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Low implantation volume, comorbidities, male sex and implantation of constrained TKA identified as risk factors for septic revision in knee arthroplasty: A register-based study from the German Arthroplasty Registry

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Abstract

Purpose: Periprosthetic joint infection (PJI) is a major cause of revision surgery after total knee arthroplasty (TKA) and unicondylar knee arthroplasty (UKA). Patient- and hospital-related risk factors need to be assessed to prevent PJI. This study identifies influential factors and differences in infection rates between different implant types.

Methods: Data were obtained from the German Arthroplasty Registry. Septic revisions were calculated using Kaplan–Meier estimates with septic revision surgery as the primary endpoint. Patients with constrained and unconstrained TKA or UKA were analysed using Holm's multiple log-rank test and Cox's proportional hazards ratio. The 300,998 cases of knee arthroplasty analysed included 254,144 (84.4%) unconstrained TKA, 9993 (3.3%) constrained TKA and 36,861 (12.3%) UKA with a maximum follow-up of 7 years.

Results: At 1 year, the PJI rate was 0.5% for UKA and 2.8% for TKA, whereas at 7 years, the PJI rate was 4.5% for UKA and 0.9% for TKA ($p < 0.0001$). The PJI rate significantly increased for constrained TKA compared to unconstrained TKA ($p < 0.0001$). The PJI rate was 2.0% for constrained TKA and 0.8% for unconstrained TKA at 1 year and 3.1% and 1.4% at 7 years. Implantation of a constrained TKA (hazard ratio [HR] = 2.55), male sex (HR = 1.84), increased Elixhauser score (HR = 1.18–1.56) and implant volume of less than 25 UKA per year (HR = 2.15) were identified as risk factors for revision surgery; an Elixhauser score of 0 (HR = 0.80) was found to be a preventive factor.

Conclusions: Reduced implant volume and constrained knee arthroplasty are associated with a higher risk of PJI. Comorbidities (elevated Elixhauser score), male sex and low UKA implant volume have been identified as risk factors for

Abbreviations: ASA, American Society of Anesthesiologists risk classification; BMI, body mass index; CI, confidence interval; DAIR, Debridement, Antibiotics, Implant Retention; EPRD, Endoprothesenregister Deutschland (German Arthroplasty Registry); HR, hazard ratio; ICD-10, 10th International Classification of Diseases; OPS, Operation and Procedure Code 301 system; OR, odds ratio; PJI, periprosthetic joint infection; TKA, total knee arthroplasty; UKA, unicondylar knee arthroplasty.

PJI. Patients who meet these criteria require specific measures to prevent infection. Further research is required on the potential impact of prevention and risk factor modification.

Level of Evidence: Level III.

KEYWORDS
cemented, constrained, infection, knee, revision, unconstrained

INTRODUCTION

A rising trend in primary total knee arthroplasty (TKA) has been observed in both the United States and in Germany [21, 23]. Projections suggest an increase of up to 45% in primary TKA implantations in Germany by 2040 [21]. Key outcome measures for arthroplasty include revision rates, functional outcomes and prosthesis survival. Septic failure stands out as a major cause of revision surgery, incurring costs of up to $74,900 per case [14, 26]. Springer et al. analysed five national arthroplasty registries and reported an annual periprosthetic joint infection (PJI) rate of 1.03% for TKA [25]. Surgical revision for sepsis significantly reduces both functional outcomes and quality of life and has an increased risk of reinfection [19, 32]. Moreover, both short- and long-term mortality rates have been found to increase in patients who develop PJI over a decade, with a hazard ratio (HR) of 1.8 (95% confidence interval: 1.6–2.1) [30]. Unicondylar knee arthroplasty (UKA) is available for patients with isolated unicondylar osteoarthritis, adequate ligament stabilization and minimal leg axis deviation [17]. In TKA, 27% of revisions are due to sepsis compared to only 4% in UKA [28]. Barbera et al. reported an annual PJI incidence in UKA of 0.8% in 2022 [2]. However, a direct comparison of PJI rates between UKA and TKA for the treatment of osteoarthritis in large patient samples is lacking, as is a detailed investigation of the factors influencing the occurrence of PJI after UKA and TKA.

Therefore, the objectives of this study were (1) to determine septic revision rates after UKA and TKA, (2) to investigate potential differences in infection risk between constrained and unconstrained TKA and (3) to identify patient- and hospital-specific risk factors after TKA and UKA. We hypothesized that arthroplasties with a larger coupling would have a higher risk of septic failure.

MATERIALS AND METHODS

Data collection

The study was approved by the Ethics Committee of the University of Kiel (ID: D473/11) and was conducted in accordance with the Declaration of Helsinki. The study is based on the prospective Endoprothesenregister Deutschland (German Arthroplasty Registry) (EPRD) and investigates the septic revisions of unconstrained and constrained TKA and UKA in patients with primary osteoarthritis of the knee. Since 2012, the EPRD has been recording arthroplasty implantations in Germany in cooperation with the statutory health insurance funds (AOK Bundesverband GbR, Verband der Ersatzkassen e.V. vdek), the German Medical Technology Association (BVMed) and several participating hospitals. More than two million procedures have been documented in the registry, representing approximately 70% of all hip and knee arthroplasties performed in Germany by 2022 [6]. The data provided by surgeons are cross-validated by including two participating health insurance companies (AOK-B, vdek), thus covering approximately 65% of the German population. Surgical revisions registered in the EPRD are followed up on the basis of insurance billing data, even if the revision is performed in a hospital not participating in the arthroplasty registry. With the exception of procedures performed outside Germany, this algorithm ensures almost perfect follow-up of patients insured by these companies [10].

The German versions of the International Classification of Procedures in Medicine, the Operation and Procedure Code (OPS) 301 system and the 10th International Classification of Diseases (ICD-10) were used to classify diagnoses and procedures.

Patients

All patients who underwent TKA or UKA for primary osteoarthritis of the knee (ICD-10: M17.0, M17.1) in Germany between November 2012 and September 2022 were included in this analysis. Patients were divided into subpopulations of constrained and unconstrained TKA and UKA. Patient characteristics such as age, sex, body mass index (BMI), Elixhauser comorbidity score and American Society of Anesthesiologists (ASA) score are reported in the registry. Hospital-related factors, such as implant volume and hospital size, are reported in the legally required annual quality reports of hospitals. The Elixhauser score is an index that aggregates a variety of comorbidities from different organ systems and entities [31]. The basis for calculating this score was comorbidities coded during the initial hospitalization for primary arthroplasty. The use of unconstrained or constrained TKA was determined by evaluating the implant used during surgery, using the classification information from the joint product library of the EPRD and the National Joint Registry. Arthroplasties with a cruciate-retaining and a posterior-stabilized designs were classified as unconstrained TKA, whereas constrained nonhinged and constrained hinged arthroplasties were classified as constrained TKA (valgus–varus constrained implant or rotating-hinged implants) [16]. BMI was classified as underweight (<20 kg/m^2), normal weight (20–25 kg/m^2), preobese (25–30 kg/m^2), obesity grade I (30–35 kg/m^2), obesity grade II (35–40 kg/m^2) and obesity grade III (>40 kg/m^2). The infection rate was determined by searching the registry for the ICD-10 code for periprosthetic infection (T84.5). According to the guidelines of the European Bone and Joint Infection Society, cases of PJI diagnosed by surgeons and coded as PJI were recorded in the registry as septic failure [15]. Analysis of OPS codes provided a detailed record of the procedure and site of interest. Surgeon registry data were cross-validated by analysis of insurance data. Exclusion criteria were patients who were not treated for primary osteoarthritis of the knee as the primary diagnosis. Patients with a follow-up of less than 12 months or with a special implant (e.g., tumour prosthesis) were also excluded from data collection. Patients without clear information on the material used were also not included in the analysis (Figure 1).

Statistical analysis

The data were analysed to ascertain infection rates and factors associated with septic revisions in both constrained and unconstrained TKA and UKA in Germany. The statistical programme R (version 4.2; R Foundation for Statistical Computing) was used for statistical analysis. First, descriptive statistics were computed for unconstrained TKA, constrained TKA and UKA. Categorical variables were presented as frequencies and percentages. The three groups were compared using the corrected multiple log-rank test with Holm's method to adjust for multiple comparisons.

Cumulative incidences for the endpoint of septic revision were then calculated using Kaplan–Meier estimates. A Cox proportional hazards model was fitted to evaluate the effect of different knee systems. However, the assumption of constant

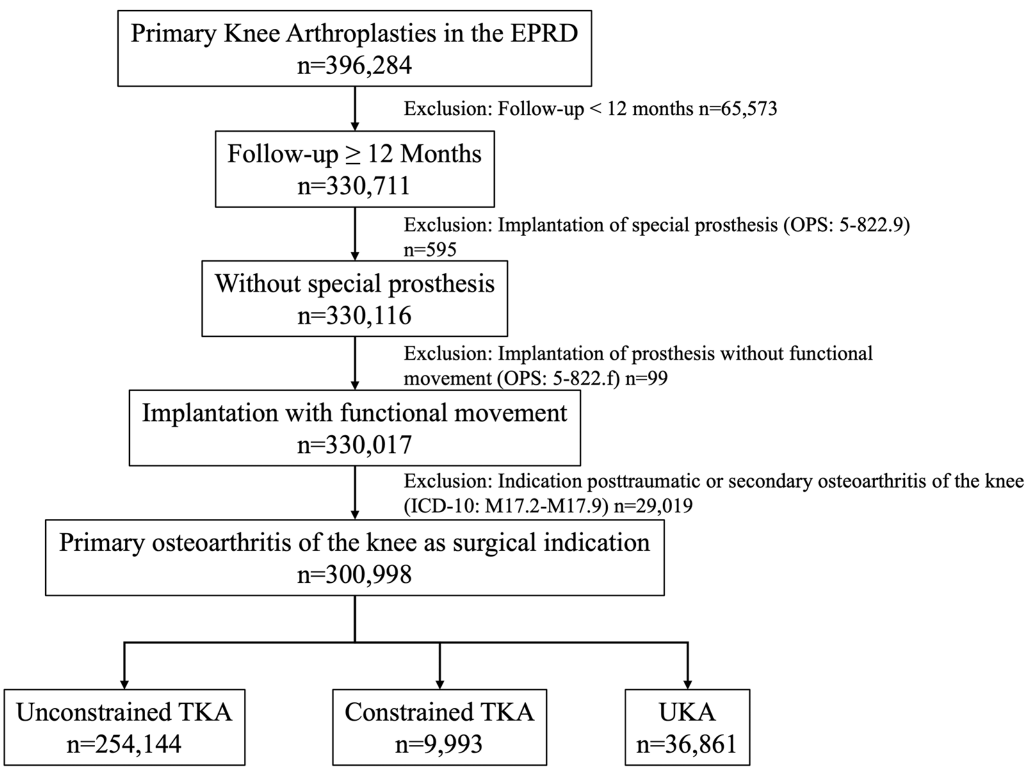

FIGURE 1 Flowchart of patient inclusion and exclusion criteria. EPRD, Endoprothesenregister Deutschland (German Arthroplasty Registry); ICD-10, 10th International Classification of Diseases; OPS, Operation and Procedure Code 301 system; TKA, total knee arthroplasty; UKA, unicondylar knee arthroplasty.

proportional hazards was found to be violated due to confounding variables such as the weighted Elixhauser score, age group and BMI. Consequently, the time axis was split at 6 months after surgery to account for this violation.

Categorical variables are presented as number of observations and frequency, while continuous variables are presented as mean and standard deviation. Significance was assessed at the 5% level. This comprehensive analytical approach ensured a robust examination of infection rates and associated factors across the different knee arthroplasty systems studied.

RESULTS

In the EPRD, 396,284 primary knee arthroplasty procedures were identified. After the exclusion of patients who did not meet the inclusion criteria, 300,998 patients were included in the final analysis, of whom 254,144 (84.4%) had undergone unconstrained TKA, 9993 (3.3%) constrained TKA and 36,861 (12.3%) UKA for primary osteoarthritis of the knee. The patient characteristics of the included TKA and UKA cases are summarized in Table 1. Hospital-related factors regarding the operative volume and size were collected in Table 2.

TABLE 1 Anthropometric data of patient cohort.

Characteristic	Primary osteoarthritis			
	TKA unconstrained, $N = 254,144$	TKA constrained, $N = 9993$	UKA, $N = 36,861$	*p* Value
BMI				<0.001
Underweight (<18.5 kg/m^2)	297 (0.2%)	39 (0.6%)	41 (0.2%)	
Normal (18.5–24.99 kg/m^2)	22,933 (13%)	1392 (20%)	3469 (14%)	
Preobese (25.0–29.99 kg/m^2)	58,596 (34%)	2271 (33%)	9325 (38%)	
Obese grade I (30.0–34.99 kg/m^2)	49,900 (29%)	1662 (24%)	7280 (30%)	
Obese grade II (35.0–39.99 kg/m^2)	25,188 (15%)	865 (13%)	3231 (13%)	
Obese grade III (>40.0 kg/m^2)	14,205 (8.3%)	625 (9.1%)	1309 (5.3%)	
Unknown	83,025	3139	12,206	
Age				<0.001
<55	16,705 (6.6%)	423 (4.2%)	5943 (16%)	
55–64	61,492 (24%)	1503 (15%)	13,373 (36%)	
65–74	86,654 (34%)	2859 (29%)	10,645 (29%)	
75+	89,293 (35%)	5208 (52%)	6900 (19%)	
Sex				<0.001
Female	168,851 (66%)	7796 (78%)	20,796 (56%)	
Male	85,293 (34%)	2197 (22%)	16,065 (44%)	
ASA score				<0.001
1	6038 (11%)	212 (10%)	1235 (15%)	
2	30,288 (56%)	1004 (48%)	5184 (63%)	
3+	17,569 (33%)	896 (42%)	1830 (22%)	
Unknown	200,249	7881	28,612	
Elixhauser score				<0.001
<0	59,003 (23%)	1844 (18%)	8460 (23%)	
0	118,592 (47%)	3882 (39%)	20,607 (56%)	
1–4	27,432 (11%)	1150 (12%)	3308 (9.0%)	
5+	49,117 (19%)	3117 (31%)	4486 (12%)	

Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index; TKA, total knee arthroplasty; UKA, unicondylar knee arthroplasty.

TABLE 2 Characteristics of hospitals performing TKA and UKA implantation in the included patient cohort.

	Primary osteoarthritis			
Characteristic	**TKA unconstrained, *N* = 254,144**	**TKA constrained, *N* = 9993**	**UKA, *N* = 36,861**	***p* Value**
Hospital size (inpatient bed places)				<0.001
Small (0–2500	33,066 (13%)	1306 (13%)	3679 (10%)	
Medium (250–500)	82,953 (33%)	3745 (39%)	10,862 (30%)	
Large (500–1000)	132,021 (53%)	4665 (48%)	21,458 (60%)	
Unknown	6104	277	862	
UKA volume per year				<0.001
0–25	134,270 (54%)	6144 (63%)	9175 (25%)	
26–50	52,058 (21%)	1562 (16%)	7761 (21%)	
51–200	48,944 (20%)	1870 (19%)	9811 (27%)	
200+	13,927 (5.6%)	234 (2.4%)	9535 (26%)	
Unknown	4945	183	579	
TKA volume per year				<0.001
0–50	14,974 (6.1%)	652 (6.7%)	1831 (5.6%)	
51–250	221,561 (90%)	8935 (91%)	25,494 (78%)	
251–500	7640 (3.1%)	144 (1.5%)	3285 (10%)	
500+	3190 (1.3%)	63 (0.6%)	2149 (6.6%)	
Unknown	6779	199	4102	

Abbreviations: TKA, total knee arthroplasty; UKA, unicondylar knee arthroplasty.

Of all patients with TKA, 2.8% required revision due to sepsis at 1 year and 4.5% at 7 years. At the same time, 0.5% of the patients with UKA were diagnosed with PJI and 0.9% needed revision at 7 years. Constrained TKA showed a significantly increased rate of PJI compared to unconstrained TKA ($p < 0.0001$) (Table 3 and Figure 2).

For constrained TKA, the PJI rate was 2.0% at 1 year and 3.1% at 7 years. For unconstrained TKA, the corresponding PJI rates were 0.8% and 1.4%. Thus, constrained TKA had a significantly increased PJI rate compared to unconstrained TKA ($p < 0.0001$) (Table 3 and Figure 3).

Factors influencing PJI in knee arthroplasty were implantation of a constrained TKA (HR = 2.55; 95% CI: 2.18–2.98; $p < 0.001$), male sex (HR = 1.84; 95% CI: 1.69–2.01; $p < 0.001$), increased Elixhauser comorbidity score (HR = 1.18–1.56; 95% CI: 1.01–1.78; $p = 0.033$-$p < 0.001$) and volume of less than 25 UKA implantations per year (HR = 2.15; 95% CI: 1.22–3.79; $p < 0.008$). A preventive factor for septic revision knee arthroplasty was an Elixhauser score of 0 (HR = 0.80; 95% CI: 0.70–0.90; $p < 0.001$). BMI, hospital size and the volume of TKA implantations per year had no significant effect on the development of PJI (Table 4).

DISCUSSION

The main finding of this registry-based study involving more than 300,000 patients was a significantly higher incidence of septic revisions after TKA than after UKA and after constrained TKA than after unconstrained TKA. Male sex comorbidities as indicated by an elevated Elixhauser score, and low UKA implant volume at the treating hospital were identified as factors influencing the development of PJI.

PJI in UKA compared to TKA

In a comprehensive analysis of several arthroplasty registries, Springer et al. reported a PJI rate of 1.0% for TKA [25], which is consistent with the findings by other authors [7, 33]. Given the current high rates of TKA implantation and projected increases, PJIs represent a significant burden to patients and healthcare systems [21, 22, 32]. Premkumar et al. estimated the annual economic burden of TKA-related PJI in the United States to be $1.1 billion [18]. Effective infection prevention requires detailed knowledge of risk factors and incidence rates for different types of implants. Our

TABLE 3 Cumulative rate of PJI for constrained and unconstrained TKA and UKA with corresponding 95% confidence interval.

	1 month	3 months	6 months	1 year	3 years	5 years	7 years
Unconstrained TKA (%) (95% confidence interval)	0.3 (0.3–0.3)	0.5 (0.5–0.5)	0.6 (0.6–0.6)	0.8 (0.7–0.8)	1.1 (1–1.1)	1.2 (1.2–1.3)	1.4 (1.3–1.4)
Constrained TKA (%) (95% confidence interval)	1 (0.8–1.2)	1.5 (1.2–1.7)	1.8 (1.5–2)	2 (1.8–2.3)	2.7 (2.4–3.1)	3 (2.6–3.4)	3.1 (2.7–3.5)
UKA (%) (95% confidence interval)	0.2 (0.2–0.3)	0.4 (0.3–0.4)	0.4 (0.3–0.5)	0.5 (0.5–0.6)	0.7 (0.7–0.8)	0.9 (0.8–1)	0.9 (0.8–1.1)

Abbreviations: PJI, periprosthetic joint infection; TKA, total knee arthroplasty; UKA, unicondylar knee arthroplasty.

research using the EPRD showed a higher percentage of septic revisions in both constrained and unconstrained TKA than in UKA. UKA had significantly lower infection rates, with only 0.9% requiring revision for sepsis at 7 years compared to 4.5% for TKA ($p < 0.0001$). Consistent with our findings, a PJI rate of up to 0.8% has been reported in the literature for UKA [2, 28, 29].

Septic revisions in constrained compared to unconstrained TKA

Literature on septic revisions in constrained TKA is scarce. Westberg et al. investigated septic revision in patients with constrained TKA and reported rates of 3% for acute PJI and 5% for late hematogenous PJI [33]. Cholewinski et al. found 9.3% of patients undergoing septic revision in constrained TKA [5]. To our knowledge, direct comparisons between constrained and unconstrained TKA are lacking. In our study, patients with primary osteoarthritis of the knee who underwent constrained TKA had significantly higher rates of PJI (2.7% required revision at 3 years and 3.1% at 7 years) than patients who underwent unconstrained TKA (1.1% and 1.4%, respectively) ($p < 0.001$).

Factors influencing septic revision

The identification of specific risk factors for the development of PJI is crucial for preventive measures. In our investigation, identified risk factors were implantation of a constrained TKA (HR = 2.55), male sex (HR = 1.84), elevated Elixhauser score (score 1–4: HR = 1.18; score >5: HR = 1.56), and a UKA implant volume below 25 in the treating hospital (HR = 2.15). Blanco et al. identified obesity with a BMI above 30 (odds ratio [OR]: 8.86), diabetes mellitus (OR: 2.33) and comorbidities measured by ASA score III or IV (OR: 15.3) as further significant risk factors [3], which is consistent with our findings and those of other investigations [9, 11, 13, 20]. A preventive factor identified in our study was an Elixhauser score of 0 (HR = 0.80; $p < 0.001$). Patient-related preventive factors are rarely discussed in the literature, but Kunutsor et al. reported a reduced risk of PJI in patients treated with arthroplasty for osteoarthritis compared with other indications and in patients living in rural areas [13].

Clinical practice

The risk of infection, particularly in case of constrained TKA, poses a significant challenge to surgeons due to

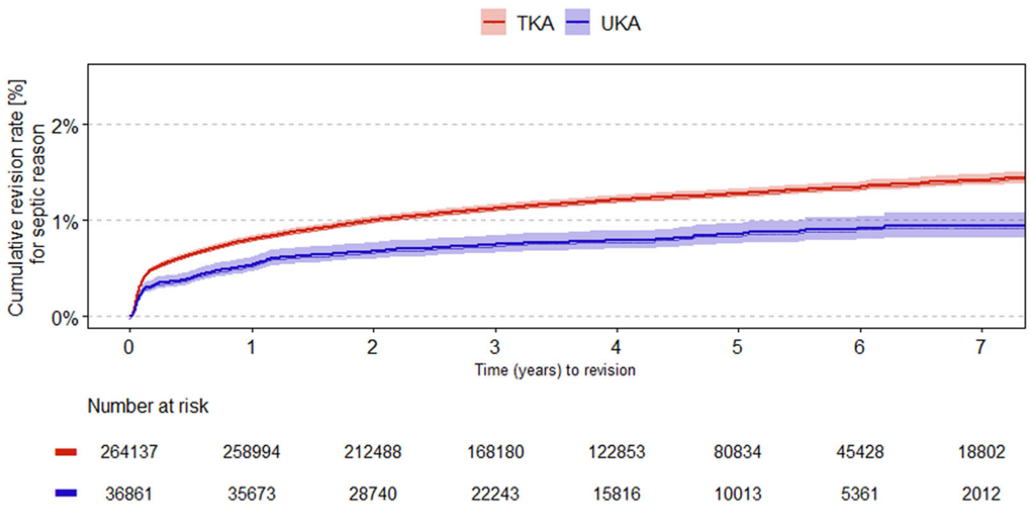

FIGURE 2 Cumulative septic revision rate for TKA (constrained + unconstrained) and UKA ($p < 0.0001$). TKA, total knee arthroplasty; UKA, unicondylar knee arthroplasty.

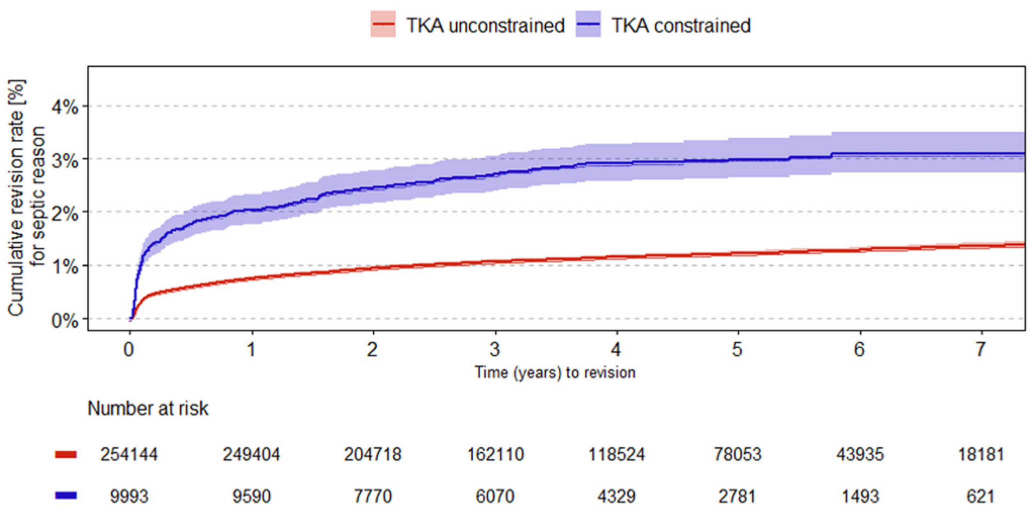

FIGURE 3 Cumulative septic revision rate for constrained and unconstrained TKA ($p < 0.0001$). TKA, total knee arthroplasty.

limited treatment options. In addition to a significant reduction in quality of life and increased mortality rates, septic revision of knee arthroplasty is costly to healthcare systems, with significant discrepancies between reimbursement and actual costs to treating hospitals of up to €8625 per case [24, 30, 32]. Patients with obesity, male sex and comorbidities indicating a higher risk of PJI warrant increased attention. Preoperative optimization of comorbidities is a viable option to reduce PJI [4, 20].

However, modification of these risk factors may take months or years, and clear cutoff values are currently lacking. With regard to diabetes mellitus, it remains unclear whether the disease itself or perioperative hyperglycaemia contributes to an increased risk of PJI. Standardized preoperative preparation, patient wash kits, perioperative antibiotic prophylaxis and close monitoring of patients with arthroplasty are recommended. Prolonged antibiotic prophylaxis has shown promise in reducing PJI rates in high-risk patients [20]. Standardized international guidelines are needed because of regional differences in the use of preventive measures [8]. Another recently reported intervention is the use of prolonged antibiotic prophylaxis. Kheir et al. showed a significant reduction in the PJI rate in high-risk patients with the use of a 7-day postoperative antibiotic prophylaxis from 2.6% to 0.9% ($p < 0.001$) [12]. Considering the adverse side effects and the increased risk of multidrug resistance, prolonged antibiotic prophylaxis remains a sufficient option to reduce PJI in high-risk patients. In the WHiTE 8 trial, the use of high-dose dual antibiotic bone cement in patients older than 60 years undergoing cemented arthroplasty for hip fracture did not significantly reduce the rate of

TABLE 4 HR for PJI in patients with unconstrained or constrained TKA or UKA.

Characteristic	HR	95% CI	*p* Value
Implanted prosthesis			
TKA unconstrained	—	—	
TKA constrained	2.55	2.18–2.98	<0.001
UKA	0.53	0.25–1.14	0.10
Age			
<55	—	—	
55–64	0.86	0.72–1.03	0.10
65–74	0.94	0.79–1.12	0.5
75+	1.04	0.87–1.24	0.7
BMI			
Underweight	—	—	
Normal	0.59	0.24–1.44	0.2
Preobese	0.64	0.27–1.55	0.3
Obese I	0.75	0.31–1.82	0.5
Obese II	1.01	0.42–2.46	>0.9
Obese III	1.51	0.62–3.67	0.4
Fixation method			
Cemented	—	—	
Hybrid	0.79	0.61–1.01	0.064
Uncemented	0.96	0.67–1.38	0.8
Sex			
Female	—	—	
Male	1.84	1.69–2.01	<0.001
Elixhauser score			
<0	—	—	
0	0.80	0.70–0.90	<0.001
1–4	1.18	1.01–1.37	0.033
5+	1.56	1.37, 1.78	<0.001
Hospital size			
Small (0–250 beds)	—	—	
Medium (251–500 beds)	1.15	1.00–1.33	0.051
Large (>500 beds)	1.01	0.88–1.17	0.9
UKA implantation volume per year			
51–200	1.58	0.89–2.78	0.12
0–25	2.15	1.22–3.79	0.008
26–50	1.59	0.88–2.86	0.12
200+			
TKA implantation volume per year			
251–500	0.99	0.53–1.86	>0.9
0-50	1.13	0.62–2.07	0.7
51–250	1.04	0.59–1.84	0.9
500+			

Abbreviations: CI, confidence interval; HR, hazard ratio; PJI, periprosthetic joint infection; TKA, total knee arthroplasty; UKA, unicondylar knee arthroplasty.

infection within 90 days of surgery [1]. Nevertheless, the use of dual antibiotic-loaded bone cements remains a potential preventive measure for patients with risk factors who are scheduled to undergo cemented knee arthroplasty.

Limitations

Despite the advantages of using the EPRD, there are certain limitations due to the study design. Differences in the indications for the implants investigated resulted in different quantities reported. Corrected multiple log-rank test and Kaplan–Meier estimates were used to address this issue. Data quality depends on the accuracy of registration by surgeons and the correct coding during registration. The registry includes cross-validated insurance data to mitigate this limitation. However, the history of the registry currently prohibits follow-up beyond 7 years, although evidence suggests that most septic failures occur within this timeframe [27]. The calculation of the Elixhauser score used comorbidities coded at the time of initial hospitalization, which are potential confounders if coded incorrectly or inadequately.

CONCLUSIONS

Reduced implant volume and constrained knee arthroplasty are associated with a higher risk of PJI. Comorbidities (elevated Elixhauser score), male sex, and low UKA implant volume have been identified as risk factors for PJI. Patients who meet these criteria require specific measures to prevent infection. Further investigations are required to determine the potential impact of preventive measures and risk factor modification.

AUTHOR CONTRIBUTIONS

Dominik Szymski, Nike Walter, Josina Straub, Yinan Wu and Markus Rupp drafted the manuscript, performed statistical analysis and conceived the study. Markus Rupp, Volker Alt and Arnd Steinbrueck supervised the study. Arnd Steinbrueck, Oliver Melsheimer, Alexander Grimberg and Markus Rupp conceived the study and participated in its design and coordination and helped to draft the manuscript. Yinan Wu and Oliver Melsheimer are responsible for data assessment and databank management. All authors read and approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data are available on request.

ETHICS STATEMENT

The study was approved by the Ethics Committee of the University of Kiel (ID: D473/11). Informed consent was obtained from all participants.

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