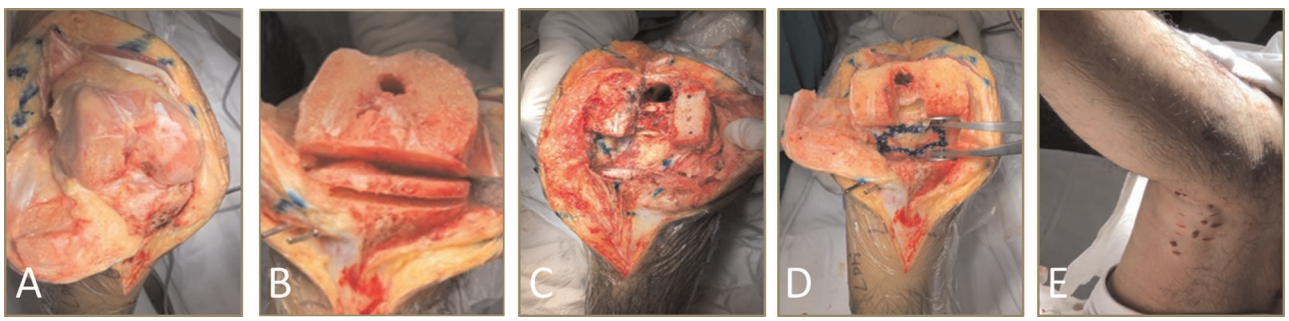

FIGURE 2 | Surgical technique. (**A**) The joint cavity was exposed using the quadriceps oblique cutting technique. (**B**) In the knee flexion position, the 10-mm standard osteotomy was performed in the distal femur, and then the knee joint cavity was opened through the "double knife method" at the height of the joint line. (**C**,**D**) The fusiform capsulectomy of the posterior capsule was used to loosen the posterior joint capsule of the knee. (**E**) Percutaneous flexion tendon release was done to loosen the posterior joint capsule of the knee joint.

splint was applied at night to correct the residual contracture deformity. The weight of 5–10 kg was lifted above the knee. The postoperative compression was fixed for 3–4 weeks. The ROMs of both knees significantly improved after surgery (**Figure 4**).

DISCUSSION

In this study, there are promising clinical and radiological results after TKA for patients with severe bony ankylosed knees in flexion with a combination of fusiform capsulectomy of the posterior capsule and percutaneous flexion tendon release.

Multiple pathological causes can induce bony ankylosed knee joints, including trauma, AS, rheumatoid arthritis, and septic disease (6). Arthrodesis, an optional treatment for correcting ankyloses of the knee, can provide a stable and painless knee joint, but the function is poor (7). Total joint replacement for young patients is controversial because of the expected duration and wear of prosthetic, as well as the fatigue of materials in certain long period.

The reason for the bony ankylosed knee is complicated. In the early stage of inflammation (especially in AS or rheumatoid arthritis patients), patients may inconsciently settle the knee in flexion position because the pain caused by joint swelling can be partially released with a larger capacity of the knee joints. The posterior joint capsule is thickened and fibrosis is accompanied by a contraction of the flexion tendon and, finally, the knee joint is fixed with bony fusion in flexion position (8).

To correct the bony deformity of the knee in flexion position, one-stage or two-stage surgery is considered. A separation of the fusion knee joint, followed by a skeletal traction of the distal

TABLE 1 | Patient demographics.

Patients	Gender	Age	Side	BMI (kg/m^2)	Cause of ankylosis	Range of motion	Degree of flexion ankylosis
1	Male	35	L	29.8	AS	0	95
			R			0	95
2	Male	27	L	27.7	AS	0	80
			R			0	90
3	Male	32	L	19.5	AS	0	95
			R			0	95

M, male; F, female; L, left; R, right; AS, ankylosing spondylitis.

TABLE 2 | Results of total knee arthroplasty in patients with flexion ankylosis of the knee after final follow-up.

Patients	Follow-up time (months)	Side	Range of motion					KSS function score		KSS clinical score		Complications
			Preop	Postop								
				6 ms Postop (°)	12 ms Postop (°)	24 ms Postop (°)	Last F/U (°)	Preop	Postop	Preop	Postop	
1	38	L	0	5–100	5–100	5–105	5–105	30	55	36	65	–
	37	R	0	5–100	5–102	5–102	7–102	30	55	36	65	–
2	63	L	0	3–60	3–65	3–64	3–64	0	55	25	52	–
	62	R	0	4–85	4–80	4–80	4–80	0	55	25	76	–
3	29	L	0	8–100	10–100	10–100	10–100	0	40	30	78	–
	28	R	0	5–104	10–100	10–100	10–100	0	40	30	78	–

F/U, follow-up; Preop, preoperative; Postop, postoperative; KSS, knee society score.

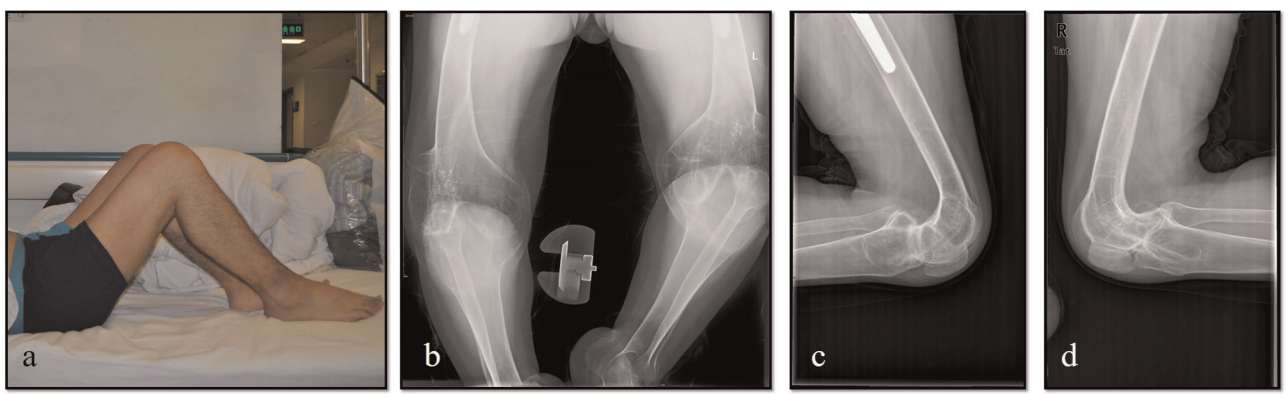

FIGURE 3 | Patient with a severe bony knee flexion contracture before surgery and was not able to walk. (**a**) Preoperative appearance of a 38-year-old female with AS showing osseous ankylosis of both knees. (**b–d**) Preoperative Anterior-Posterior and lateral views of both knee showed osseous ankylosis fixed at degree of 95° without range of motion.

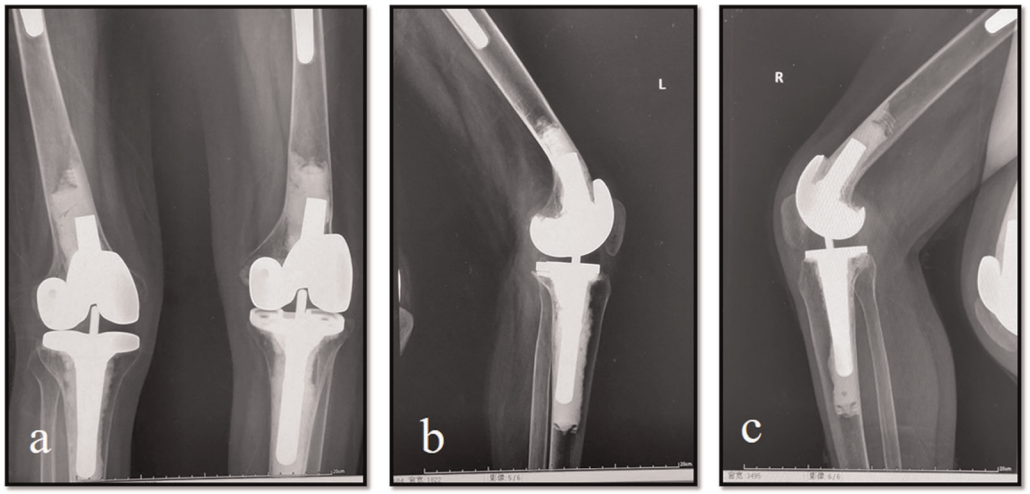

FIGURE 4 | The range of motion and bony flexion contracture significantly improved after surgery. (**a**) Postoperative radiographs following bilateral total knee arthroplasty at 12 months. (**b**) Left knee can be flexed to 100° postoperatively. (c) Right knee can be flexed to 102° postoperatively.

tibia, is required before TKA. A proper soft tissue release around the knee is often necessary. A complete correction of the flexion contracture can not only eliminate pain as much as possible but also provide a significant improvement in the quality of life of the patient (9, 10). Therefore, any effort to correct the deformity is essential during TKA. A common solution to deal with severe bony ankylosed knees in flexion is to increase the osteotomy of the distal femur. Its effectiveness and feasibility have been proved by many studies (4, 11, 12). However, excessive osteotomy can damage the collateral ligaments and weaken the quadriceps muscle. In order to avoid the elevation of the joint level, the maximal range of distal femur cutting was kept at 14 mm in this study. Soft tissue release was needed to correct the resident deformity after judicious bone osteotomy. As mentioned above, soft tissue release, particularly for the posterior soft tissue, plays a crucial role in improving contracture. Selective capsulotomy was reported in a previous study. Taylor et al. reported that posterior capsule incision is effective in the treatment of the knee flexion contracture in children with cerebral palsy (13). Masuda's study describes that posteromedial vertical capsulotomy is an effective method to increase the extension gap and achieve gap balance during TKA (14). The percutaneous pie-crusting technique was proved to be effective in correcting the quadriceps tendon contracture in extension stiffness knees (15, 16). Our previous study introduced a safe and effective fusiform capsulectomy technique that could correct severe flexion contracture during primary TKA (5). Rather than simply incision or vertical capsulotomy of the posterior capsule, fusiform capsulectomy can enlarge the articular cavity and effectively open the posterior gap. The resection depth should be limited to 2–3 mm to avoid the popliteal vessels and prevent nerve injuries.

Most of the patients can realize a satisfying extension ROM during surgery, but the long-time bony fusion may induce not only the posterior capsule contracture but also other soft tissue behind the contracture knee joint shortening, including the gastrocnemius muscles. Scarring of the flexion mechanism with fibrosis and shortening of the gastrocnemius muscles contribute partially to the flexion contracture. To fully correct the contracture joint, we performed a percutaneous flexion tendon release with the percutaneous pie-crusting technique. No. 11 surgical blade with a limited depth of 5 mm was used in the flexion tendon release. This minimally invasive technique can further improve the clinical results and acquire no major complications. Postoperative compression and straight splint were used to eliminate the potential risk of recurrence of postoperative flexion contracture.

Several limitations existed in this study. First, the sample size was not large enough. Therefore, more cases with longer follow-up times need to be studied in the future. Second, this was a retrospective study, which could provide only limited clinical evidence. Lastly, a cadaveric study is needed to define the depth and range of the percutaneous pie-crusting skills.

CONCLUSION

The technique of a combination of fusiform capsulectomy of the posterior capsule and percutaneous flexion tendon release to

correct a fused knee with severe flexion contracture during primary TKA is both effective and safe.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**; further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethical Committee of the Fourth Medical Center of the PLA general hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

Q-QC and M-CH: contributed equally to the study as co-first authors. Q-QC: carried out the clinical data analysis and drafted the original manuscript. M-CH: critically revised the manuscript. ZC: revised the manuscript and provided technical assistance in preparing the manuscript. X-PK: carried out the statistical analysis. WC: supervised the project and critically revised the manuscript for important intellectual content. H-BW and WC: contributed equally to the study design and clinical studies and critically revised the manuscript for important intellectual content as corresponding authors. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/article/10.3389/fsurg.2022.859426/full#supplementary-material.

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A novel predictive model of hospital stay for Total Knee Arthroplasty patients

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Objective: This study aimed to explore the main risk factors affecting Total Knee Arthroplasty (TKA) patients and develop a predictive nomogram of hospital stay.
Methods: In total, 2,622 patients undergoing TKA in Singapore were included in this retrospective cohort study. Hospital extension was defined based on the 75% quartile (Q3) of hospital stay. We randomly divided all patients into two groups using a 7:3 ratio of training and validation groups. We performed univariate analyses of the training group, in which variables with *P*-values < 0.05 were included and then subjected to multivariate analysis. The multivariable logistic regression analysis was applied to build a predicting nomogram, using variable *P*-values < 0.01. To evaluate the prediction ability of the model, we calculated the C-index. The ROC, Calibration, and DCA curves were drawn to assess the model. Finally, we verified the accuracy of the model using the validation group and by also using the C-index. The ROC curve, Calibration curve, and DCA curve were then applied to evaluate the model in the validation group.
Results: The final study included 2,266 patients. The 75% quartile (Q3) of hospital stay was six days. In total, 457 (20.17%) patients had hospital extensions. There were 1,588 patients in the training group and 678 patients in the validation group. Age, Hb, D.M., Operation Duration, Procedure Description, Day of Operation, Repeat Operation, and Blood Transfusion were used to build the prediction model. The C-index was 0.680 (95% CI: 0.734–0.626) in the training group and 0.710 (95% CI: 0.742–0.678) for the validation set. The calibration curve and DCA indicated that the hospital stay extension model showed good performance in the training and validation groups.
Conclusion: To identify patients' risk factors early, medical teams need to plan a patient's rehabilitation path as a whole. Its advantages lie in better resource allocation, maximizing medical resources, improving the functional recovery of patients, and reducing the overall cost of hospital stay and surgery, and will help clinicians in the future.

KEYWORDS

total knee arthroplasty, hospital stay, the risk factor, nomogram, predictive model, a cohort study

Abbreviations
TKA, total knee arthroplasty; ROC, receiver operating characteristic; OR, odds ratio; AUC, area under the curve; CI, confidence interval; DM, diabetes Mellitus; IHD, ischemic heart disease; CHF, congestive hearts failure; SE, standard error.

Introduction

Total Knee Arthroplasty (TKA) is the primary surgical procedure for treating severe knee disorders, relieving knee pain, and reestablishing knee function (1). It can help patients restore knee joint function and improve their quality of life (2). The increased life expectancy and aging of society have led to a dramatic increase in the number of patients with knee disorders. TKA is currently the most important and effective way to solve knee disorders, indicating that the demand for TKA will increase dramatically (3, 4). It is estimated that more than 700,000 TKA surgeries are performed in the United States annually and that this number will increase to nearly 3.5 million by 2030. It is therefore important that TKA is performed economically and effectively (5).

The costs of surgical procedures, inpatient care, and postoperative care have substantially increased due to enhanced intra- and peri-operative management (6). Meanwhile, there has been a noticeable decline in the global economy, and medical insurance expenditure has increased significantly. Some countries have removed TKA from the List of Medicare Outpatient Payment System Rules (7). The main focus of attempts to reduce hospitalization costs is to minimize hospital stays as shortening them will reduce medical expenses and society's medical burden (8).

TKA surgery may be accompanied by severe complications, which affect patients' prognosis and increase the possibility of disability and death (9). However, an extended hospital stay is a risk factor for postoperative complications. It is essential to reduce postoperative complications such as postoperative infection, thromboembolism, postoperative delirium, and cognitive dysfunction (10). The main factors of hospital stay, the incidence of surgical complications, hospitalization expenses, and medical resources are intractable issues that should be solved as soon as possible. This study aimed to explore the main risk factors and establish a predictive nomogram of Hospital Stay in undergoing Total Knee Arthroplasty (TKA).

Patients and methods

Patient and dates

Our secondary analysis was based on a single-center retrospective cohort study of patients who underwent TKA at Singapore General Hospital from January 2013 to June 2014 (11). We downloaded the raw data uploaded at the "DATADRYAD" website (www.datadryad.org). Abdullah et al. (11) shared the original data to the dryad database. We utilized these data for secondary analysis on a different hypothesis without violating the authors' rights.

The Beijing Ditan Hospital of Capital Medical University Ethics Committee approved our study. The Ethics Committee confirmed that informed consent was not required because the data are available publicly *via* the "DATADRYAD" Website (www.datadryad.org), and data were analyzed anonymously. The ethics committee waived the requirement for informed consent from all patients.

Methods

The study included 2,622 patients undergoing TKA in Singapore in a retrospective cohort study. We removed patients whose variables contained missing values, for example, BMI, D.M., D.M. on insulin, etc, which meant that 2,266 patients met the criteria and were included in the study. The prolonged hospital stay was defined as over the 75% quartile (Q3) of hospital stay (12–14). We randomly divided all patients into two groups in a 7:3 ratio: training and validation groups. We performed a univariate analysis in the training group, in which variables with P-values < 0.05 were included and then subjected to multivariate analysis. Multivariable logistic regression analysis was then applied to build a predicting nomogram using the variables the P-values were < 0.01. Furthermore, ROC, Calibration, and DCA curves were drawn to assess the model in the training and validation group.

Statistical analysis

R software (version 4.1.2) was used for all statistical analyses. (https://www.R-project.org). Using the R package "tableone", Chi-squared tests (categorical variables) and one-way analysis of variance, or K–W test (continuous variables of a normal distribution or skewed distribution) we verified significant differences between different groups. Using the R package "caret", we randomly divided all patients into two groups, using a 7:3 ratio for the training and validation groups. We first conducted univariate analysis, then multivariable regression under the package "rms". P-value < 0.05 (bilateral) was considered statistically significant in the univariate analysis, and a P-value < 0.01 (bilateral) was considered statistically significant in the multivariable logistic regression. Predictors with a P-value < 0.01 were applied to develop the model that predicted the prolonged hospital stay.

The C-index (the concordance index) was used to evaluate the model's predictive ability. The C-index refers to the proportion of all patients whose predicted outcome is concordant with the actual result. Similarly, the ROC curve was used for the prediction accuracy of X to Y, enabling us to judge whether a specific factor has a diagnostic value for identifying a particular disease. The ROC curve reflects the relationship between sensitivity and specificity (package = "ROCR"). The DCA curve was performed by quantifying the net benefit at different threshold probabilities (package = "rmda"). Furthermore, the ROC curve, the calibration, and the decision curve analysis were used to evaluate the nomograms in the validation group.

Results

The demographic characteristics of patients who underwent TKA

In total 2,266 of the patients who underwent TKA between January 2013 and June 2014 in the retrospective cohort were included, and 356 patients were excluded because the variable had a missing value (Figure 1). The two groups had no significant differences in BMI, Gender, Smoking habits, and OSA distribution. However, patients had a higher ASA score, longer operation time, higher ratio of bilateral TKA, higher incidence of anemia, higher risk of Blood Transfusion, repeated operation, and general anesthesia in the extended hospital stay group (Table 1). We randomized 1,788 patients into the training group and 678 patients into the validation group. The 75% quartiles (Q3) of hospital stays were six days, with 457 patients (20.17%) hospitalized for over six days (Tables 2, 3).

The result of univariate and multivariate analysis for prolonged hospital stay patients

We used univariate logistic analysis to identify variables associated with a prolonged hospital stay in patients who underwent TKA, and 19 predictive factors were analyzed.

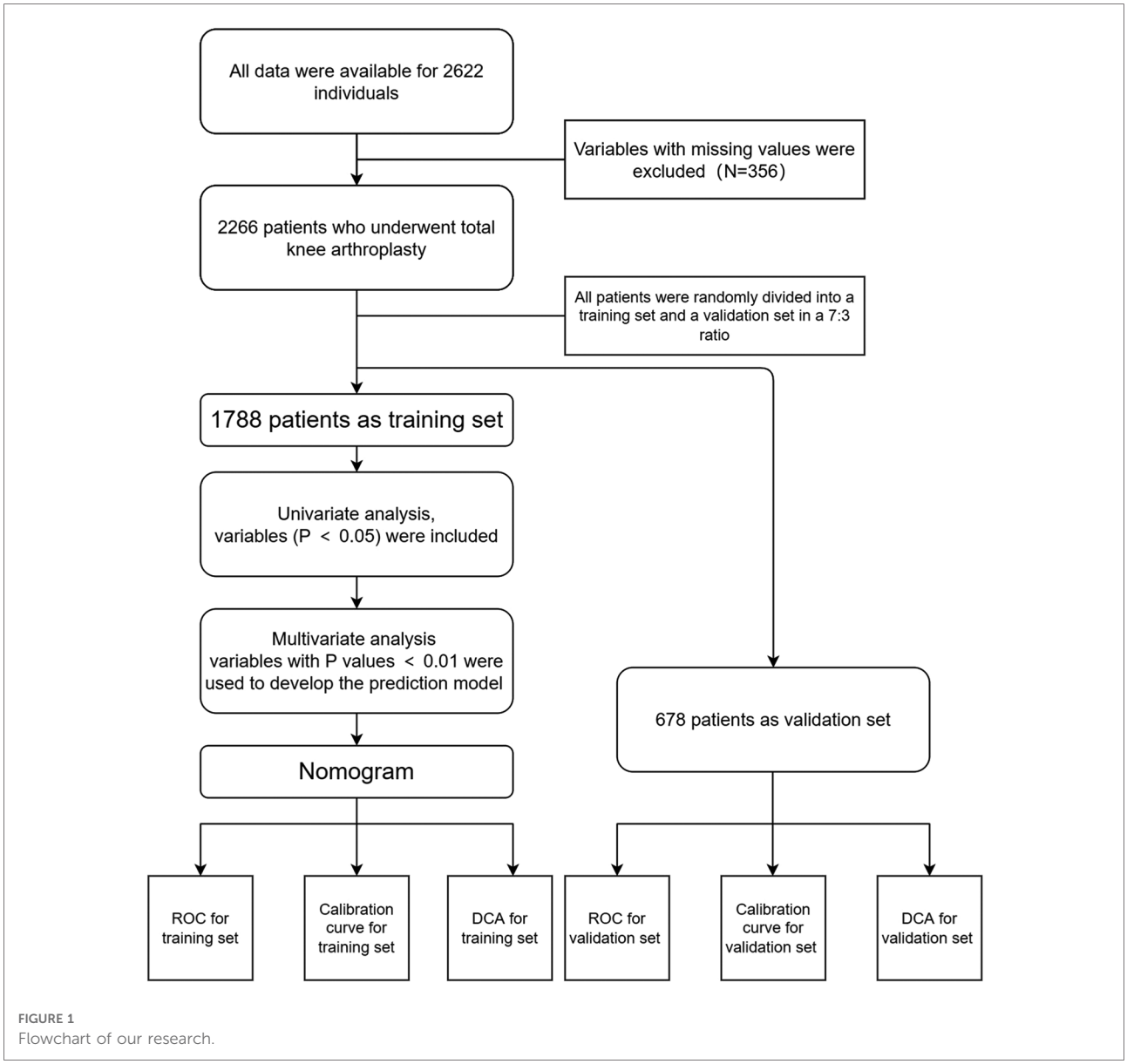

FIGURE 1
Flowchart of our research.

TABLE 1 The demographic characteristics of patients.

	Overall ($n = 2266$)	Hospital stay ≤6 days ($n = 1809$)	Hospital stay >6 days ($n = 457$)	*P*-value
BMI (mean ± SD)	27.85 ± 5.75	27.89 ± 5.90	27.65 ± 5.14	**0.422**
Age (mean ± SD)	66.20 ± 8.03	65.76 ± 7.97	67.96 ± 8.03	<0.001
Hb (mean ± SD)	13.10 ± 1.45	13.19 ± 1.39	12.78 ± 1.63	<0.001
Operation_duration_in_mins [median (IQR)]	80.00 [65.00, 100.00]	80.00 [65.00, 95.00]	85.00 [70.00, 105.00]	<0.001
Periop_blood_units (mean ± SD)	0.09 ± 0.47	0.04 ± 0.25	0.28 ± 0.90	<0.001
ASA_status (%)				
1	156 (6.9)	126 (7.0)	30 (6.6)	<0.001
2	1,972 (87.0)	1,592 (88.0)	380 (83.2)	
3	138 (6.1)	91 (5.0)	47 (10.3)	
Race (%)				
Chinese	1,901 (83.9)	1,514 (83.7)	387 (84.7)	0.014
Indian	134 (5.9)	102 (5.6)	32 (7.0)	
Maly	167 (7.4)	147 (8.1)	20 (4.4)	
Other	64 (2.8)	46 (2.5)	18 (3.9)	
Gender (%)				
Male	551 (24.3)	439 (24.3)	112 (24.5)	**0.963**
Female	1,715 (75.7)	1,370 (75.7)	345 (75.5)	
Type_of_anaesthesia (%)				
GA	815 (36.0)	613 (33.9)	202 (44.2)	<0.001
RA	1,426 (62.9)	1,176 (65.0)	250 (54.7)	
GA_RA	25 (1.1)	20 (1.1)	5 (1.1)	
Procedure_description (%)				
Unilateral	2,078 (91.7)	1,697 (93.8)	381 (83.4)	<0.001
Bilateral	167 (7.4)	104 (5.7)	63 (13.8)	
Revision	21 (0.9)	8 (0.4)	13 (2.8)	
Smoking (%)				
No	2,061 (91.0)	1,648 (91.1)	413 (90.4)	**0.694**
Yes	205 (9.0)	161 (8.9)	44 (9.6)	
OSA (%)				
No	2,048 (90.4)	1,627 (89.9)	421 (92.1)	**0.185**
Yes	218 (9.6)	182 (10.1)	36 (7.9)	
DM (%)				
No	1,829 (80.7)	1,491 (82.4)	338 (74.0)	<0.001
Yes	437 (19.3)	318 (17.6)	119 (26.0)	
IHD (%)				
No	2,137 (94.3)	1,718 (95.0)	419 (91.7)	**0.189**
Yes	129 (5.7)	91 (5.0)	38 (8.3)	
CHF (%)				
No	2,244 (99.0)	1,796 (99.3)	448 (98.0)	0.03
Yes	22 (1.0)	13 (0.7)	9 (2.0)	
CVA (%)				
No	2,221 (98.0)	1,783 (98.6)	438 (95.8)	<0.001
Yes	45 (2.0)	26 (1.4)	19 (4.2)	
Creatinine_ > _2 mg/dl (%)				
No	2,247 (99.2)	1,799 (99.4)	448 (98.0)	0.007
Yes	19 (0.8)	10 (0.6)	9 (2.0)	

(*continued*)

TABLE 1 Continued

	Overall ($n = 2266$)	Hospital stay ≤6 days ($n = 1809$)	Hospital stay >6 days ($n = 457$)	*P*-value
Day_operation (%)				
Mon	368 (16.2)	277 (15.3)	91 (19.9)	0.001
Tue	500 (22.1)	387 (21.4)	113 (24.7)	
Wed	404 (17.8)	321 (17.7)	83 (18.2)	
Thu	516 (22.8)	445 (24.6)	71 (15.5)	
Fri	361 (15.9)	285 (15.8)	76 (16.6)	
Sat	117 (5.2)	94 (5.2)	23 (5.0)	
Blood_transfusion (%)				
No	2,143 (94.6)	1,751 (96.8)	392 (85.8)	<0.001
Yes	123 (5.4)	58 (3.2)	65 (14.2)	
Repeat_Op_within_30_days (%)				
No	2,250 (99.3)	1,805 (99.8)	445 (97.4)	<0.001
Yes	16 (0.7)	4 (0.2)	12 (2.6)	

The results showed that 14 predictive factors were associated with a prolonged hospital stay in patients who underwent TKA. Our study showed that Age, Hb, ASA Status, Operation Duration, Race, Type of Anaesthesia, Procedure Description, D.M., CHF, CVA, Creatinine, Day operation, Blood transfusion, and reoperation were the predictor risk factors for prolonged hospital stay in patients who underwent TKA (Table 2).

The multivariate logistics regression model was also performed to screen for independent risk factors. The results showed that Age ($P \leq 0.001$), Hb ($P \leq 0.001$), Operation Duration in mins ($P \leq 0.001$), Procedure Description ($P \leq 0.001$), D.M. ($P \leq 0.001$), Day operation ($P \leq 0.001$), Blood transfusion ($P \leq 0.001$), Repeat Op within 30 days ($P \leq 0.001$) were independent prognostic factors of prolonged hospital stay (Table 2).

Development of the prediction model and evaluation of the accuracy of the nomogram in the training group

Based on eight independent risk factors, we established a nomogram for prolonged hospital stay in TKA patients (Figure 2). Meanwhile, the area under the ROC curve was 0.710 in the training group (Figure 3A). This indicated that the prediction model established based on the results of multivariate logistics regression analysis had a high predictive value. In addition, we also plotted the calibration curve and DCA for the nomogram in the training sets. The results showed that the nomogram could be a good tool for predicting prolonged hospital stay in TKA patients (Figures 4A, 5A).

Evaluating the accuracy of the nomogram in the validation group

The ROC curve shows that the rosette has high predictive performance, and its AUC is 0.680 (Figure 3B). It indicates that the prediction model has a strong prediction ability. The calibration curves used to predict the prolonged hospital stay in the validation cohort showed good consistency and prediction ability (Figure 4B). The DCA of prolonged hospital stay indicated that this nomogram could be an excellent diagnostic tool for patients undergoing TKA (Figure 5B).

Discussion

Our study aimed to develop and validate a prolonged hospital stay risk prediction model for TKA patients. The risk factors were Age, Hb, Operation Duration, Procedure Description, D.M., Day operation, Blood transfusion, and Repeat Operation within 30 days. We built the nomogram using the above risk factors for prolonged hospital stay in TKA patients. The nomogram transforms the complex regression equation into a visual graph, making the prediction model's results more readable and convenient for clinicians. Because of the intuitive and easy-to-understand characteristics of the nomogram, it has gradually received more attention and has been applied in medical research and clinical practice.

Our study found that age was an independent risk factor for prolonged hospitalization after TKA. This might be because elderly patients are at high risk and prone to many diseases. Factors such as poor autoimmune ability, health status, and

TABLE 2 Clinical characteristics of patients who underwent TKA in training and verification group.

	Training Group (n = 1588)	Validation Group (n = 678)	Overall (n = 2266)
BMI (mean ± SD)	27.9 ± 6.15	27.7 ± 4.71	27.8 ± 5.75
Age (mean ± SD)	66.3 ± 8.12	65.9 ± 7.81	66.2 ± 8.03
ASA_status			
1	111 (7.0%)	45 (6.6%)	156 (6.9%)
2	1,380 (86.9%)	592 (87.3%)	1,972 (87.0%)
3	97 (6.1%)	41 (6.0%)	138 (6.1%)
Hb (mean ± SD)	13.1 ± 1.48	13.2 ± 1.36	13.1 ± 1.45
Hospital stay in_days (mean ± SD)	5.48 ± 5.15	5.23 ± 3.46	5.41 ± 4.71
Hospital stay			
≤6 days	1,258 (79.2%)	551 (81.3%)	1,809 (79.8%)
>6 days	330 (20.8%)	127 (18.7%)	457 (20.2%)
Operation_duration_in_mins (mean ± SD)	84.8 ± 27.9	84.8 ± 27.0	84.8 ± 27.6
Race			
Chinese	1,324 (83.4%)	577 (85.1%)	1,901 (83.9%)
Indian	96 (6.0%)	38 (5.6%)	134 (5.9%)
Maly	122 (7.7%)	45 (6.6%)	167 (7.4%)
other	46 (2.9%)	18 (2.7%)	64 (2.8%)
Gender			
Male	371 (23.4%)	180 (26.5%)	551 (24.3%)
Female	1,217 (76.6%)	498 (73.5%)	1,715 (75.7%)
Type_of_anaesthesia			
GA	576 (36.3%)	239 (35.3%)	815 (36.0%)
RA	997 (62.8%)	429 (63.3%)	1,426 (62.9%)
GA_RA	15 (0.9%)	10 (1.5%)	25 (1.1%)
Procedure_description			
Unilateral	1,459 (91.9%)	619 (91.3%)	2,078 (91.7%)
Bilateral	114 (7.2%)	53 (7.8%)	167 (7.4%)
Revision	15 (0.9%)	6 (0.9%)	21 (0.9%)
Smoking			
No	1,442 (90.8%)	619 (91.3%)	2,061 (91.0%)
Yes	146 (9.2%)	59 (8.7%)	205 (9.0%)
OSA			
No	1,427 (89.9%)	621 (91.6%)	2,048 (90.4%)
Yes	161 (10.1%)	57 (8.4%)	218 (9.6%)
DM			
No	1,271 (80.0%)	558 (82.3%)	1,829 (80.7%)
Yes	317 (20.0%)	120 (17.7%)	437 (19.3%)
IHD			
No	1,505 (94.8%)	632 (93.2%)	2,137 (94.3%)
Yes	83 (5.2%)	46 (6.8%)	129 (5.7%)
CHF			
No	1,573 (99.1%)	671 (99.0%)	2,244 (99.0%)
Yes	15 (0.9%)	7 (1.0%)	22 (1.0%)
CVA			
No	1,564 (98.5%)	657 (96.9%)	2,221 (98.0%)
Yes	24 (1.5%)	21 (3.1%)	45 (2.0%)
Creatinine_ > _2 mg/dl			
No	1,575 (99.2%)	672 (99.1%)	2,247 (99.2%)
Yes	13 (0.8%)	6 (0.9%)	19 (0.8%)
Day_operation			
Mon	256 (16.1%)	112 (16.5%)	368 (16.2%)
Tue	340 (21.4%)	160 (23.6%)	500 (22.1%)
Wed	305 (19.2%)	99 (14.6%)	404 (17.8%)
Thu	349 (22.0%)	167 (24.6%)	516 (22.8%)
Fri	255 (16.1%)	106 (15.6%)	361 (15.9%)
Sat	83 (5.2%)	34 (5.0%)	117 (5.2%)
Periop_blood_units (mean ± SD)	0.100 ± 0.520	0.0634 ± 0.340	0.0891 ± 0.474
Blood_transfusion			
No	1,494 (94.1%)	649 (95.7%)	2,143 (94.6%)
Yes	94 (5.9%)	29 (4.3%)	123 (5.4%)
Repeat_Op_within_30_days			
No	1,574 (99.1%)	676 (99.7%)	2,250 (99.3%)
Yes	14 (0.9%)	2 (0.3%)	16 (0.7%)

other reasons, coupled with the increased risk of infection due to blood loss during surgery, contribute to increasing their hospital stay. Davide Tornese et al. (15) found that the average LOS was 5.08 ± 2.52 days in the Department of Orthopedic Surgery, and the age was predictive of a more extended stay. In Corentin Roger et al. (16) study, the predictors of LOS were identified using a survival model that considered age as a continuous variable, individual comorbidities, and the discharge destination.

This study shows that preoperative hemoglobin is related to hospital stay. The hospitalization time decreased with the increase in hemoglobin value (17). We suggest that anemia be corrected before the operation to shorten hospital stays. Raut et al. (18) found a negative correlation between the level of Hb and LOS before and on the first day after the operation. However, there was still no correlation between the level of Hb decline and LOS, emphasizing the importance of improving the level of Hb before the operation.

Similarly, the longer the operative time, the higher the risk of prolonged patient hospitalization. Cregar (19) and Garbarino (20) indicated that less time spent in the operating theatre could lead to shorter LOS for revision and primary TKA patients. Lu (21) found that Total knee arthroplasty (TKA) frequently results in significant blood loss with accompanying hemoglobin loss and potentially increased transfusion rates. Unfortunately,

TABLE 3 Univariate and multivariate analysis of prolonged hospital stay in undergoing TKA patients.

	Univariable				Multivariable			
	OR	5%Cl	95%Cl	*P*	OR	5%Cl	95%Cl	*P*
Age (year)	1.04	1.02	1.05	**<0.001**	1.04	1.02	1.06	**<0.001**
Race								0.089
Chinese	Ref							
Indian	1.11	0.68	1.82	0.683	1.03	0.60	1.77	
Maly	0.52	0.30	0.91	**0.022**	0.52	0.28	0.96	
other	1.47	0.76	2.83	0.250	1.51	0.75	3.05	
Hb	0.81	0.74	0.88	**<0.001**	0.83	0.76	0.91	**<0.001**
BMI (kg/m^2)	0.98	0.96	1.01	0.224				
Gender								
Female	Ref							
Male	1.02	0.77	1.36	0.873				
ASA_status								0.485
1	Ref							
2	1.15	0.70	1.90	0.590	0.98	0.57	1.68	
3	2.24	1.18	4.26	**0.014**	1.34	0.66	2.73	
Operation_duration_in_mins	1.01	1.01	1.02	**<0.001**	1.0084	1.0031	1.0137	**0.002**
Type_of_anaesthesia								0.035
GA	Ref							
RA	0.65	0.51	0.84	**<0.001**	0.69	0.53	0.91	
GA_RA	0.74	0.20	2.65	0.639	0.77	0.20	2.89	
Procedure_description								**0.003**
Unilateral	Ref							
Bilateral	2.67	1.79	3.98	**<0.001**	1.99	1.18	3.37	
Revision	4.86	1.75	13.5	**0.002**	4.33	1.40	13.38	
Smoking								
No	Ref							
Yes	1.18	0.78	1.76	0.434				
OSA								
No	Ref							
Yes	0.82	0.54	1.25	0.362				
DM								
No	Ref							
Yes	1.81	1.37	2.40	**<0.001**	1.72	1.27	2.33	**<0.001**
IHD								
No	Ref							
Yes	1.4	0.85	2.32	0.189				
CHF								
No	Ref							
Yes	3.39	1.22	9.41	**0.019**	1.87	0.60	5.85	0.281
CVA								
No	Ref							
Yes	2.78	1.22	6.31	**0.015**	2.95	1.17	7.42	0.021
Creatinine_ > _2 mg/dl								
No	Ref							
Yes	3.31	1.10	9.92	**0.033**	1.94	0.55	6.82	0.301

(*continued*)

TABLE 3 Continued

	Univariable				Multivariable			
	OR	5%Cl	95%Cl	*P*	OR	5%Cl	95%Cl	*P*
Day_operation								**0.002**
Mon	Ref							
Tue	0.89	0.61	1.30	0.543	1.1	(0.72,1.66)	0.665	
Wed	0.81	0.55	1.20	0.296	0.77	0.50	1.18	0.235
Thu	0.49	0.33	0.74	**<0.001**	0.47	0.30	0.74	**<0.001**
Fri	0.83	0.55	1.24	0.362	0.80	0.50	1.25	0.32
Sat	0.6	0.31	1.13	0.113	0.74	0.38	1.46	0.388
Blood_transfusion								
No	Ref							
Yes	4.93	3.22	7.54	**<0.001**	2.80	1.74	4.51	**<0.001**
Repeat_Op_within_30_days								
No	Ref							
Yes	9.8	3.05	31.44	**<0.001**	6.93	1.82	26.36	**0.005**

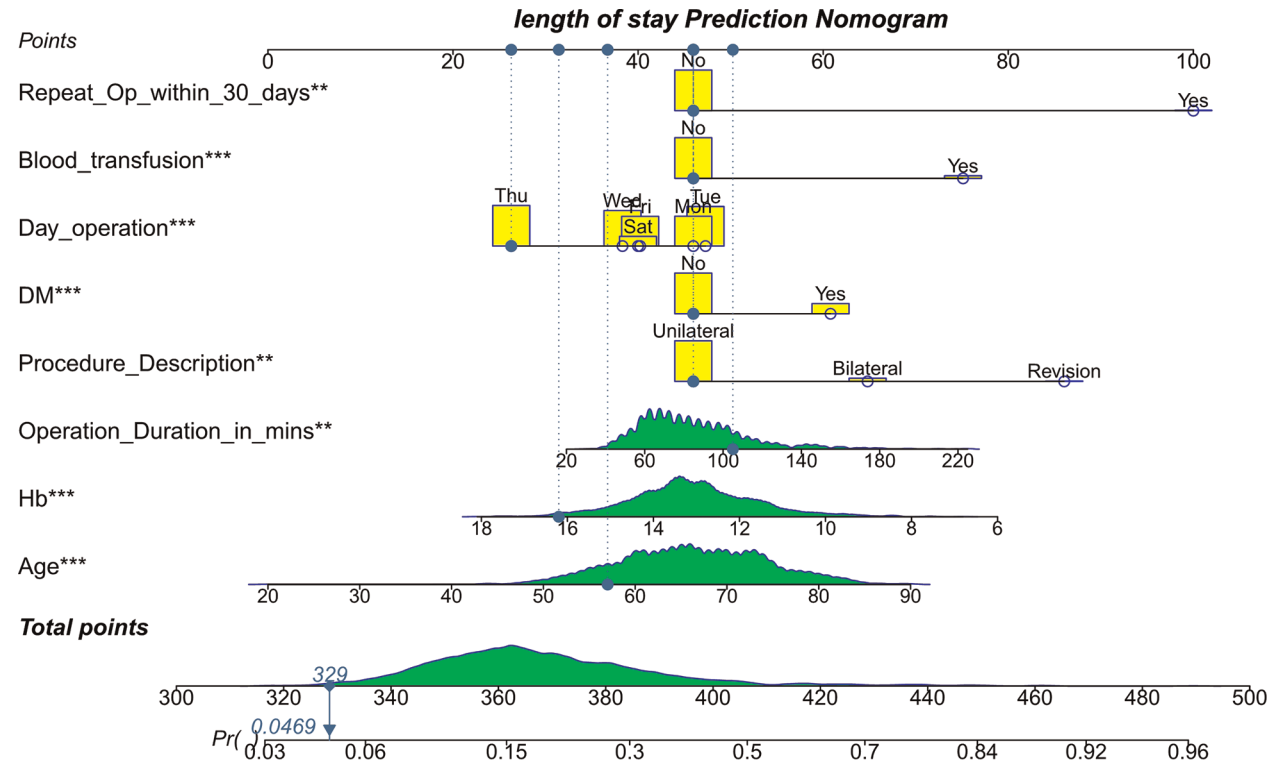

FIGURE 2
The nomogram for a prolonged hospital stay in undergoing TKA patients.

transfusions have associated risks, including postoperative confusion, infection, cardiac arrhythmias, fluid overload, prolonged hospital stay, and increased mortality.

The highest risk score in the independent predictor was blood transfusion, many studies have come to the same conclusion, and the transfusion rate was directly related to the hospital stay (22–24). Autologous blood transfusion is often required when the blood loss is between 1000 and 1500 ml. Research shows that the total blood loss after TKA may be as high as 2000 ml, and the proportion of blood transfusion may be as high as 67% (25, 26). In a cohort of 228,316 TKA patients at 922 hospitals, the mean predicted probability of

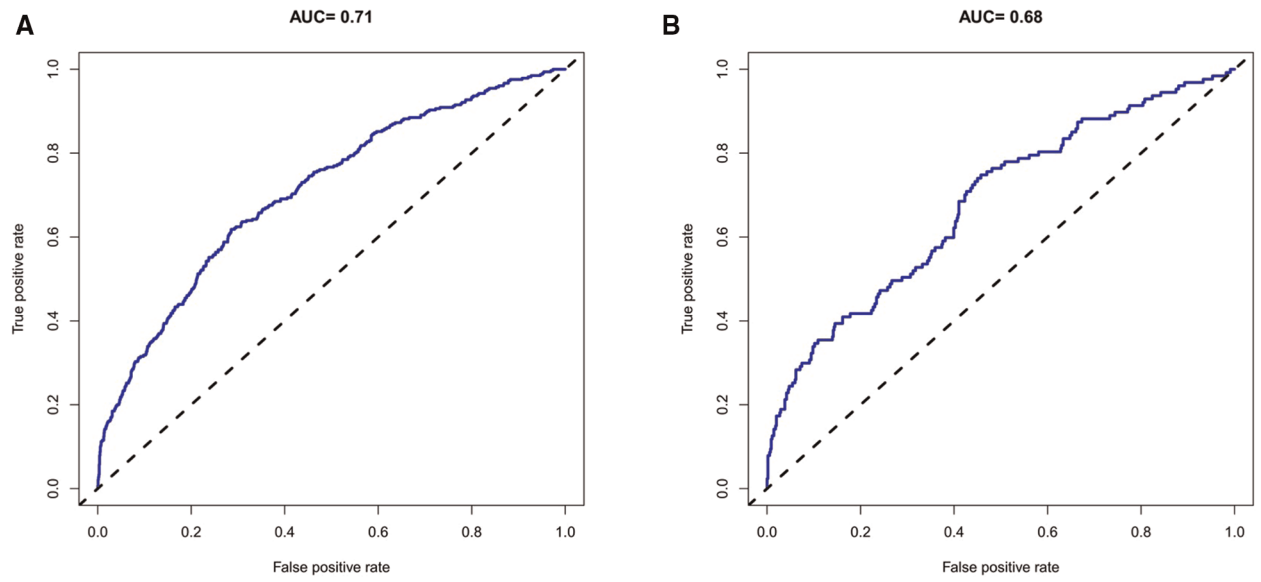

FIGURE 3
The ROC curves of prolonged hospital stay in the training set (A) and validation set (B).

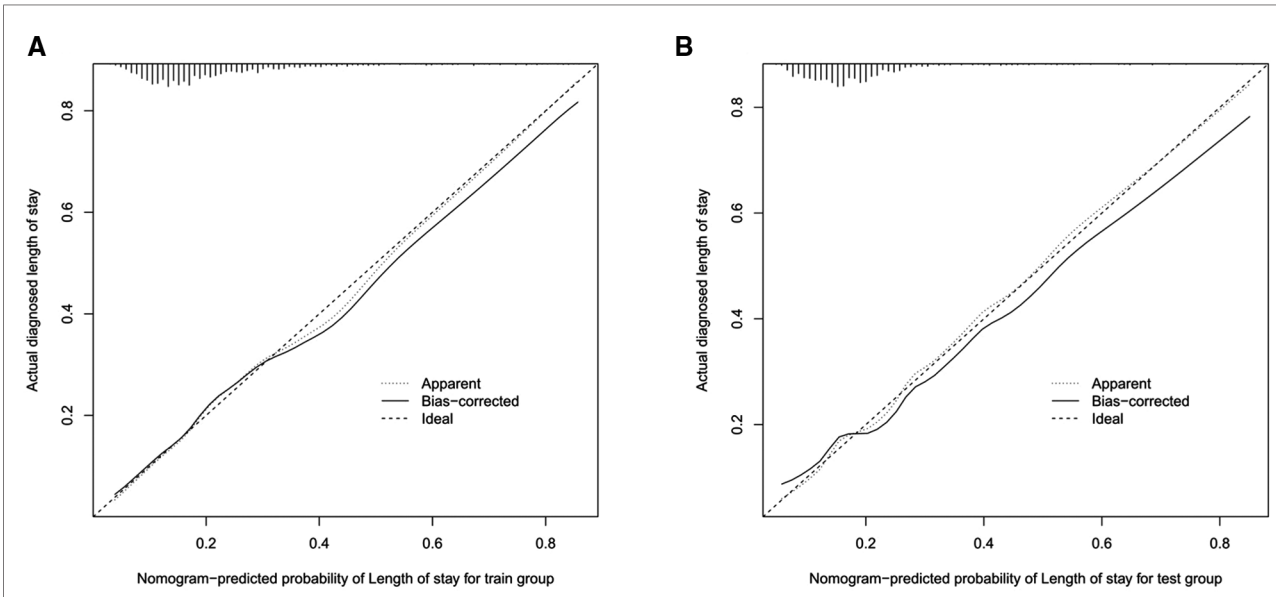

FIGURE 4
The Calibration curves of prolonged hospital stay in the training set (A) and validation set (B).

TKA transfusion was 7.9%, with 60% (95% CI, 36%–87%) of patients having hospital stays of more than three days (22). In a cross-sectional study of 4,544,999 patients who received TKA between January 2000 and December 2009, blood transfusions were associated with in-hospital mortality, and hospital stay increased by 0.71 ± 0.01 days (23). In addition, Danninger et al. (24) showed a significantly higher rate of significant complications in patients receiving transfusion (19.1% vs. 11.2%, $P < 0.0001$), and the mean length of hospital stay was significantly increased.

Our study found that the operation date was a significant factor in predicting the risk of hospital stays after blood transfusion. Similarly, studies demonstrated that operation procedures or factors related to doctors and nurses provide clinically relevant improvements in explaining hospital stay and patient-related risk factors (7). In a prospective cohort

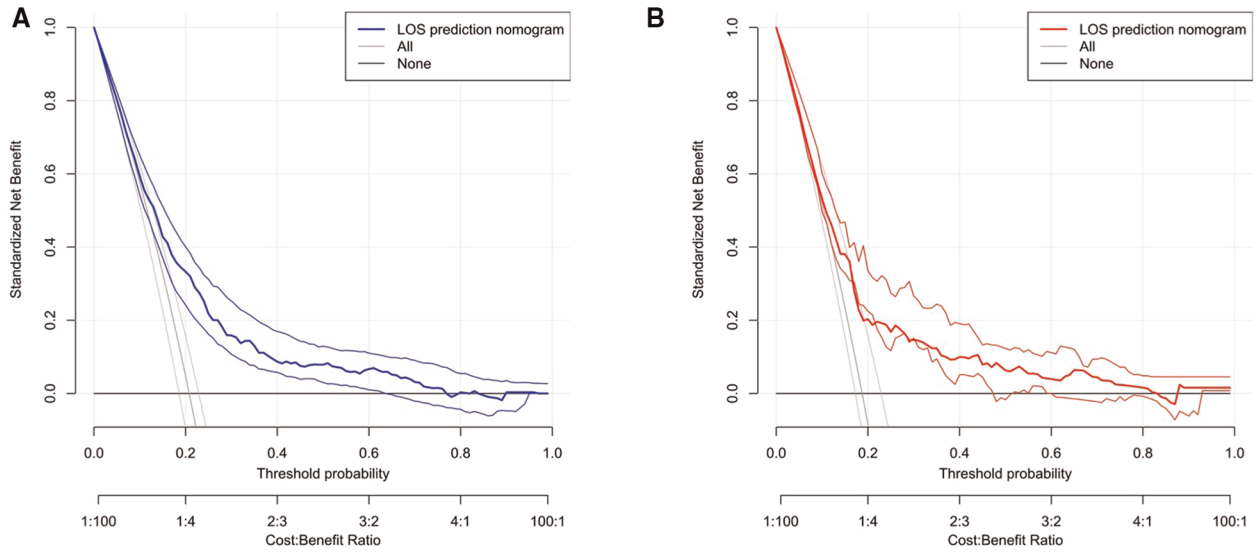

FIGURE 5
The DCA curve of prolonged hospital stay in the training set (A) and validation set (B).

study of 4,509 patients who underwent initial TKA at four hospitals between January 1, 2016, and September 30, 2017, who received surgery later in the day were predicted to have a more extended hospital stay, with patients who had surgery on Friday having a significantly longer hospital stay than patients who had surgery on Monday (7). Our study showed that the risk prediction scores of operations on Monday, Tuesday, and Friday were much higher than those on Thursday. The length of hospital stay was related to operation data. Possible reasons for this result include patients coming from different countries, surgical hospital systems, and doctors' moods and preferences.

Diabetes is a chronic disease that can lead to multiple systemic comorbidities. This study found that the higher the comorbidity index, the longer the hospital stays were. Swain et al. (27) showed that 67% of patients with osteoarthritis had at least one other chronic condition, 20% more than those without osteoarthritis. The DM was the independent predictor of prolonged hospital stay. Similarly, other previous studies have suggested that TKA patients with comorbidities had prolonged hospital stays (28–31). Higuera et al. (30) showed that chronic heart failure was associated with extended hospital stays and increased rates of major postoperative complications in TKA patients. In a study of 15,321 TKA patients, 18.2% had a medical comorbidity D.M., with a 300% increase in overall mortality. Belmont et al. (31) found that DM was an independent predictor of hospitalization for four days or more.

Our study found that unilateral TKA under epidural anesthesia is economical, efficient, and has an ideal surgical effect for patients with osteoarthritis. For patients with bilateral knee arthritis, a comprehensive health assessment should be conducted before surgery. For high-risk patients, especially those with severe cardiovascular diseases, simultaneous bilateral total knee replacement should be avoided as far as possible (32–35). The reasons for reoperation TKA were that the patients had cardiac complications, pulmonary complications, and renal and cerebrovascular complications before the operation. The local complications of patients after operation include non-infection-related complications, wound infection, and peripheral nerve injury. Furthermore, we also found that the causes of revision surgery were periprosthetic infection, aseptic loosening, osteolysis, abrasion, joint dislocation, periprosthetic fracture, and patellar-related complications. These factors will lead to prolonged hospitalization (16, 36–38).

There are still some limitations to our study. First, this study is retrospective, using clinical data from a single center. Therefore, there may be differences in treatment strategies and race, etc. Second, because of differences in healthcare settings and practices, the predictive models developed in one country are unlikely to be directly applicable in another, requiring external validation and an updating of the predictive performance of models in other new patients. Finally, some influencing factors may not be included in this paper, including patient income, medical expenses, medical insurance, hospital location, etc. Potential factors not included may also have some influence on the results.

Conclusion

To make better use of these factors and identify patients' risk factors early, the medical team should plan a patient's rehabilitation path as a whole. Advantages of this approach include better resource allocation, maximizing medical resources, improving the functional recovery of patients, and reducing the overall cost of hospital stay and surgery. We also hope that these results will help clinicians in the future.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found below: https://datadryad.org/stash/dataset/doi:10.5061/dryad.73250.

Ethics statement

This study was approved by the Ethics Committee of Beijing Ditan Hospital, Capital Medical University. The Ethics Committee approved that informed consent was not required because the DRYAD was supported and data were analyzed anonymously. The ethics committee waived the requirement for informed consent from all patients.

Author contributions

BL performed the data analysis. BL, CXZ wrote the manuscript. BL, CXZ, and YJM. contributed to the manuscript revision. YJM contributed to the literature search and data extraction. BL, ZJW, and QZ Conceived and designed the study. All authors have read and approved the final version of the manuscript.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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