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Original Article

Outcome and cost analysis of primary total knee arthroplasty in end-stage renal disease patients: A nationwide population-based study

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ABSTRACT

Background: A number of patients with end-stage renal disease (ESRD) undergo total knee arthroplasty (TKA) due to advanced knee joint osteoarthritis. There are few studies describing the incidence, morbidities, mortality rate, and cost analysis regarding ESRD patients receiving TKA.

Methods: We retrospectively retrieved patient data from National Health Insurance Research Database in Taiwan during 2005–2011, and evaluated the outcomes of TKA in patients with (ESRD group) and without ESRD (non-ESRD group). Patients' demographic data, comorbidities, mortality, and in-hospital cost were recorded.

Results: A total of 578 TKAs and 110,895 TKAs were identified in the ESRD and non-ESRD group, respectively. The incidence of patients receiving TKA was higher in the ESRD than in non-ESRD group by at least 2 folds. The ESRD group showed significantly more medical complications (pneumonia, peptic ulcer disease, and acute myocardial infarction) after surgery. In prosthesis-related complications, the ESRD group also had more peri-prosthetic joint infections, and prosthetic loosenings by one year. The one-year mortality rate was more than 6 times higher in the ESRD than in the non-ESRD group. The ESRD group had higher in-hospital medical expense than the non-ESRD group, especially when there were complications, even when the dialysis-related costs were exempted.

Conclusion: The complication rate, mortality rate, and cost were higher in the ESRD patients receiving TKA. When considering TKA in ESRD patients, it is crucial to weigh the risks against benefits of TKA, and have a thorough discussion with the patients.

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At a glance commentary

Scientific background on the subject

A number of patients with end-stage renal disease (ESRD) undergo total knee arthroplasty (TKA) due to advanced knee joint osteoarthritis. There are few studies describing the incidence, morbidities, mortality rate, and cost analysis regarding ESRD patients receiving TKA.

What this study adds to the field

The incidence of patients receiving TKA was higher in the ESRD than in non-ESRD group. The complication rate, mortality rate, and cost were higher in the ESRD patients receiving TKA. When considering TKA in ESRD patients, it is crucial to weigh the risks against benefits of TKA, and have a thorough discussion with the patients.

As many as 70% of end-stage renal disease (ESRD) patients report joint symptoms. The discomfort can be attributed to β2-microglobulin or amyloid deposition, preexisting autoimmune or inflammatory disease, intra-articular crystals, or osteonecrosis of femoral condyle from steroid use [1].

The characteristic of ESRD patients is that they have compromised immune system caused by repeated percutaneous vascular access with bacteremia, impaired lymphocyte and granulocyte function because of uremic toxin, and malnutrition [2]. Furthermore, coagulopathy due to heparinization during hemodialysis and preexisting autoimmune or inflammatory disease further complicate the disease.

There were some studies regarding ESRD patients receiving total hip arthroplasty. Sunday et al. reported 3 out of 7 ERSD patients died after hip arthroplasties during the same hospital stay [3]. Sakalkale et al. revealed higher deep infection, dislocation, prosthesis loosening, and fracture rate in such patients [4]. However, there are limited reports on total knee arthroplasty (TKA) for ESRD patients. McCleery et al. found that renal failure and renal dialysis are independent risk factors for early infection and revision respectively if they received TKA [5]. With increasing number of TKA and prolonged life expectancy in ESRD patients, it is imperative for the orthopaedic society to have more knowledge concerning the outcome of TKA in ESRD patients. Taiwan, a country of more than 23 million people, has the highest prevalence of ESRD patients, up to 2902 per million population [6]. It underlines the importance of the current study.

The aims of the present study were to report the incidence of TKA, complication rate, mortality rate, and total in-hospital cost in end-stage renal disease (ESRD) and non-ESRD patients.

Material and methods

Database

This retrospective nationwide population-based study is derived from National Health Insurance Research Database (NHIRD), which is released by Taiwan National Health Research Institute. Taiwan implemented a single-payer National Health Insurance (NHI) Program in 1995 to finance health care for all residents. Enrollment in the program is mandatory for citizens, and foreigners in Taiwan are also eligible for inclusion. As of June 2012, more than 23.2 million individuals were enrolled in the NHI (coverage rate >99% of the population) and 190,885 healthcare providers contracted with NHI, representing 92.62% of all healthcare providers in Taiwan [7]. A previous study has described NHIRD and validated its accuracy [8]. There have been more than 1000 peer-reviewed journal papers published in Pubmed using NHIRD. The database includes patients' demographic data, diagnostic codes, outpatient care visits, hospitalization, prescription claims, procedures and surgeries, and expenditures.

Study design and identification of cases

We identified ESRD patients from the entire cohort, and analyzed the outcome of ESRD and non-ESRD groups after receiving TKA during January 2005 to December 2011 in Taiwan. We used the number of TKA procedures, rather than patients receiving TKA, to calculate TKA incidence, morbidity, mortality, and medical expenditure in both groups. Bilateral TKAs performed during the same hospital stay were excluded to avoid confounding factors.

Patients receiving TKA were identified by International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) procedure code 81.54. Patients with ESRD were identified on the basis of the Registry for Catastrophic Illness Patients. Additional information such as sex, age, and medical expenditure without dialysis were also recorded. Complications were identified using ICD-9-CM 9966 (periprosthetic joint infection), 9964 (prosthetic complication), 486 (pneumonia), 531 (peptic ulcer disease), 998 (wound complication), 410 (myocardial infarction), 430–437 (cerebrovascular disease), 415.1 (pulmonary embolism), and 453.4 (deep vein thrombosis).

Statistical analysis

We utilized independent t-test and chi-square analysis for the demographic data. The TKA incidences were age-adjusted in ESRD and non-ESRD groups. After matching the ESRD and non-ESRD groups for age, sex, and Charlson comorbidity index in a 1:10 ratio, we compared the morbidity as well as mortality rate by Poisson regression. The cost analysis was conducted by one-

way ANOVA test, and Student–Newman–Keuls test was used for post-hoc analysis.

IBM SPSS Statistics 20 and STATA 12 were used to analyze the data. Data are presented as absolute frequencies (percentages), mean ± standard deviation (SD), or median. The odds ratio (OR) is presented with a 95% confidence interval (CI). The level of significance was set at 0.05.

Ethics

All researchers who plan to use the NHIRD are required to sign a written agreement declaring that the data in the NHIRD would not be used to obtain information that could potentially violate patient privacy. The study protocol was reviewed by the National Health Research Institute, who gave their agreement to the planned analysis of the NHIRD data. The present study was also approved by the Institutional Review Board of the of the authors' affiliated institution.

Results

There were 578 TKAs in the ESRD group, with 163 men (28.2%) and 415 women (71.8%), mean age 67.06 ± 9.06 years (Table 1), from our study period of January 2005 to December 2011. There were 110,895 TKAs in the non-ESRD group, with 28,177 men (25.41%) and 82,718 women (74.6%), mean age 69.41 ± 8.55 years. Approximately 0.52% of patients receiving TKA in Taiwan were ESRD patients.

The crude incidence of TKA in both groups are presented in Fig. 1A. The TKA incidence increased in the study period in both groups, but reached a plateau in the ESRD group after the year 2008, then declined gradually. The age-adjusted TKA incidence demonstrated a more than two-fold probability of ESRD patients receiving TKA than non-ESRD patients (Fig. 1B).

The complications following TKA are summarized in Table 2. Regarding the medical comorbidities, the ESRD group had significantly higher incidence of pneumonia, peptic ulcer

Table 1 Demographic data.

	ESRD	non-ESRD	*p* value
TKA No.	578	110,895	
Male (%)	163 (28.2)	28,177 (25.41)	0.124*
Female (%)	415 (71.8)	82,718 (74.59)	
age (mean ± SD)	67.06 ± 9.06	69.41 ± 8.55	0.116†

Abbreviations: ESRD: end-stage renal disease; TKA: total knee arthroplasty; SD: standard deviation.
*Chi-square analysis.
†Independent *t*-test.

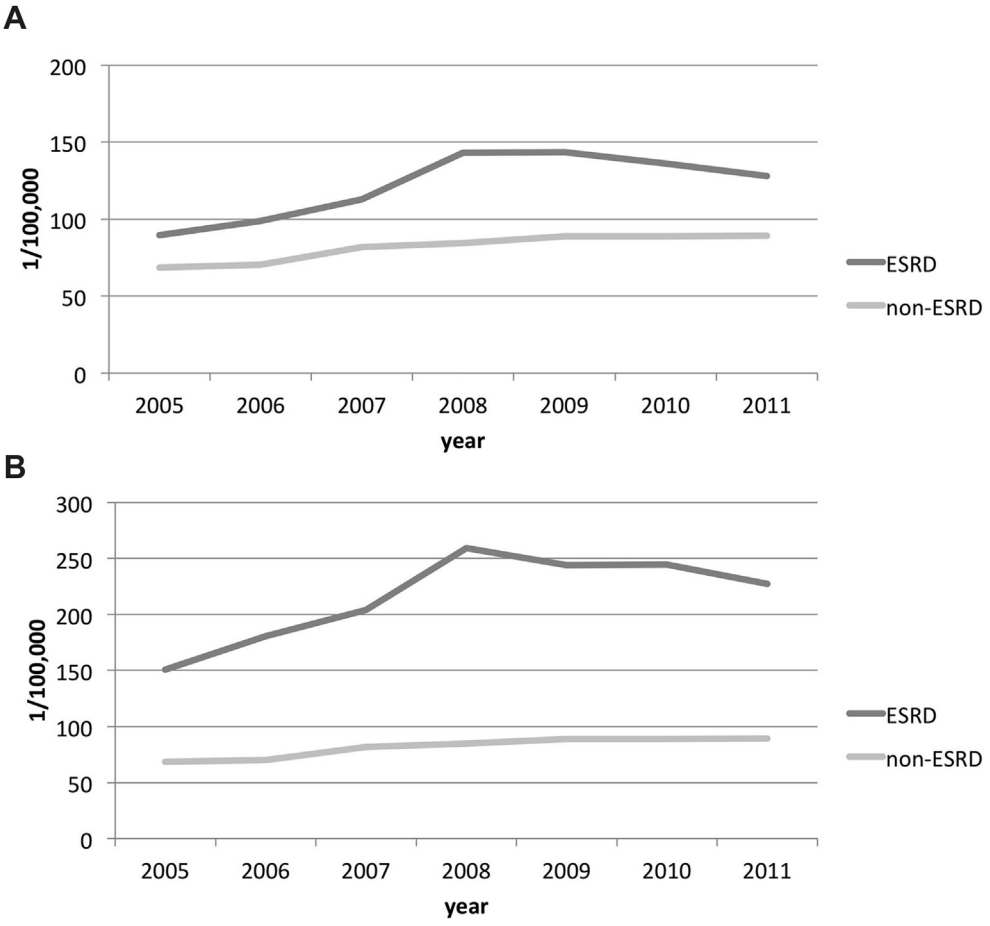

Fig. 1 (A) TKA incidence (before age-matching). (B) TKA incidence (after age-matching).

disease, cerebrovascular accident, and acute myocardial infarction in 1 month, 3 months, 6 months, and 1 year. Regarding surgical complications, ESRD patients had more periprosthetic joint infection in every time point. In addition, ESRD patients were more prone to have aseptic loosening of prosthesis in 1 year follow-up.

The age-adjusted accumulated mortality rate after TKA is illustrated in Fig. 2. The mortality rate after TKA was significantly higher in the ESRD group by 3 months (4.84% vs 0.35%, $p < 0.05$), 6 months (6.06% vs 0.87%, $p < 0.05$), and one year (8.48% vs 1.30%, $p < 0.05$).

The length of hospital stay (LOS) were 7.45 ± 0.83 days for non-ESRD, and 8.23 ± 1.32 days for ESRD patients when there was no complication ($p = 0.032$). When there was complication, the LOS were 9.19 ± 1.38 days for non-ESRD, and 12.11 ± 3.68 days for ESRD patients ($p = 0.028$). The total in-hospital medical expenditure was also grouped according to ESRD or non-ESRD, and occurrence of complication or not (Table 3). There was a trend of increasing expense from non-ESRD without complication (3791.2 ± 307.3 USD), ESRD without complication (4210.1 ± 382.8 USD), non-ESRD with complication (4340.8 ± 391.8), and ESRD with complication (5952.1 ± 459.2) ($p < 0.05$). For each group, patients older than 70 years had higher expense, though they did not reach statistical significance.

Table 2 Cumulative incidence of complications after total knee arthroplasty.

Post-OP	1M	3M	6M	12M
Wound complication				
ESRD	2.33	1.00	0.66	0.39
non-ESRD	1.78	0.78	0.43	0.26
p	0.083	0.276	0.049*	0.058
PJI				
ESRD	2.03	1.17	0.76	0.58
non-ESRD	0.52	0.49	0.31	0.22
p	<0.001*	<0.001*	<0.001*	<0.001*
Loosening				
ESRD	0.81	0.76	0.47	0.37
non-ESRD	0.77	0.60	0.37	0.24
p	0.233	0.373	0.329	0.032*
Pneumonia				
ESRD	1.93	1.08	0.82	0.72
non-ESRD	0.49	0.39	0.37	0.35
P	<0.001*	<0.001*	<0.001*	<0.001*
PUD				
ESRD	3.81	3.54	2.42	1.63
non-ESRD	2.51	2.63	1.72	1.15
p	0.013*	0.021*	0.003*	<0.001*
CVA				
ESRD	0.51	0.48		
non-ESRD	0.18	0.20		
p	<0.001*	<0.001*		
AMI				
ESRD	0.53	0.40		
non-ESRD	0.09	0.08		
p	<0.001*	<0.001*		

Abbreviations: PJI: periprosthetic joint infection; PUD: peptic ulcer disease; CVA: cerebrovascular accident; AMI: acute myocardial infarction.
*Statistically significant

Discussion

This is by far the largest study comparing the outcome and cost of TKA in ESRD and non-ESRD patients, using a nationwide database with inclusion of more than 99% of the population. TKA is one of the most successful surgical procedures with high patient satisfaction [9]. Despite the benefit of TKA, the perioperative complications may sometimes be serious and unexpected, especially in cohorts with underlying comorbidities. Patients with ESRD have a complicated medical condition with compromised immune system, poor bone quality, diminished blood supply, and lower wound healing potential [10–13]. The altered immune system also contributes to immunoactivation and results in inflammation that may lead to cardiovascular disease, as well as a higher mortality rate [2]. Previous reports were against total joint arthroplasty in patients with ESRD due to high complication and mortality rate [3].

In the current study, the incidence of ESRD patients receiving TKA was around 90–140/100,000. To our knowledge, this is the first study to report TKA incidence in patients with ESRD. The TKA incidence was significantly higher in ESRD patients compared with non-ESRD patients. It is best explained by the higher prevalence of joint symptoms in patients with dialysis, mainly due to osteoarthritis, avascular necrosis, crystal-induced arthritis, and amyloid deposition [1,10,13]. β2-Microglobulin is a subunit of amyloid protein, which is present in serum, urine, and synovial fluid. It is elevated in ESRD patients due to the decreased ability to remove it through the kidney, while its synthesis rate often exceeds clearance rate achieved by dialysis.

The complication rate in ESRD patients following TKA was higher compared with the general population. Periprosthetic joint infection (PJI) is a devastating complication, which is difficult to treat and also imposes a large economic burden on the healthcare system. Patients with renal failure have worse immune response and higher infection rate [12]. McCleery et al. reported early and late infection rate of 0.62% and 8.03% for dialysis patients. Cavanaugh et al. reported TKA surgical site infection of 15.0% in dialysis patients. Despite the heterogeneity of study design, the TKA infection rate is significantly higher in dialysis patients compared with the general population across all studies.

Prosthetic loosening with early failure is also an important complication following total joint arthroplasty. To the best of our knowledge, there is limited research that has focused on early TKA failure in dialysis patients. Shiota et al. reported that eight renal dialysis patients undergoing TKA had good results without significant complications [14]. On the other hand, McCleery et al. found that dialysis patients had significantly higher rate of early revision than non-renal patients undergoing TKA in a joint registry database [5]. In our study, we found aseptic loosening of TKA prosthesis to be significantly higher in the dialysis group, with a 12-month accumulated incidence of 2.41%.

Other complication rates were also higher in the ESRD group, such as pneumonia, acute myocardial infarction (AMI), and peptic ulcer. With the loss of renal functions, activation of and interaction between innate and adaptive immune

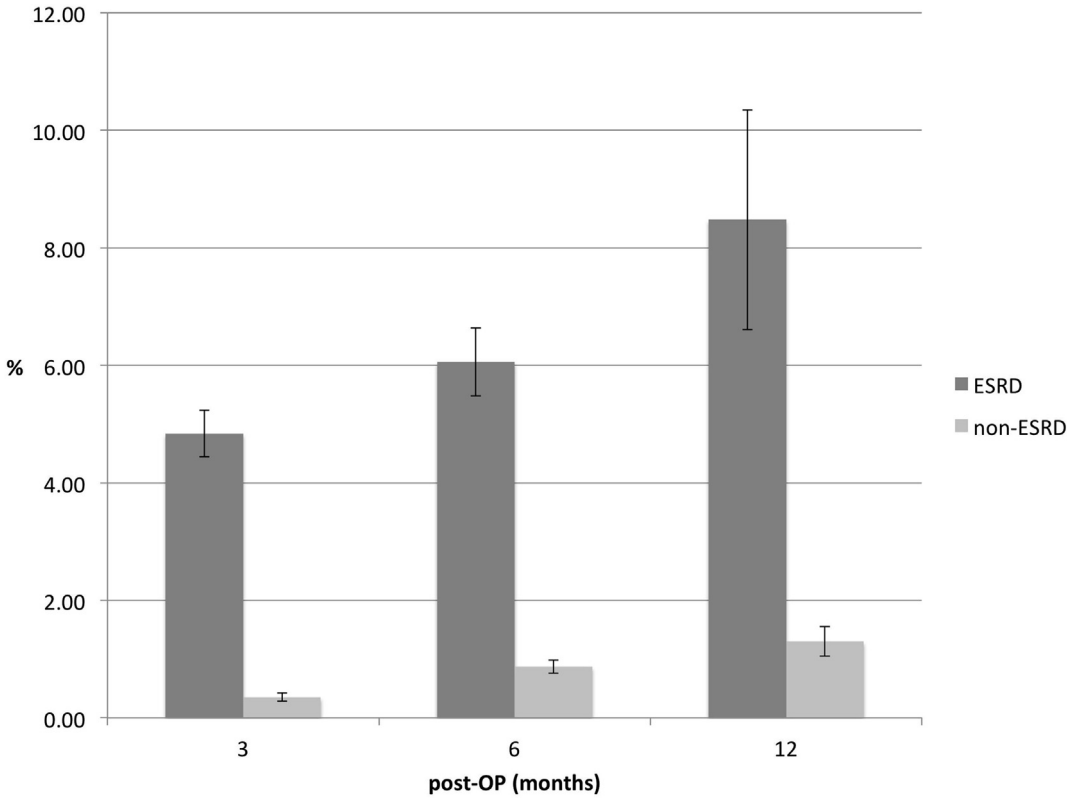

Fig. 2 Accumulated age-adjusted mortality rate after TKA. Error bar: 95% confidence interval.

systems are defective [11]. Previous data revealed that pneumonia may occur frequently in dialysis patients, and mortality from pulmonary infections are 15 times higher than in the general population [15]. ESRD is thought to be a state of inflammatory and redox dysfunction, and inflammation is a crucial factor for atherosclerosis and myocardial infarction [16]. TKA itself is a major surgery and may lead to systemic inflammatory response, thus further increasing the risk of AMI. Kumar et al. found that AMI risk was elevated within one year after TKA in hemodialysis patients [17]. Hemodialysis patients are prone to various kinds of gastrointestinal diseases, especially peptic ulcer disease (PUD) [18]. Total joint arthroplasty itself is a risk factor for upper gastrointestinal bleeding postoperatively [19]. Hence, it is crucial to use gastroprotective agents in ESRD patients in the perioperative periods.

Mortality in hemodialysis patients after TKA is significantly higher than in the general population [20]. Our data resonated with previous studies showing that the mortality rate was significantly higher at 3, 6, and 12 months in the ESRD group. Various organ diseases are associated with ESRD, such as cardiovascular disease, diabetes mellitus, and hypertension,

Table 3 In-hospital medical cost of the index surgery.

	Expense			95% CI	*p* value
non-ESRD	overall	3791.2 ± 307.3	vs ESRD	385.8–452.2	0.014*
			vs non-ESRD wc	499.3–598.7	0.037*
	<70	3786.7 ± 297.4			0.121†
	>70	3797.4 ± 330.5			
ESRD	overall	4210.1 ± 382.8	vs ESRD wc	1498.5–1985.5	0.019*
	<70	4202.2 ± 379.9			0.274†
	>70	4219.6 ± 393.4			
non-ESRD wc	overall	4340.8 ± 391.8	vs ESRD wc	1393.2–1830.8	0.015*
	<70	4215.3 ± 375.1			0.073†
	>70	4420.1 ± 412.4			
ESRD wc	overall	5952.1 ± 459.2			
	<70	4914.3 ± 433.8			0.054†
	>70	7013.2 ± 502.4			

Abbreviations: CI: confidence interval; wc: with complication.
*Post-hoc analysis.
†Independent *t*-test.

which are all risk factors for mortality. In addition to the common comorbidities, ESRD patients often have other problems that would be a negative influence on mortality, for example, liver disease, metabolic syndrome, or subclinical infections [20]. These should all be taken into consideration when deciding whether to receive TKA or not.

The economic burden of TKA should also be taken into account in ESRD patients. In our series, the LOS and in-hospital cost at the time of TKA was significantly higher in the dialysis patients than in the control group. These results were consistent with previous researches. Rozell et al. reported longer LOS in patients with chronic kidney disease in 802 primary total joint arthroplasties [21]. O'Malley et al. found the correlation between renal disease and increasing LOS [22]. Inneh et al. discovered renal comorbidity is associated with hospitalization for more than 4 days [23]. The difference of cost was larger if the patient had perioperative complications. Our study illustrated the increased economic burden of ESRD patients undergoing TKA. In the comparison between ESRD patients and the general population without complication, the average cost in the ESRD group was about 400 US dollars more than that in the non-ESRD group. The difference was nearly constant throughout all age groups. However, when comparing the two groups with complications, the cost in the ESRD group showed an even larger rise than in the non-ESRD group, and the difference increased significantly with the advancement of age. This implied that the complications in the ESRD group were not only higher in number, but also were more difficult and costly to treat. While not presented in this study, the higher periprosthetic joint infection rate also imposes a great economic burden on the healthcare system [24,25]. However, there is no other management option if the patient develops end-stage osteoarthritis. If left untreated, the socio-economic burden is also remarkable, considering the loss of mobility, ability to work, and additional expense on caregivers. Thus, meticulous preoperative evaluation and perioperative optimization of physiologic status are necessary for the patient to receive TKA.

There are some limitations in the current study. NHIRD in Taiwan is a secondary database. First, there might be some registration bias such as missed reports, patients receiving therapy outside Taiwan, or patients not covered by National Health Insurance, although rare. Second, it is difficult to assess severity and complexity of the disease, because it is not possible to obtain detailed medical records and laboratory data. As a result, there is minimal adjustment of confounders in the current study. Third, the improvement of functional score after TKA cannot be obtained from the database. Fourth, only patients receiving TKA during 2005–2011 are included in the study. Longer follow-up may be needed since bacteremia caused by hemodialysis is a long term problem, which might lead to higher infection and complication rates. Fifth, further studies are necessary to assess the function and quality of life improvement in these patients, in order to see if the benefits of TKA justify the risks.

Conclusions

End-stage renal disease patients undergoing TKA have increased risk of perioperative medical complications, periprosthetic joint infection, prosthetic loosening, and mortality. The in-hospital cost of TKA in the ESRD group is higher than in the non-ESRD group, and the difference of medical expenditure is even higher if there are complications. When considering TKA in ESRD patients, it is crucial to weigh the risks against the benefits of TKA, and have a thorough discussion with the patients.

Conflicts of interest

The authors declare they have no conflicts of interest.

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