The effect of HIV prevalence, CD4 counts and disease severity on the outcome of total knee arthroplasty for haemophilic arthropathy: A systematic review and meta-analysis.

Abstract

Purpose. End-stage knee arthropathy is a recognised complication of haemophilia. It is often treated by total knee arthroplasty (TKA), which is more technically challenging in patients with haemophilia (PwH). It remains unclear what factors may predict implant survivorship and deep infection rate. Therefore, we systematically review the evidence regarding TKA survivorship and infection in PwH, compared to the general population, and determine the important factors influencing survivorship, particularly HIV and CD4+ count.

Methods. A systematic literature review was conducted using MEDLINE, EMBASE, and PubMed for studies reporting Kaplan-Meier survivorship for TKA in PwH (PROSPERO CRD42021284644). Meta-analysis was performed for survivorship, and the results compared to <55-year-olds from the National Joint Registry (NJR). Meta-regression was performed to determine the impact of relevant variables on 10-year survivorship, with a sub-analysis focusing on HIV.

Results. Twenty-one studies were reviewed, totalling 1338 TKAs (average age 39 years). Implant survivorship for PwH at 5, 10, and 15 years was 94%, 86%, and 76% respectively. NJR-reported survivorship for males <55 years was 94%, 90%, and 86%. Survivorship improved over time (1973-2018), and correlated inversely with HIV prevalence. Infection rate was 5%, compared to 0.5-1% in the NJR. Infection was not significantly increased with higher HIV prevalence, and CD4+ count had no effect. Complications were inconsistently reported.

Conclusion. Survivorship was similar at 5 years but declined thereafter, and infection rate was six-fold higher. HIV was related to worse survivorship, but not increased infection. Meta-analysis was limited by inconsistent reporting, and standardised reporting is required in future studies.

Main Text

1. Introduction

Arthropathy of the knee is a recognised complication of haemophilia, most commonly treated by total knee arthroplasty (TKA), with the aims of reducing pain and improving range of motion and function [1–3].

Patients with haemophilia (PwH) are at higher risk of implant failure, revision, complications and poor clinical outcomes than non-haemophiliac patients following TKA, due to a number of factors. PwH undergoing TKA are relatively young, which is an independent predictor of higher revision rates [4]. Haemophilic arthropathy often results in deformity, making surgery more technically challenging [3] and can result in poor bone quality, increasing the risk of peri-prosthetic fractures and aseptic loosening [3, 5]. PwH are predisposed to peri- and post-operative bleeding, which may lead to joint stiffness [3, 6]. They are more likely to have human immunodeficiency virus (HIV), and this has been posited to result in a higher rate of prosthetic joint infection and revision surgery [7, 8].

Establishing the true survivorship, complication rates and clinical outcomes is of importance to both surgeon and patient in taking the decision to operate, despite which, there remains limited data on the outcomes of TKA in PwH. Moore et al (2016) [7] conducted a systematic review of 10 studies, reporting data on complication rates, range of movement (ROM), and patient-reported outcome measures (PROMS). However, they did not report implant survivorship or analyse complications in detail. Fenelon et al (2022) [9] conducted an excellent review, reporting that average implant survivorship was 95.7% at 5 years and 86.5% at 10 years, ROM improved by 22.3°, Knee Society Score function improved by 35.9 points, and infection and loosening rates fell over time. Since these reviews, subsequent studies have provided additional relevant data, and neither review examined the effect of HIV and CD4+ count. HIV has been thought to cause higher infection rates in PwH, and low CD4+ count has been an exclusion criterion for TKA (<200 cells/ml^3) [8, 10].New evidence suggests it has become less relevant since the introduction of highly active antiretroviral therapy (HAART) in the 1990s [10–12], although a recent large study not limited to PwH demonstrated increased infection rates even in patients taking HAART compared to those without HIV [13]. The aim of the current review was to provide an up-to-date analysis of implant survivorship, outcomes and complications, and to determine the effect of HIV, CD4+ count and other relevant variables.

2. Methods

A literature search was performed in September 2021 using the HDAS tool (hdas.nice.org.uk) for the EMBASE and MEDLINE databases (repeated and updated July 2022), as well as on the native PubMed interface, and Cochrane and OpenGrey registries. The detailed search strategy are outlined in Supplementary Tables 1-2; briefly, the search terms encompassed variants and MESH terms for “total knee arthroplasty”, “haemophilia” and “inherited clotting factor disorder”. The reference lists of included studies were also screened for relevant articles.

Inclusion criteria:

- Population: patients with a diagnosis of haemophilia (studies including a minority of patients with similar hereditary coagulation disorders such as von Willebrand’s disease were also acceptable)
- Intervention: primary total knee arthroplasty
- Comparator: outcomes and survivorship data from the NJR for patients < 55 years (providing the closest age match to the PwH who are young at time of surgery)

- Outcomes: studies with a Kaplan-Meier analysis of implant survivorship (primary outcome) also reporting one or more of the following: complications, range of motion, or scores from a validated PROMS tool for knee arthroplasty.
- Full text available
- In English or translation available

Exclusion criteria: case reports and studies for which full text was not available.

The protocol was created using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [14] (Figure 1) and registered on PROSPERO (CRD42021284644).

Titles and abstracts were independently screened by two authors (HF, CP), and those deemed potentially relevant were independently screened with their full text. Studies were independently graded for risk of bias using the MINORS tool (a validated tool for assessing the methodological quality of non-RCT studies) [15], and level of evidence using the CEBM level of evidence framework. Disagreements were resolved by discussion with the senior author (DHS).

2.1. Statistics and meta-analysis

A series of random-effects models were performed for combining survivorship (at 5, 10, 15, and 20 years) and infection rates in the literature. DerSimonian-Laird (DL) or profile likelihood (PL) methods were used in the random-effects models as suggested by Kontopantelis and Reeves [16]. Heterogeneity was measured using the I^2 statistic. The meta-analyses were performed using the "metan" package [17] in Stata 17 (StataCorp, College Station, Texas, USA), and the results presented in forest plots. In addition, to explore which factors were contributing to the heterogeneity in terms of survivorship, we conducted a series of meta-regression of 10-year survivorship using a range of covariates such as year of operation, age, number of surgeons, and if the patients have haemophilia A, severe haemophilia, or HIV. Given the small number of studies, univariate meta-regression was performed using the DL method in Stata.

3. Results

3.1. Characteristics of included studies

Twenty-one studies were included, reporting data from 20 patient cohorts (two reporting the same cohort 5 years apart), totalling 1002 patients with 1338 TKAs [10, 12, 18–36] (Table 1). Average age at surgery was 39 years, with operation dates ranging from 1973 to 2018 and prevalences of clotting factor inhibitors and HIV ranging from 0 to 100% (Table 2). All studies were level IV evidence according to the CEBM criteria [37], and MINORS scores indicated that all were at high risk of bias, due to significant loss to follow-up, poor outcomes reporting, and lack of blinding and prospective sample size calculation. There was variation in sample size, duration of follow-up, geographic location, and HIV prevalence. The models and designs of the implants (CR vs PS) were poorly reported (Supplementary Table 3).

3.2. Survivorship, revision, and disease severity

Implant survivorship was reported at a variety of different time-points, and fewer than half quoted confidence intervals (Table 3, Figure 2). Meta-analysis of the most consistent studies revealed an overall survivorship of 94% at 5 years, 86% at 10, 76% at 15, and 74% at 20 years (Figure 3A-D). By comparison, the NJR [4] survivorship for male patients under 55 years at 5, 10, and 15 years was 94.2%, 90.1%, and 85.8% respectively.

The indications for revision surgery were varied (Table 4). In eight studies, infection was the only or most common indication [10, 18, 26, 28, 30–33] and in seven, aseptic loosening predominated [12, 19–23, 29].

To identify variables associated with survivorship, univariable meta-regression analysis was performed (Table 5). Studies with TKAs performed more recently had higher 10-year survivorship. Each percentage-point increase in HIV prevalence was associated with a 0.3 percentage-point decrease in 10-year survivorship ($p > 0.001$). Each percentage-point increase in the prevalence of severe haemophilia [as defined by World Federation of Haemophilia criteria [38]] was associated with a 0.1 percentage-point decrease in survivorship, although this was statistically insignificant ($p = 0.709$). Other potentially relevant variables were inconsistently reported and could not be further analysed.

3.3. Infection, HIV, and CD4+ count

Prosthetic joint infection was the most commonly reported complication (0 to 18%, Table 6). Meta-analysis demonstrated an overall rate of 5% at a mean follow-up of 8.2 years (Figure 4A), with a downward trend in infection rate over time (Spearman's Rho = -0.60, $p = 0.01$, Figure 4B).

The infection rate increased somewhat with HIV prevalence, but was not statistically significant (Spearman's Rho = 0.42, $p = 0.1$, Figure 4B). Nine studies sub-analysed infection data by HIV status, only one of which found any evidence for a relationship. Four studies found no statistically significant relationship [12, 29, 31, 32], one found a lower infection rate in HIV +ve patients [10], and three had only one infection among their HIV +ve patients and could not draw firm conclusions [20, 22, 23] (Table 7B). Similarly, of the three studies which compared CD4+ counts, two found no significant difference between the average CD4+ counts of the HIV patients with infection and without [10, 31].

3.4 Other orthopaedic complications

After infection, stiffness was the second most common complication [mean 11.0%, range 1.5% to 24% [31]], but only two studies clearly stated their definition of stiffness [21, 33]. The most common treatment was manipulation under anaesthetic, but arthroscopic arthrolysis [12] and Judet arthrolysis [20] were also used (Supplementary table 4). Wound problems were also frequently reported, but this was a broad category encompassing superficial wound infection, wound dehiscence, skin blistering, and delayed wound healing. The reports of these as well as periprosthetic fractures, nerve injuries, and other important complications are summarised in Table 7.

3.4. Haematological management and complications

Clotting factor replacement was most commonly administered as boluses, but many studies failed to specifically report this, as well as the use of tranexamic acid, transfusion requirements and haemoglobin levels (Supplementary Tables 5-6). Four studies reported giving factor replacement to support outpatient physiotherapy post-operatively [18, 23, 28, 31].

The most commonly reported haematological complication was haemarthrosis, but there was no correlation with either 10-year survivorship (Spearman's Rho, $p = 0.53$) or infection rate (Spearman's Rho, $p = 0.90$).

Deep vein thrombosis (DVT) and pulmonary embolism (PE) were reported in some studies. Thromboprophylaxis regimens were inconsistently reported and could not be correlated with rates of thrombo-embolism (Supplementary Table 7).

3.5. ROM and PROMs

Thirteen studies reported overall ROM, with nine reporting a statistically significant improvement of 10-20° (Table 8). Meta-analysis of the five studies which reported consistent summary statistics found an overall ROM improvement of 18.83° (from 65.32° to 84.15°, Figure 5). All studies reporting flexion contracture found significant improvements, but of the six specifically reporting maximum flexion, only one found a statistically significant improvement [29].

PROMS were reported in 15 studies using a variety of scoring tools (Supplementary Table 6). The Knee Society Score (KSS) was the most commonly used, and demonstrated statistically significant improvements of 37-47 points in Clinical score, and 16-45 in Functional score (Table 9). These are greater than previously reported Minimum Clinically Important Difference (MCID) values, which are 9 for Clinical and 10 for Functional scores respectively [39]. Across all scoring tools used, the studies reported large and statistically significant improvements in PROMS following TKA [18, 21, 22, 25, 29, 32, 33].

4. Discussion

4.1. Survivorship

The reported survivorship of TKA in PwH has been generally acknowledged to be worse than in non-PwH, but the figures reported vary widely. The current meta-analysis shows that survivorship is the same in PwH as the NJR data for patients aged < 55 at 5 years, but declined thereafter with 10- and 15-year survivorship being 4% and 10% lower [4]. The PwH data was limited and less reliable at later time points.

In the current meta-regression, survivorship was negatively correlated with HIV prevalence, but was increasing over time, as surgical technique, implant technology, and haematological treatment improved [no haemophilia patient has contracted HIV from contaminated blood products in the UK since 1986 (22)].

Reasons for revision were mixed, with similar numbers of studies reporting a predominance of aseptic loosening over infection and vice versa. Haemophilic arthropathy may predispose to aseptic loosening due to reduced bone quality, or due to severe pre-op deformity affecting implant alignment [18, 40]. Several reviewed studies reported wear and fracture of the polyethylene inserts [10, 20, 21, 31] and severe instability [12]. Some authors have suggested an alternative mechanism, by which periarticular microhaemorrhages cause reactive destruction of the peri-prosthetic bone and cement interfaces [22, 23, 41, 42].

4.2. Infection, HIV, and CD4+ count

The prosthetic joint infection rate was 5% at a mean follow-up of 8.2 years, although this varied widely (0-18.7%). By comparison, the NJR reports 0.87 revisions for infection per 1000 prosthesis-years [4], and a 2012 systematic review reported a 0.5-1% infection rate at 10 years [43]. The infection rate was lower in more recent studies, which may be due to improvements in haematological management, anti-retroviral therapy, or the use of antibiotic-loaded bone cement.

Infection rates increased with higher prevalence of HIV, although this was not statistically significant. Nine studies performed sub-group analyses of infection rate versus HIV status or CD4+ counts, and all except one [24] found no evidence to support a causal relationship. This contradicts the earlier results of Ragni et al (1995) which suggested that patients with low CD4+ counts were at increased risk of infection, and counselled against TKA in patients with <200 cells/ml^3 [8]. The present

analysis suggest that since the introduction of HAART in 1996 [11], the HIV no longer has a major impact on infection risk in PwH.

The data suggest that PwH are at increased risk of infection regardless of HIV status. Possible mechanisms include increased incidence of wound healing problems [20, 32] and infection of haemarthroses [28, 44]. Many studies also stressed the importance of haematogenous seeding of skin flora during infusions of coagulation factors, which PwH require frequently and may self-administer at home. This is consistent with reports that *Staphylococcus aureus, epidermidis*, and *Streptococci* dominated the cultures isolated from infected prostheses [10, 21, 26, 31]. Several authors stressed the importance of promoting rigorous aseptic technique via training and education for PwH [12, 18, 21, 23, 31, 33]. Although there is no comparative trial evidence that this decreases infection rate, it is a low-cost and risk-free intervention which merits universal adoption.

4.3. Other complications

The true rate of complications was difficult to establish due to inconsistencies in reporting. Many studies did not report either the presence or absence of complications such as nerve injury or peri-prosthetic fracture, leaving uncertainty as to whether they were not observed, or not included in the data collection. Most did not clearly define the complications observed, making it difficult to interpret reports of 'nerve injury', 'stiffness', and 'bleeding', and precluding formal comparison with non-PwH.

Peri-prosthetic fractures were reported in seven studies, totalling 15 cases, an incidence of 1.2% [15/1264, excluding Hicks et al [24] who only collected infection data]. The reported incidence in the general TKA population ranges from 0.3-2.5% [45] but given the heterogeneity of the studies reviewed, as well as of the previous literature, it was not possible to conclude whether PwH are at increased risk of peri-prosthetic fracture.

Arterial injury was reported in two TKAs (0.16%), with previous literature estimating the incidence of arterial injury after TKA at 0.03-0.2% [46]. Geniculate artery pseudoaneurysm was reported in two TKAs (0.16%), but was rarer in the general TKA population, with one previous study of 4350 patients reporting three cases (0.07%) [47].

Most studies did not comment on nerve injury. Three studies reported a total of four cases of neuropraxia which fully recovered [23, 29, 36], one reporting 10 cases of "nerve impairment" [26] and another reporting two cases of "nerve injury" without further details [27]. The incidence ranged from 0.9-18.5% in individual studies, or 1.3% across all studies (16/1264), compared to 0.16-1.3% in the general TKA population [48, 49].

VTE was reported in five studies, with four cases of DVT (two symptomatic) across three studies, and three cases of PE across three studies (7/1264, 0.55%) compared to 0.4% to 3% in non-PwH [50]. Reporting was however inconsistent, with some studies including only symptomatic VTEs while others used ultrasound to detect asymptomatic cases, and the incidence being reported at different time points [inpatient, 10 or 90 days [50]]. Acknowledging these limitations, the VTE rate in PwH was not to be increased in the reviewed studies, despite the consensus practice that haemophilia patients required either no thromboprophylaxis or compression stockings only. The broader literature is divided on this topic, some studies reporting a higher incidence of DVTs, bleeding, and requirement for transfusion [51] in PwH, while others report no difference [52].

4.4. ROM and PROMs

The ROM improvements were modest (10-20°), but the PROMS data demonstrated large improvements above MCID thresholds. Several studies commented that PROMS improved disproportionately to the ROM gains, suggesting that because PwH had adapted to their disability, they had different expectations, and had developed the skills and supportive care to derive greater

function from a given ROM than non-PwH [33, 34]. The data suggested that the ROM gains were largely due to reduction of flexion contracture rather than improved maximum flexion. Biomechanically, relatively small gains in extension can allow patients to stand, weight-bear and walk more efficiently, as well as lying supine more comfortably [53].

4.5. Limitations

The available evidence on this topic was of limited quality. There was high risk of bias, and all studies were retrospective cohorts, with the exception of one small series of 13 prospectively identified cases [25]. There was no consistency in the reporting of follow-up duration, survivorship time-points, complications, PROMS or statistics, the heterogeneity precluding meta-analysis for much of the data.

5. Conclusion

Patients with haemophilia undergoing TKA had lower implant survivorship after the first 5 years and a six-fold higher rate of infection than non-haemophiliac patients aged < 55 years. Survivorship has improved over time with advances in surgical and medical management. HIV status influenced survivorship, but did not have a significant effect on infection rate, even with a low CD4+ count. In light of this, excluding patients from TKA who have CD4+ count below 200 cells/mm^3 may no longer be valid. PwH experienced a modest gain in range of movement but a significant improvement in quality of life.

TKA remains the best management option for patients with end-stage haemophilic arthropathy, but high quality data is required on survivorship, complications and outcomes, with the use of modern techniques and implants, to inform consent and decision making. Due to the relative rarity of PwH, this will require prospective multicentre studies, with standardised reporting, which will facilitate meta-analysis.

References

1. Beeton K, Rodriguez-Merchan EC, Alltree J (2000) Total joint arthroplasty in haemophilia. Haemoph Off J World Fed Hemoph 6:474–481. https://doi.org/10.1046/j.1365-2516.2000.00443.x

2. Solimeno LP, Pasta G (2017) Knee and Ankle Arthroplasty in Hemophilia. J Clin Med 6:. https://doi.org/10.3390/jcm6110107

3. Mortazavi SJ, Bagheri N, Farhoud A, et al (2020) Total Knee Arthroplasty in Patients with Hemophilia: What Do We Know? Arch Bone Jt Surg 8:470–478. https://doi.org/10.22038/abjs.2019.42247.2149

4. National Joint Registry Editorial Board and Contributors 18th Annual Report 2021. National Joint Registry of England, Wales, Northern Ireland, the Isle of Man, and Guernsey

5. Rodriguez-Merchan EC (2012) Aspects of current management: orthopaedic surgery in haemophilia. Haemoph Off J World Fed Hemoph 18:8–16. https://doi.org/10.1111/j.1365-2516.2011.02544.x

6. Chiasakul T, Buckner TW, Li M, et al (2020) In-Hospital Complications and Readmission in Patients with Hemophilia Undergoing Hip or Knee Arthroplasty. JB JS Open Access 5:e0085. https://doi.org/10.2106/JBJS.OA.19.00085

7. Moore MF, Tobase P, Allen DD (2016) Meta-analysis: outcomes of total knee arthroplasty in the haemophilia population. Haemoph Off J World Fed Hemoph 22:e275-285. https://doi.org/10.1111/hae.12885

8. Ragni MV, Crossett LS, Herndon JH (1995) Postoperative infection following orthopaedic surgery in human immunodeficiency virus-infected hemophiliacs with CD4 counts < or = 200/mm3. J Arthroplasty 10:716–721. https://doi.org/10.1016/s0883-5403(05)80065-8

9. Fenelon C, Murphy EP, Fahey EJ, et al (2022) Total Knee Arthroplasty in Hemophilia: Survivorship and Outcomes-A Systematic Review and Meta-Analysis. J Arthroplasty 37:581-592.e1. https://doi.org/10.1016/j.arth.2021.10.015

10. Norian JM, Ries MD, Karp S, Hambleton J (2002) Total knee arthroplasty in hemophilic arthropathy. J Bone Joint Surg Am 84:1138–1141. https://doi.org/10.2106/00004623-200207000-00007

11. Mocroft A (2004) Starting highly active antiretroviral therapy: why, when and response to HAART. J Antimicrob Chemother 54:10–13. https://doi.org/10.1093/jac/dkh290

12. Westberg M, Paus AC, Holme PA, Tjønnfjord GE (2014) Haemophilic arthropathy: long-term outcomes in 107 primary total knee arthroplasties. The Knee 21:147–150. https://doi.org/10.1016/j.knee.2013.09.010

13. Sax OC, Douglas SJ, Chen Z, et al (2022) Has modern human immunodeficiency virus therapy decreased complications following total knee arthroplasty? The Knee 36:97–102. https://doi.org/10.1016/j.knee.2022.04.006

14. Page MJ, Moher D, Bossuyt PM, et al (2021) PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. BMJ n160. https://doi.org/10.1136/bmj.n160

15. Slim K, Nini E, Forestier D, et al (2003) Methodological index for non-randomized studies (minors): development and validation of a new instrument. ANZ J Surg 73:712–716. https://doi.org/10.1046/j.1445-2197.2003.02748.x

16. Kontopantelis E, Reeves D (2012) Performance of statistical methods for meta-analysis when true study effects are non-normally distributed: A simulation study. Stat Methods Med Res 21:409–426. https://doi.org/10.1177/0962280210392008

17. Fisher D, Harris R, Bradburn M, et al (2006) METAN: Stata module for fixed and random effects meta-analysis

18. Bae J-K, Kim K-I, Lee S-H, Yoo M-C (2020) Mid-to Long-Term Survival of Total Knee Arthroplasty in Hemophilic Arthropathy. J Clin Med 9:E3247. https://doi.org/10.3390/jcm9103247

19. Carulli C, Innocenti M, Linari S, et al (2021) Joint replacement for the management of haemophilic arthropathy in patients with inhibitors: A long-term experience at a single Haemophilia centre. Haemoph Off J World Fed Hemoph 27:e93–e101. https://doi.org/10.1111/hae.14169

20. Chevalier Y, Dargaud Y, Lienhart A, et al (2013) Seventy-two total knee arthroplasties performed in patients with haemophilia using continuous infusion. Vox Sang 104:135–143. https://doi.org/10.1111/j.1423-0410.2012.01653.x

21. Chiang CC, Chen PQ, Shen MC, Tsai W (2008) Total knee arthroplasty for severe haemophilic arthropathy: long-term experience in Taiwan. Haemoph Off J World Fed Hemoph 14:828–834. https://doi.org/10.1111/j.1365-2516.2008.01693.x

22. Ernstbrunner L, Hingsammer A, Catanzaro S, et al (2017) Long-term results of total knee arthroplasty in haemophilic patients: an 18-year follow-up. Knee Surg Sports Traumatol Arthrosc Off J ESSKA 25:3431–3438. https://doi.org/10.1007/s00167-016-4340-6

23. Goddard NJ, Mann HA, Lee CA (2010) Total knee replacement in patients with end-stage haemophilic arthropathy: 25-year results. J Bone Joint Surg Br 92:1085–1089. https://doi.org/10.1302/0301-620X.92B8.23922

24. Hicks JL, Ribbans WJ, Buzzard B, et al (2001) Infected joint replacements in HIV-positive patients with haemophilia. J Bone Joint Surg Br 83:1050–1054. https://doi.org/10.1302/0301-620x.83b7.11242

25. Jenkins PJ, Ekrol I, Lawson GM (2013) Total knee replacement in patients with haemophilia: the Scottish experience. Scott Med J 58:223–227. https://doi.org/10.1177/0036933013507870

26. Jiang C, Zhao Y, Feng B, et al (2018) Simultaneous bilateral total knee arthroplasty in patients with end-stage hemophilic arthropathy: a mean follow-up of 6 years. Sci Rep 8:1608. https://doi.org/10.1038/s41598-018-19852-7

27. Li Z, Feng B, Du Y, et al (2020) Complications of total knee arthroplasty in patients with haemophilia compared with osteoarthritis and rheumatoid arthritis: A 20-year single-surgeon cohort. Haemoph Off J World Fed Hemoph 26:861–866. https://doi.org/10.1111/hae.14115

28. Oyarzun A, Barrientos C, Barahona M, et al (2020) Knee haemophilic arthropathy care in Chile: Midterm outcomes and complications after total knee arthroplasty. Haemoph Off J World Fed Hemoph 26:e179–e186. https://doi.org/10.1111/hae.14004

29. Panotopoulos J, Ay C, Trieb K, et al (2014) Outcome of total knee arthroplasty in hemophilic arthropathy. J Arthroplasty 29:749–752. https://doi.org/10.1016/j.arth.2013.07.014

30. Santos Silva M, Rodrigues-Pinto R, Rodrigues C, et al (2019) Long-term results of total knee arthroplasty in hemophilic arthropathy. J Orthop Surg Hong Kong 27:2309499019834337. https://doi.org/10.1177/2309499019834337

31. Silva M, Luck JV (2005) Long-term results of primary total knee replacement in patients with hemophilia. J Bone Joint Surg Am 87:85–91. https://doi.org/10.2106/JBJS.C.01609

32. Solimeno LP, Mancuso ME, Pasta G, et al (2009) Factors influencing the long-term outcome of primary total knee replacement in haemophiliacs: a review of 116 procedures at a single institution. Br J Haematol 145:227–234. https://doi.org/10.1111/j.1365-2141.2009.07613.x

33. Song SJ, Bae JK, Park CH, et al (2018) Mid-term outcomes and complications of total knee arthroplasty in haemophilic arthropathy: A review of consecutive 131 knees between 2006 and 2015 in a single institute. Haemoph Off J World Fed Hemoph 24:299–306. https://doi.org/10.1111/hae.13383

34. Zingg PO, Fucentese SF, Lutz W, et al (2012) Haemophilic knee arthropathy: long-term outcome after total knee replacement. Knee Surg Sports Traumatol Arthrosc Off J ESSKA 20:2465–2470. https://doi.org/10.1007/s00167-012-1896-7

35. Chen C-F, Yu Y-B, Tsai S-W, et al (2022) Total knee replacement for patients with severe hemophilic arthropathy in Taiwan: A nationwide population-based retrospective study. J Chin Med Assoc JCMA 85:228–232. https://doi.org/10.1097/JCMA.0000000000000646

36. Lee HW, Park CH, Bae DK, Song SJ (2022) How much preoperative flexion contracture is a predictor for residual flexion contracture after total knee arthroplasty in hemophilic arthropathy and rheumatoid arthritis? Knee Surg Relat Res 34:20. https://doi.org/10.1186/s43019-022-00146-2

37. Howick J, Chalmers I, Glasziou P, et al (2011) Explanation of the 2011 Oxford Centre for Evidence-Based Medicine (OCEBM) Levels of Evidence (Background Document)

38. Srivastava A, Santagostino E, Dougall A, et al (2020) WFH Guidelines for the Management of Hemophilia, 3rd edition. Haemophilia 26:1–158. https://doi.org/10.1111/hae.14046

39. Lizaur-Utrilla A, Gonzalez-Parreño S, Martinez-Mendez D, et al (2020) Minimal clinically important differences and substantial clinical benefits for Knee Society Scores. Knee Surg Sports Traumatol Arthrosc 28:1473–1478. https://doi.org/10.1007/s00167-019-05543-x

40. Rodriguez-Merchan EC, Valentino LA (2016) Orthopedic disorders of the knee in hemophilia: A current concept review. World J Orthop 7:370–375. https://doi.org/10.5312/wjo.v7.i6.370

41. Figgie MP, Goldberg VM, Figgie HE 3rd, et al (1989) Total knee arthroplasty for the treatment of chronic hemophilic arthropathy. Clin Orthop 98–107

42. Nelson I, Sivamurugan S, Latham P, et al (1992) Total hip arthroplasty for hemophilic arthropathy. Clin Orthop 276:210–213

43. Carr AJ, Robertsson O, Graves S, et al (2012) Knee replacement. Lancet Lond Engl 379:1331–1340. https://doi.org/10.1016/S0140-6736(11)60752-6

44. Solimeno L, Luck J, Fondanesche C, et al (2012) Knee arthropathy: when things go wrong. Haemoph Off J World Fed Hemoph 18 Suppl 4:105–111. https://doi.org/10.1111/j.1365-2516.2012.02834.x

45. Kim K-I, Egol KA, Hozack WJ, Parvizi J (2006) Periprosthetic Fractures after Total Knee Arthroplasties: Clin Orthop 446:167–175. https://doi.org/10.1097/01.blo.0000214417.29335.19

46. Smith DE, McGraw RW, Taylor DC, Masri BA (2001) Arterial complications and total knee arthroplasty. J Am Acad Orthop Surg 9:253–257. https://doi.org/10.5435/00124635-200107000-00005

47. Wilson JS, Miranda A, Johnson BL, et al (2003) Vascular injuries associated with elective orthopedic procedures. Ann Vasc Surg 17:641–644. https://doi.org/10.1007/s10016-003-0074-2

48. Shetty T, Nguyen JT, Sasaki M, et al (2018) Risk factors for acute nerve injury after total knee arthroplasty. Muscle Nerve 57:946–950. https://doi.org/10.1002/mus.26045

49. Carender CN, Bedard NA, An Q, Brown TS (2020) Common Peroneal Nerve Injury and Recovery after Total Knee Arthroplasty: A Systematic Review. Arthroplasty Today 6:662–667. https://doi.org/10.1016/j.artd.2020.07.017

50. Santana DC, Emara AK, Orr MN, et al (2020) An Update on Venous Thromboembolism Rates and Prophylaxis in Hip and Knee Arthroplasty in 2020. Med Kaunas Lith 56:E416. https://doi.org/10.3390/medicina56090416

51. Rosas S, Buller LT, Plate J, et al (2021) Total Knee Arthroplasty among Medicare Beneficiaries with Hemophilia A and B Is Associated with Increased Complications and Higher Costs. J Knee Surg 34:372–377. https://doi.org/10.1055/s-0039-1696691

52. Wang S-H, Chung C-H, Chen Y-C, et al (2019) Does Hemophilia Increase Risk of Adverse Outcomes Following Total Hip and Knee Arthroplasty? A Propensity Score-Matched Analysis of a Nationwide, Population-Based Study. J Arthroplasty 34:2329-2336.e1. https://doi.org/10.1016/j.arth.2019.05.062

53. Su EP (2012) Fixed flexion deformity and total knee arthroplasty. J Bone Joint Surg Br 94-B:112–115. https://doi.org/10.1302/0301-620X.94B11.30512

Figures and tables

2. Methods

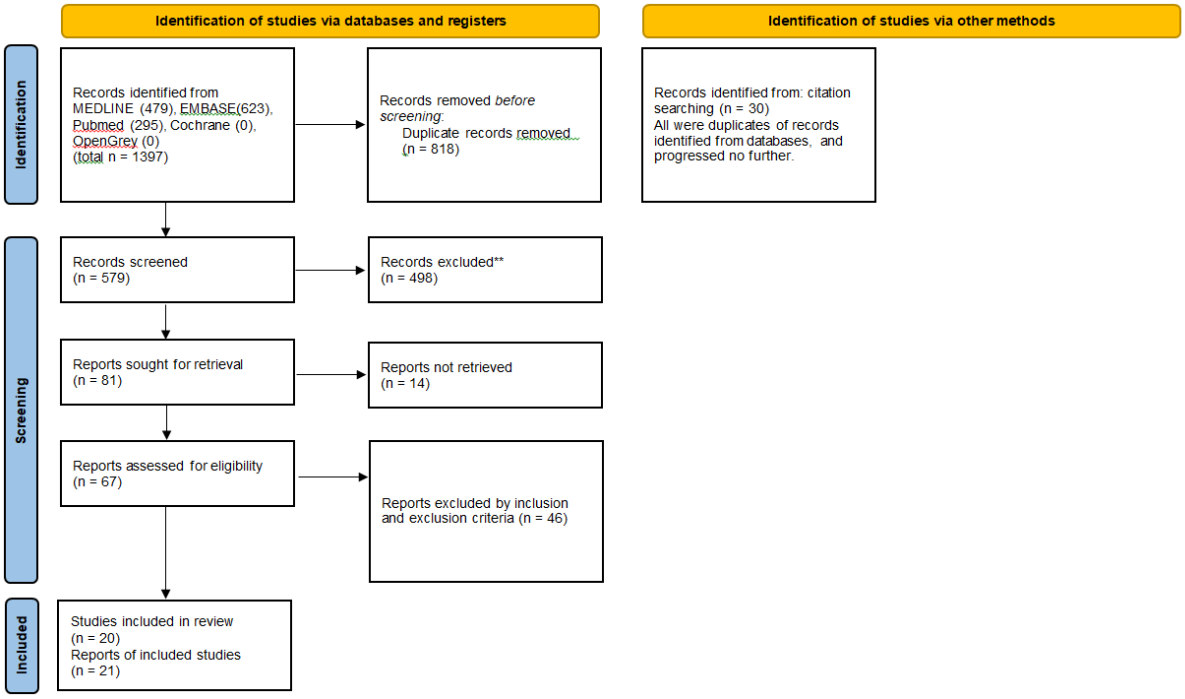

Figure 1 PRISMA flowchart

3. Results

Study	Country	Operation year range	Num. of patients	Num. of TKAs	Average follow-up (yrs)	Study design	CEBM level of evidence	MINORS score
Bae 2020	South Korea	2007-2015	56	78	10.2	Retrospective review, single-centre, two-surgeon, non-comparative, TKA using navigation assistance or robotic assistance (ROBODOC) unless contraindicated	4	10/16
Carulli 2021	Italy	1999-2017	13	19	12.2	Retrospective review, single-centre, non-comparative	4	11/16
Chen 2022	Taiwan	1995-2011	75	103	6.49	Retrospective review, single-centre, non-comparative	4	11/16
Chevalier 2013	France	1992-2010	51	72	7.8	Retrospective review, single-centre, non-comparative	4	11/16
Chiang 2008	Taiwan	1985-2006	26	35	6.9	Retrospective review, single-centre, single-surgeon, non-comparative	4	7/16
Ernstbrunner 2017 †	Switzerland		30	43	18	Further follow-up of patients in previous retrospective review at a single centre (Zingg 2012, below), non-comparative	4	8/16
Goddard 2010	UK	1983-2007	57	70	9.2	Retrospective review, single-centre, non-comparative	4	10/16
Hicks 2001	UK, US, Australia	1973-1998	73	74	5.7	Multicentre retrospective review, HIV +ve patients only, collecting data only on infection and revision, non-comparative	4	7/16
Jenkins 2013	UK	1999-2007	8	13	0	Prospective follow-up, single-centre, two-surgeon, non-comparative	4	10/16
Jiang 2018	China	2005-2015	36	54	6.2	Retrospective review, single-centre, single-surgeon, comparison of simultaneous bilateral vs unilateral TKA	4	11/16
Lee 2022	South Korea	2002-2018	37	48	8.8	Retrospective review, multi-centre, comparison of unilateral vs simultaenous vs staged bilateral TKA	4	10/16
Li 2020	China	1997-2017	78	109	6.1	Retrospective review, single-centre, single-surgeon, comparison between patients with haemophilic arthropathy vs osteoarthritis vs rheumatoid arthritis	4	16/24

Norian 2002	USA	1976-1998	38	53	9.2	Retrospective review, single-centre, non-comparative	4	10/16
Oyarzun 2020	Chile	2007-2013	41	60	7	Retrospective review, single-centre, three-surgeon, non-comparative	4	9/16
Panotopoulos 2014	Austria		32	45	7.4	Retrospective review, single-centre, single-surgeon, non-comparative	4	10/16
Santos Silva 2019	Portugal	1990-2013	15	18	11.3	Retrospective review, single-centre, single-surgeon, non-comparative	4	10/16
Silva 2005	USA	1975-2001	68	90	7.8	Retrospective review, single-centre, single-surgeon, non-comparative	4	10/16
Solimeno 2009	Italy	1993-2007	92	116	5.1	Retrospective review, single-centre, non-comparative	4	12/16
Song 2018	South Korea	2006-2015	102	131	6.8	Retrospective review, single-centre, non-comparative	4	11/16
Westberg 2014	Norway	1979-2011	74	107	11.2	Retrospective review, single-centre, non-comparative	4	10/16
Zingg 2012 †	Switzerland	1985-2004	30	43	9.4	Retrospective review, single-centre	4	10/16

Table 1 Summary of included studies. †, these two studies report on the same cohort of patients at different time points; UK, United Kingdom; US, United States of America

Study	Average age	Age range	Haemophilia type (%)			Severe disease (%)	Inhibitor +ve (%)	HIV +ve (%)	HCV +ve (%)
			A	B	Other				
Bae 2020	38.7	26-69	89.7	10.3		96.2	7.7	1.3	70.5
Carulli 2021	32‡	25-56	100			100	100		
Chen 2022	32.3	17-56	84	16			0	0	
Chevalier 2013	41	25-69	74.5	25.5		90.2	0	23.5	100
Chiang 2008	34.2	23.4-47	88.5	11.5		88.5	0	0	15.4
Ernstbrunner 2017 †	44		87	13		70		17	
Goddard 2010	43	25-70	71.9	28.1		100	3.5	28	
Hicks 2001	39‡	22-60	92	3	NS (5)	88		100	
Jenkins 2013	44‡	27-60	87.5	12.5		87.5	37.5	37.5	100
Jiang 2018	32.7	15-61							
Lee 2022	46.7		86	14		11	16	0	73
Li 2020			93.6	6.4		44.87			
Norian 2002	33.7	22-67	87	13				76.3	
Oyarzun 2020	42‡	24-72						20	51.2
Panotopoulos 2014	40.7	20-58	75	12.5	vWD (9.4), V/VIII def (3.1)	100	6.3	15.6	100
Santos Silva 2019	39	22-49	93.3	6.7		93.3		46.7	86.7
Silva 2005	40.1	17.5-70.5	88	12		92		67	

Solimeno 2009	39	20-71	96	4		90	8	36	95
Song 2018	41	25-73	87.3	13.7		96.1	7.8	2	68.6
Westberg 2014	41	20-82	78.4	12.2	vWD (5.4), VII def (4.1)	94.6	6.8	9.5	
Zingg 2012 †	44	23-68	86.7	13.3		70	3.3	13	

Table 2 Patient baseline characteristics. ‡, median; inhibitor +ve, patients with clotting factor inhibitors; NS, not specified; vWD, von Willebrand disease; V/VII/VIII def, factor V/VII/VIII deficiency

3.1. Survivorship and revision

Study	Num. of TKAs	Average follow-up (yrs)	% Survivorship (95% confidence interval)							
			1 year	5 years	7 years	10 years	13 years	15 years	20 years	25 years
Bae 2020	78	10.2				97.1	93.20			
Carulli 2021	19	12.2						94.7		
Chen 2022	103	6.49				88.6				
Chevalier 2013	72	7.8		97.3 (89.7-100)		88.4 (77.3-99.5)				
Chiang 2008	35	6.9				85				
Ernstbrunner 2017†	43	18.0		97		86		78	59	
Goddard 2010	70	9.2	100	97 (90-100)		80 (60-98)		80 (60-98)	80 (60-98)	
Hicks 2001	74	5.7				55				
Jenkins 2013	13			100						
Jiang 2018	54	6.2				94.4				
Lee 2022	48	8.8				92				
Li 2020	109	6.1							83.1 (60-94)	
Norian 2002	53	9.2		90 (78-96)						
Oyarzun 2020	60	7.0		92 (82-96)		79 (51-92)				

Panotopoulos 2014	45	7.4						86.4		
Santos Silva 2019	18	11.3				94.3				
Silva 2005	90	7.8	100	90.8 (84-95)		82.7 (72-90)		79.3 (59-88)	79.3 (46-88)	79.3 (12-88)
Solimeno 2009	116	5.1			81.00					
Song 2018	131	6.8		98.5		97.7				
Westberg 2014	107	11.2	99 (97-100)	92 (89-97)		88 (80-94)		73 (62-84)	58 (44-73)	
Zingg 2012†	43	9.4		97		86		86		

Table 3 Survivorship to all cause revision by study. †, these two studies report on the same cohort of patients at different time points

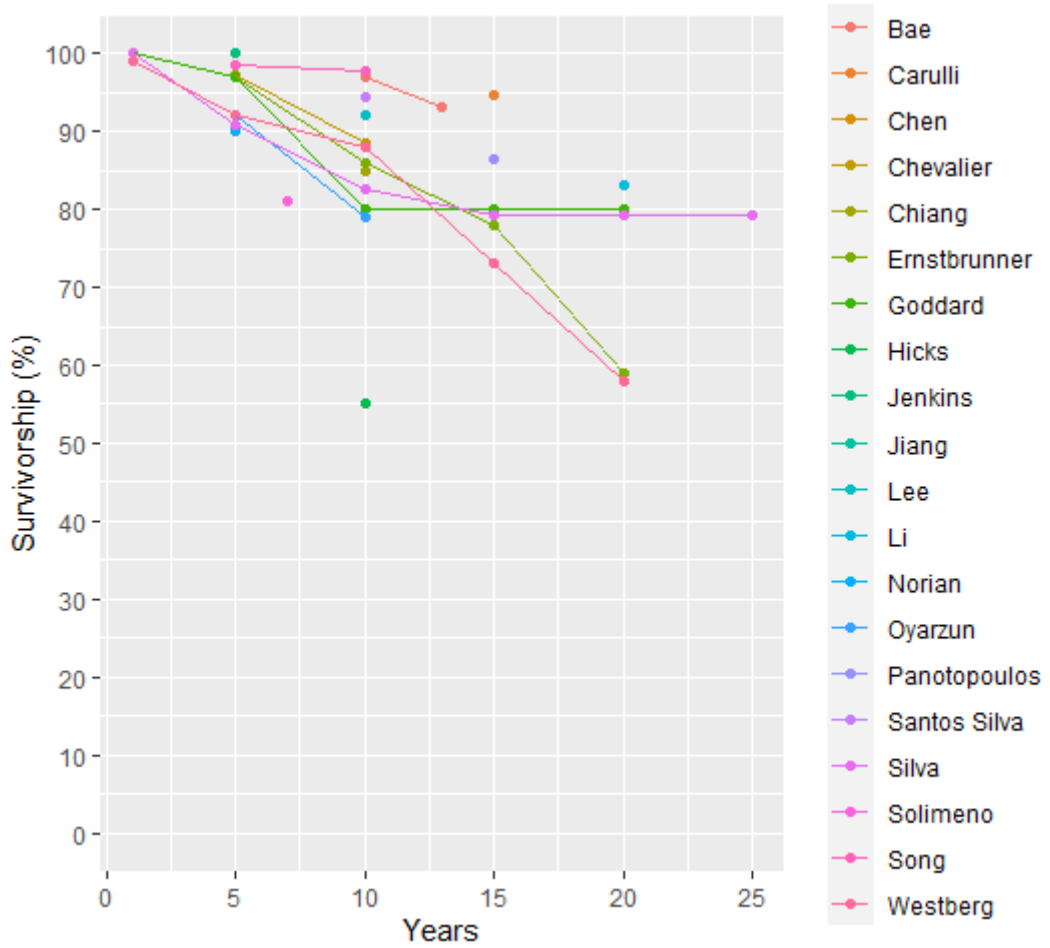

Figure 2 Survivorship over time. Lines connect data points from the same study

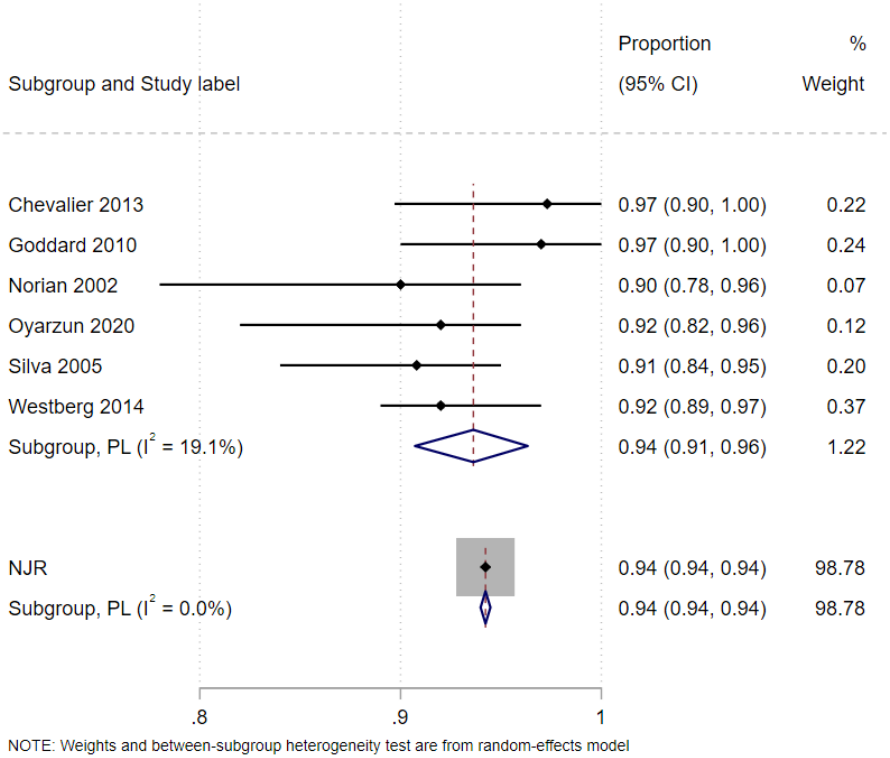
Subgroup and Study label
Proportion
(95% CI)
%
Weight
Chevalier 2013
0.97 (0.90, 1.00)
0.22
Goddard 2010
0.97 (0.90, 1.00)
0.24
Norian 2002
0.90 (0.78, 0.96)
0.07
Oyarzun 2020
0.92 (0.82, 0.96)
0.12
Silva 2005
0.91 (0.84, 0.95)
0.20
Westberg 2014
0.92 (0.89, 0.97)
0.37
Subgroup, PL (I^2 = 19.1%)
0.94 (0.91, 0.96)
1.22
NJR
0.94 (0.94, 0.94)
98.78
Subgroup, PL (I^2 = 0.0%)
0.94 (0.94, 0.94)
98.78
.8
.9
1
NOTE: Weights and between-subgroup heterogeneity test are from random-effects model

Figure 3A Pooled estimate of 5-year survivorship, with NJR data appended for ease of comparison

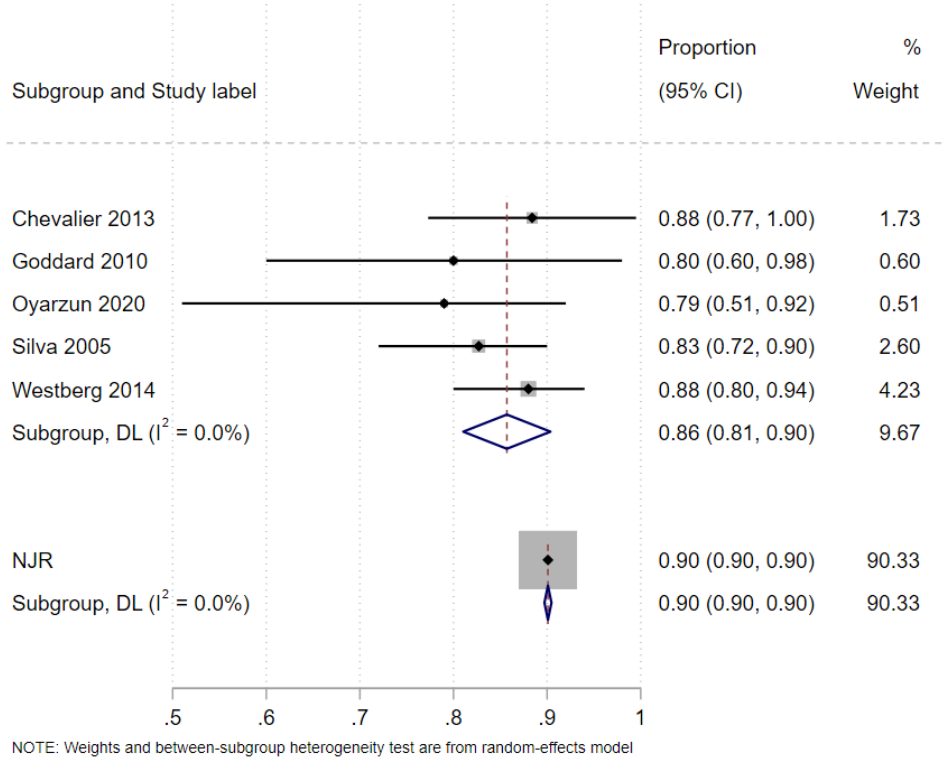

Figure 3B Pooled estimate of 10-year survivorship, with NJR data appended for ease of comparison

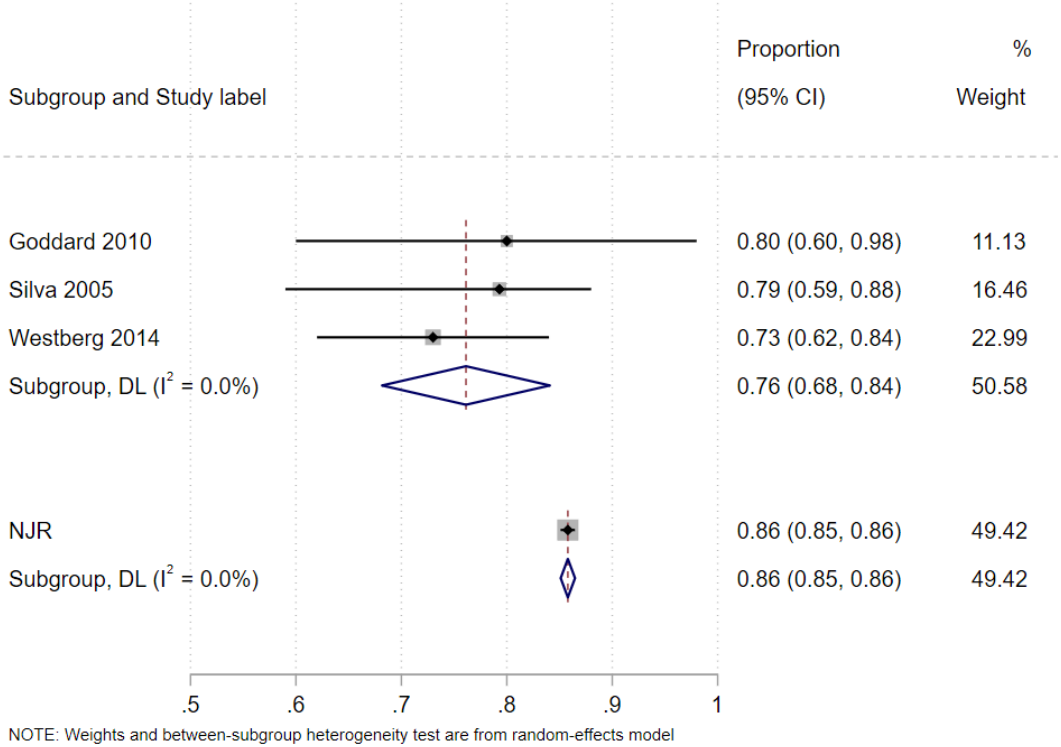

Figure 3C Pooled estimate of 15-year survivorship, with NJR data appended for ease of comparison

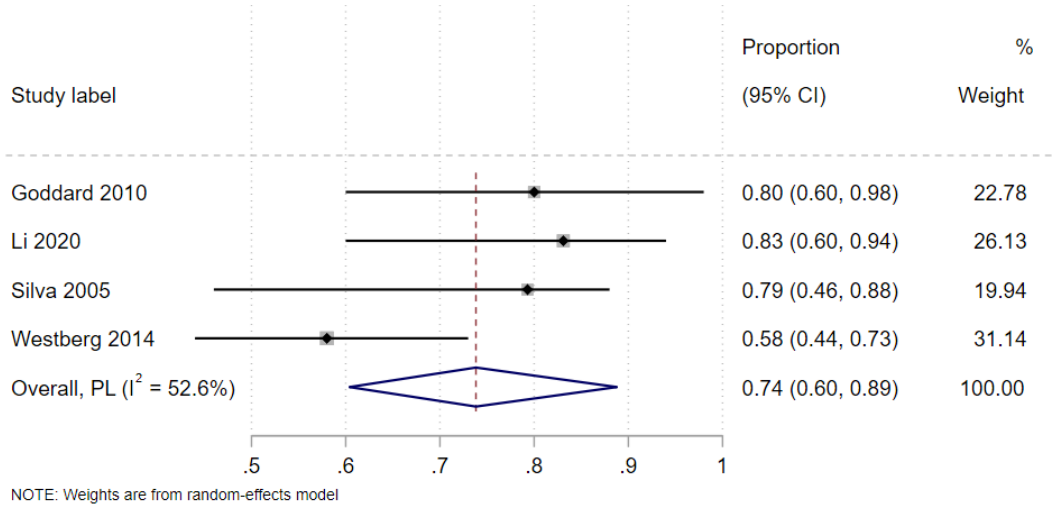

Figure 3D Pooled estimate of 20-year survivorship

Study	Num. of TKAs	Revision rate (%)	Num. revisions (n)	Reasons for revision		
				Infection	Aseptic loosening	Other
Bae 2020	78	3.8	3	2	1	
Carulli 2021	19	4.8	1		1	
Chen 2022	103	7.8	8	4	4	
Chevalier 2013	72	5.6	4		4‡	
Chiang 2008	35	8.6§	3§	1	2	
Ernstbrunner 2017†	43	33	14	5	8	1 trauma knee perforation
Goddard 2010	70	10	7	1	6	
Hicks 2001	74	-				
Jenkins 2013	13	0	0			
Jiang 2018	54	5.6	3	2	1	
Lee 2022	48	8.3	4	3	1	
Li 2020	109	-				
Norian 2002	53	18.9	10	6	1	3 polyethylene wear and osteolysis
Oyarzun 2020	60	10	6	6		
Panotopoulos 2014	45	10	6	2	4	
Santos Silva 2019	18	11.1	2	2		
Silva 2005	90	14.4	13	9	1¶	1 supracondular fracture femur at 3 yrs, 1 recurrent haemarthrosis due to synovial impingement under patellar

						implant, 1 fractured polyethylene insert
Solimeno 2009	116	14	16	9	7	
Song 2018	131	2.3	3	3		
Westberg 2014	107	26	28	7	14	3 pain, 3 severe instability, 1 recurrent haemarthrosis
Zingg 2012†	43	7	3	1	1	1 trauma causing knee perforation

Table 4 Reasons for revision surgery. †, these two studies report on the same cohort of patients at different time points; ‡ 6 loose but only 4 revised; § additional 2 patients with infection had open debridement after which prosthesis was successfully retained; ¶ aseptic loosening due to pseudotumour of tibia

Variable	Coefficient	p-value	95% CI	Number of studies
Year of first operation	0.007	0.002**	(0.003, 0.011)	9
Year of last operation	0.015	0.000***	(0.008, 0.021)	9
Patient average age	0.002	0.782	(-0.015, 0.020)	9
% patients with haemophilia A	-0.004	0.518	(-0.016, 0.008)	9
% patients with severe haemophilia	-0.001	0.709	(-0.004, 0.002)	8
% patients HIV positive	-0.003	0.000***	(-0.004, -0.001)	9
Number of surgeons	0.001	0.968	(-0.046, 0.048)	5

Table 5 Univariate meta-regression of 10-year survivorship against well-reported patient and study characteristics

3.2. Orthopaedic Complications

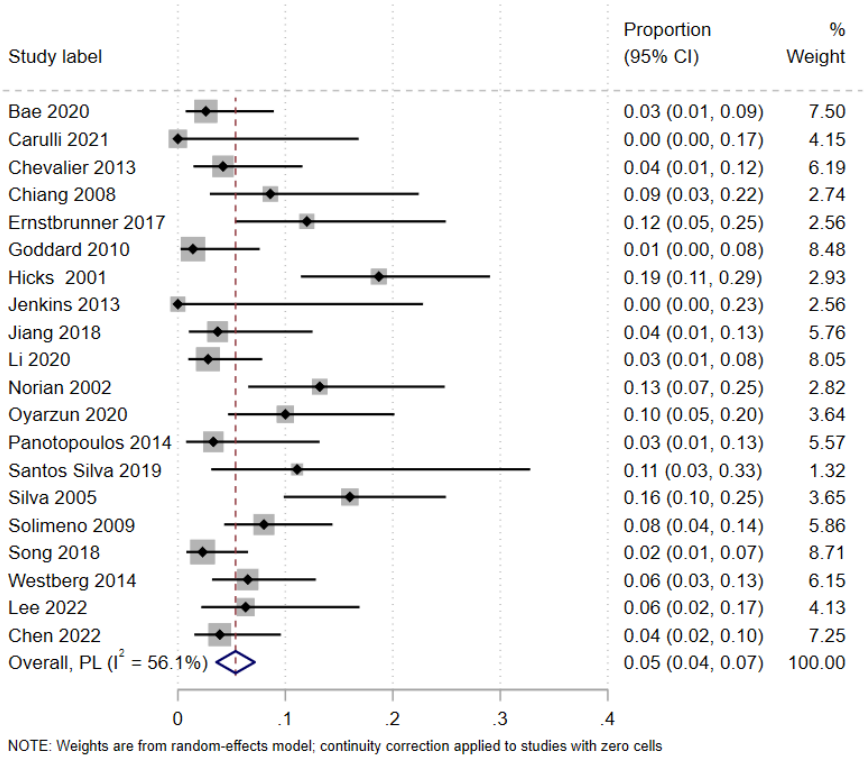

Figure 4A Pooled estimate of prosthetic joint infection rate

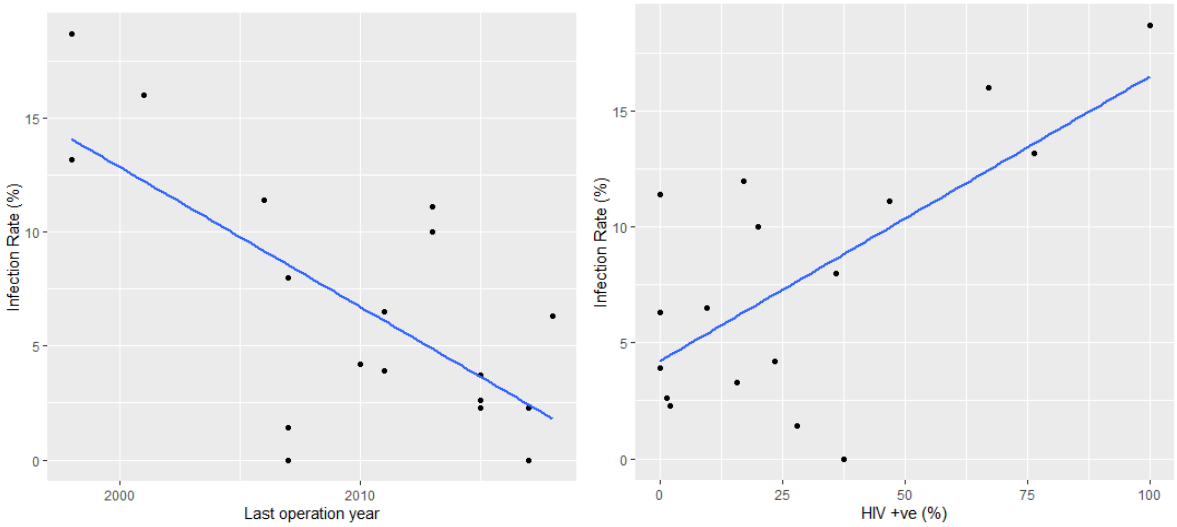

Figure 4B Infection rate over time (p = 0.006) and against HIV prevalence (non-significant, p = 0.1)

Study	Effect of HIV	Details	Effect of CD4 count	Details
Chevalier 2013	No	4 patients with infection, of which 1 was HIV positive and CD4 at time of surgery was 0.378 x 10^9 cells / L Prevalence of HIV in cohort: 23% Overall infection rate: 4.2%; Infection rate in HIV positive patients: 6%"	-	Mean CD4 count: 0.487x10^9 cells/L +/- 0.166 SD
Ernstbrunner 2017	No	Infection rate overall: 12% Infection rate in HIV patients: 20% (1 patient) Prevalence of HIV in cohort: 17%	-	CD4 count at FU: 776 ± 683 sd cells/mm^3
Goddard 2010	No	1 patient developed infection, who was HIV+ve. Authors state no difference in complication rate between the 16 HIV+ve patients and the 41 HIV -ve patients.	-	pre-op CD4 count mean 380 cells/mm^3 post op mean 283 cells/mm^3
Hicks 2001	‡		Yes	Patients with low CD4 count more likely to have sepsis; No prosthetic infection: 400 cells/mm^3 (range 90 – 1210) Prosthetic infection: 310 (30-1300); p <0.01 **
Norian 2002	No	Infection in HIV +ve patients: 4 knees, 10% Infection in HIV -ve patients: 3 knees, 25% Authors stated “HIV positivity did not increase risk of infection	No	No significant difference between infected and uninfected Non-significantly higher in those with infection: 480 ± 363 vs 274 ± 184 cells/mm^3, p = 0.15
Panotopoulos 2022	No	Both infections were in HIV -ve patients Regression model did not find HIV +ve status as a risk factor for infection		
Silva 2005	No	HIV -ve: 13% infection HIV +ve: 17% infection p = 0.5	No	Infection: 434 cells/mm^3 No infection: 450 cells/mm^3 No significant difference
Solimeno 2009	No	Infected patients: 3 patients HIV positive (33%) Uninfected patients: 30 HIV positive (36%), p = not significant	-	-
Westburg 2014	No	No difference in infection rate between patients with or without HIV, p = 0.47 Infection occurred in 1 HIV +ve patient 3 of the 5 patients with infection were IV drug users	-	-

Table 6 Reported relationship between prosthetic infection and HIV status or CD4 count. -, not stated; ‡, 100% of patients were HIV positive

Study	Num. of TKAs	Periprosthetic fracture % (n)	Neuropraxia % (n)	Nerve injury % (n)	Arterial injury % (n)	Wound problems % (n)	Prosthetic infection % (n)	Revised due to infection (n)	Other	Notes
Bae 2020	78	2.6 (2)				1.3 (1)	2.6 (2)	2		Wound dehiscence - secondary closure
Carulli 2021	19	0					0	0		
Chen 2022	103						3.9 (4)	4		
Chevalier 2013	72	2.8 (2)				2.8 (2)	8.3 (6)	0		Fractures occurred at 2 weeks post-op without trauma; "difficult wound healing". Infections: 3 during index admission, of which 2 related to peripheral venous catheters. 3 late post op, at 11, 4, 11 yrs; the lst required surgical washout and others had abx only.
Chiang 2008	35	0	0	0		0	8.6 (3)	1		2 infections had open debridement and implant was retained
Ernstbrunner 2017†	43	0					12 (5)	4		1 infection had open debridement and implant retained. Revisions: 1 arthrodesis, 1 debridement + exchange of polyethylene, 1 antibiotic spacer, 1 removal of components planned but patient died pre-op
Goddard 2010	70	0	2.9 (2)				1.4 (1)	1	1	2 temporary neuropraxia, 1 ulnar 1 sciatic; 1 geniculate artery aneurysm
Hicks 2001	74						18.7 (17)			
Jenkins 2013	13	0				7.7 (1)	0	0		Blisters and epidermolysis in 1 pt with inhibitors

Jiang 2018	54	0	18.5 (10)			11.1 (6)	3.7 (2)	2		Reported "nerve impairment"; 2 superficial wound infection, 4 blisters
Lee 2022	48	2.1 (1)		2.1 (1)			6.3 (3)	3		1 intra-op fracture treated with cannulated screw, 1 post op periprosthetic fracture treated with ORIF, 1 peroneal nerve palsy fully recovered with conservative management
Li 2020	109	0.9 (1)		1.8 (2)	0.9 (1)	3.7 (4)	2.8 (3)			Reported "nerve injury"; 4 wound dehiscence
Norian 2002	53	0					13.2 (7)	6		
Oyarzun 2020	60	0	0	0			10 (6)	6	1	1 geniculate artery pseudoaneurysm
Panotopoulos 2014	45	0	4.4 (2)			2.2 (1)	3.3 (2)	2		2 peroneal nerve palsies which fully recovered with steroids and electrophysical therapy, 1 delayed wound healing
Santos Silva 2019	18	0	0	0	0	0	11.1 (2)	2		
Silva 2005	90	1.1 (1)				1.1 (1)	16 (14)	9	2 knees heterotopic ossification in same patient	1 supracondular femoral fracture at 3 years post-op; 1 wound dehiscence during MUA
Solimeno 2009	116	0			0.9 (1)		8 (9)	9		1 damaged branch of popliteal artery
Song 2018	131	3.1 (4)					2.2 (3)	3	1 MCL injury managed with bracing and altered rehab	4 fractures: 3 femoral needing ORIF and one patella conservatively managed;
Westberg 2014	107	3.7 (4)					6.5 (7)	7		Fractures: "osteosynthesis" without removing TKA
Zingg 2012†	43							1		

Table 7 Orthopaedic complications excluding stiffness. †, these two studies report on the same cohort of patients at different time points

3.4. ROM and PROMs

	Study	ROM pre-op, °	ROM post-op, °	p-value	Flexion pre-op, °	Flexion post-op, °	p-value	Flexion contracture pre-op, °	Flexion contracture post-op, °	p-value
Reporting mean +/- standard deviation	Bae 2020	64.2 ± 37.9	84.2 32.7	< 0.001***				19.2 ± 10.7	4.3 ±4.2	< 0.001***
	Chevalier 2013	78 ± 29	87.8 ± 30 at 3 weeks; 86.1 ± 29 at last visit	0.032*				12.5 ± 11	3.4 ± 4.9	< 0.0001***
	Ernstbrunner 2017†				89 ± 26	89 ± 25 at 2 years; 87 ± 21 at 12 years	not significant	18 ± 12	6 ± 5	< 0.001***
	Jiang 2018	unilateral: 63.89 ± 13.10 bilateral: 67.92 ± 27.13	Unilateral: 88.91 ± 12.90; bilateral: 89.39 ± 13.66	‡						
	Lee 2022	51.9 ± 34.3	74.2 ± 23.3		38.1 ± 32.0	79.8 ± 21.8		16.5 ± 32.0	5.6 ± 6.5	
	Song 2018	63.6 ± 40.9	80.9 ± 30.5	< 0.001***	80.9 ± 37.3	85.6 ± 27.6	0.135	17.3 ± 12.5	4.7 ± 9.5	< 0.001***
	Zingg 2012†				89 ± 26	89 ± 25	not significant	18 ± 12	8 ± 10	< 0.001***
Reporting mean (range)	Carulli 2021	74 (65-105)	102 (90-115)	< 0.005**						
	Goddard 2010	68 (20-130)	79 (20-120)							
	Panotopoulos 2014				82.9 (30-140)	94.1 (30-140)	< 0.0001***	16.3 (0-60)	3.4 (0-40)	< 0.0001***
	Santos Silva 2019		88 (70-120)							
	Silva 2005	59 (5-130)	69 (31-115) early 75 (0-124) late	0.003 early, 0.0002				18 (0-50)	9 (0-25) early, 8 (0-30) latest	< 0.0001***

				late***						
	Westberg 2014	70 (5-125)	79 (15-115)	0.07						
Reporting mean only	Chiang 2008	63.2	79.8	0.02*				15	5.5	< 0.01**
Reporting median (IQR)	Jenkins 2013	35 (17.5-60)	45 (27.5-62.5)	0.007**	52.5 (30-81.25)	55 (45-65)	0.439	15 (1.25-27.5)	2.5 (0-12.5)	0.011*
	Solimeno 2009	75 (45-85)	90 (80-95)	p < 0.01**				5 (0-10)	0 (0-0)	< 0.01**
	Oyarzun 2020	70 (43-80)	83 (73.5-90)	< 0.001***				20 (11-28)	0 (0-10)	< 0.001***
Reporting none	Chen 2022									
	Hicks 2001									
	Li 2020									
	Norian 2002									

Table 8 ROM outcomes. Empty cells = not stated; †, these two studies report on the same cohort of patients at different time points ‡, p values given by authors were for comparison between unilateral and bilateral at each time point, not pre- vs post-op

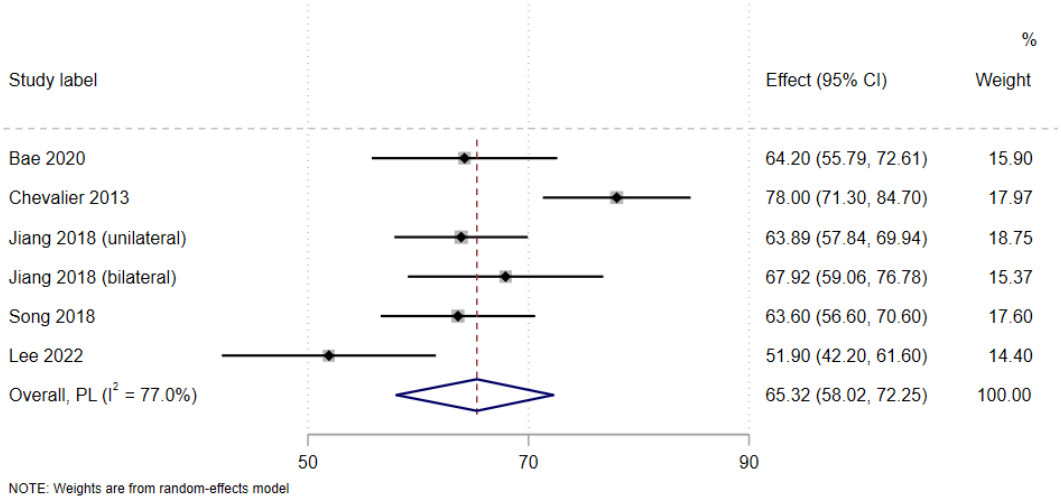

Figure 5A meta-analysis of range of motion pre-op

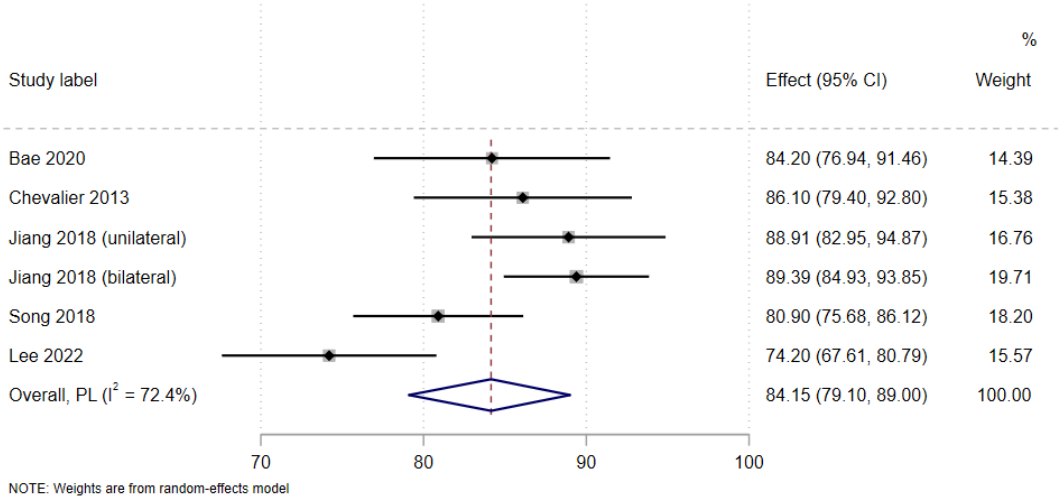

Figure 5B meta-analysis of range of motion post-op

Study	KSS clinical Pre-op	KSS clinical at follow-up	Difference	p-value	KSS functional pre-op	KSS functional at follow-up	Difference	p-value
Chiang 2008					42 (range: 20-50)	77.1 (range: 60-90)		< 0.01**
Ernstbrunner 2017†	36 ± 16	2 years: 73 ±18; 12 years: 73 ± 15	37	< 0.001***	62 ± 19	2 years: 83 ± 19; 12 years: 78 ± 18	16	< 0.001***
Lee 2022	33.5 ± 5.2	76.9 ± 7.3	43.4		33.4 ± 5.5	78.1 ± 4.9	44.7	
Oyarzun 2020		Median: 88 (range: 59-97)				Median: 100 (range: 30-100)		
Silva 2005		81.3 ± 12.3				88.7 ± 15.7		
Song 2018	34.4 ± 13.1	80.9 ± 10.2	46.5	< 0.001***	37.0 ± 9.8	70.3 ± 11.8	33.3	< 0.001***
Zingg 2012†	36 ± 16	73 ± 18	37	< 0.001***	62 ± 19	83 ± 15	21	< 0.001***

Table 9 Reported KSS outcomes. Values are mean +/- standard deviation unless specified otherwise. †, these two studies report on the same cohort of patients at different time points