

Total knee replacement for patients with severe hemophilic arthropathy in Taiwan: A nationwide population-based retrospective study

Cheng-Fong Chen^{a,b,c,*}, Yuan-Bin Yu^{c,d}, Shang-Wen Tsai^{a,b,c}, Jan-Wei Chiu^{c,e}, Liang-Tsai Hsiao^{c,d}, Jyh-Pyng Gau^{c,d}, Hui-Chi Hsu^{c,d}

^aDivision of Joint Reconstruction, Department of Orthopaedics and Traumatology, Taipei Veterans General Hospital, Taipei, Taiwan, ROC; ^bDepartment of Surgery, School of Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan, ROC; ^cHaemophilia and Thrombosis Comprehensive Treatment Center, Taipei Veterans General Hospital, Taipei, Taiwan, ROC; ^dDivision of Hematology and Oncology, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan, ROC; ^eDepartment of Physical Medicine and Rehabilitation, Taipei Veterans General Hospital, Taipei, Taiwan, ROC

Abstract

Background: Total knee replacement (TKR) surgery is a treatment option for advanced hemophilic arthropathy. Due to its rarity and complexity, previous reports could only demonstrate the results of single-site studies including few cases. This population-based study aimed to investigate the major epidemiological characteristics, mean consumption of coagulation factors, length of hospital stays, complications, and failure rate of primary TKR for severe hemophilia patients in Taiwan.

Methods: A cohort of 996 hemophilia patients registered between 1995 and 2011 was included, and 103 primary TKRs were performed on 75 patients. Unilateral TKR was performed on 47 patients and bilateral TKRs on the remaining 28 patients, including 12 simultaneous and 16 staged surgeries. The mean age at surgery was 32.3 years (range, 17.3–55.7), and the mean follow-up duration was 77.9 months (range, 2.3–176.8).

Results: Failure was noted in 8 patients (8.5%) at mean 32.8 months (range, 2.3–95) after surgery. Four patients revealed aseptic loosening, whereas infection in 4. The 10-year prosthesis survivorship was 88.6%. For patients receiving unilateral TKR, the mean length of hospital stay was 15 days (range, 7–32). The mean cost of factor supplement was United States Dollar (USD) 43543 with a mean 4-unit packed red blood cells transfusion (range, 0–38). The total admission cost was USD 48326 (range, USD 4165–262619).

Conclusion: The prevalence of TKA for hemophilia patients was 7.5% in Taiwan. The mean hospital stay was 14 days, and the 10-year prosthesis survivorship was 88.6%. The mean daily factor usage was decreased from 235.7 units preoperatively to 202.1 units postoperatively. In comparison with the staged-bilateral TKRs, the simultaneous procedures significantly reduced the mean total cost from USD 101923 to USD 61587 ($p = 0.023$). Therefore, in terms of cost-effectiveness, bilateral simultaneous TKR is more preferable than staged procedures.

Keywords: Arthroplasty, Replacement, Knee; Epidemiology; Hemophilia A; Taiwan

1. INTRODUCTION

The knee is the most commonly involved joint tissue in hemophilia patients.^{1–4} Recurrent hemoarthrosis may result in chronic synovitis and advanced hemophilic arthropathy at the end stage of the disease. The symptoms include severe pain, limited range of motion (ROM), and impaired knee function.

Total knee replacement (TKR) is an effective surgery in association with sustainable pain relief and function recovery for the general population. However, for patients with hemophilic arthropathy, severe deformity, soft tissue contracture, and disused juxta-articular osteoporosis compromise the advantages of TKR. Hence, an improved surgical technique is required for this purpose. Few of the earliest reports of TKR in patients with hemophilia were published in the mid-1970s.^{5,6} With the improvement in the surgical techniques and medical management, the outcomes of TKR performed on hemophilic patients are presently satisfactory.^{7–9} However, high incidences of complications including bleeding, deep infection, prosthetic failure, and limited ROM have been reported in several studies.^{8,10}

Bilateral involvement of hemarthrosis over knee joints is frequent in patients with severe hemophilia, and TKR is the standard management. In this setting, it is not clear whether simultaneously bilateral TKR or staged TKR should be performed in those hemophilic patients. Therefore, we conduct the nationwide study to investigate the safety and cost-effectiveness of TKR in Taiwanese hemophilic patient population.

*Address correspondence. Dr. Cheng-Fong Chen, Department of Orthopaedics and Traumatology, Taipei Veterans General Hospital, 201, Section 2, Shi-Pai Road, Taipei 112, Taiwan, ROC. E-mail address: cf_chen@vghtpe.gov.tw (C.-F. Chen).

Conflicts of interest: Dr. Hui-Chi Hsu, an editorial board member at Journal of the Chinese Medical Association, had no role in the peer review process of or decision to publish this article. The other authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

Journal of Chinese Medical Association. (2022) 85: 228–232.

Received July 4, 2021; accepted August 25, 2021.

doi: 10.1097/JCMA.0000000000000646.

Copyright © 2021, the Chinese Medical Association. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>)

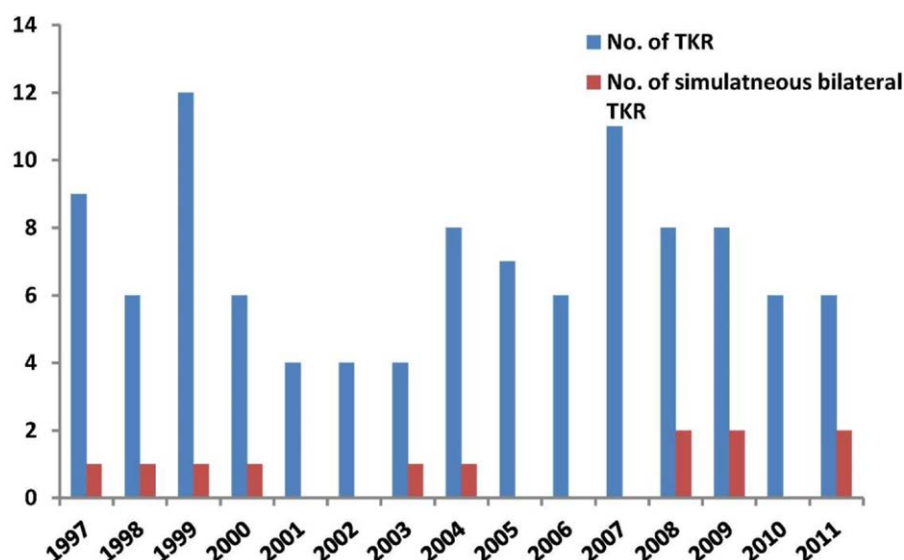


Fig. 1 The distribution of total knee replacement (TKR) numbers for Taiwan hemophilia patients between 1997 and 2011.

2. METHODS

2.1. Study population and cohort

Since 1995, the National Health Insurance (NHI) program initiated by the Taiwanese government has been providing mandatory health insurance policies. By the end of year 2011, $\approx 99.59\%$ of Taiwanese citizens were registered under effective medical coverage. The present study is a retrospective population-based study that explored the authentic data extracted from the NHI Research Database (NHIRD) of Taiwan. The NHIRD nearly contains all inpatient and outpatient medical benefit claims for about 23 million Taiwanese residents. The claim files comprise of outpatient and inpatient medical records, including diagnosis, treatment, and all management incurring expenses. This study was exempted from full review by the institutional review board.

2.2. Data mining

We identified all patients diagnosed with hemophilia (International Classification of Diseases, Ninth Revision, Clinical Modification codes 286) for the first time between January 1, 1995, and December 31, 2011. Simultaneous TKR was defined as bilateral TKR performed at the same surgical day, while staged-bilateral TKR was defined as two TKR procedures performed at different hospitalization. Implant failure was defined as revision

or removal of prosthesis. The diagnosis was confirmed by the Registry for Catastrophic Illness Patient Database (RCIPD)—a subset of the NHIRD. Laboratory confirmation of the clotting factor was required for patients to be registered in the RCIPD.

By using the data extracted from NHIRD, we obtained a cohort of 996 hemophilia patients between 1995 and 2011. The study inclusion criteria were registration in the claim-specific reimbursement codes of primary TKR (64164B), revision TKR (64198B), and prosthesis removal (64202B). The end point of implant survival was determined by revision or removal of prosthesis due to infection or aseptic loosening. Prosthesis survivorship was calculated, with failure defined as revision or removal of the prosthesis. Surgical failure characterized as revision or removal of the prosthesis was used to calculate the prosthesis survivorship. The follow-up time began at the first admission date and ended at the implant failure date, patient's death, or the end of 2011, whichever came first. Our follow-up study continued until the end of 2011. For each enrolled subject, the data, including demographic variables, year of receiving surgery,

Table 1

The prevalence of TKR procedures in hemophiliacs in Taiwan (1997–2011)

	Total (n = 996)	Hemophilia A (n = 830)	Hemophilia B (n = 166)
Total number of patients who received TKR	75 (7.5%)	63	12
Total number of TKRs	103	86	17
Unilateral TKR	47	40	7
Bilateral TKR	28	23	5
Simultaneous	12	10	2
Staged	16	13	3
Failure	8 (7.8%)	8 (9.3%)	0 (0%)
Aseptic loosening	4 (3.8%)	4 (4.7%)	0 (0%)
Deep infection	4 (3.8%)	4 (4.7%)	0 (0%)

TKR = total knee replacement.

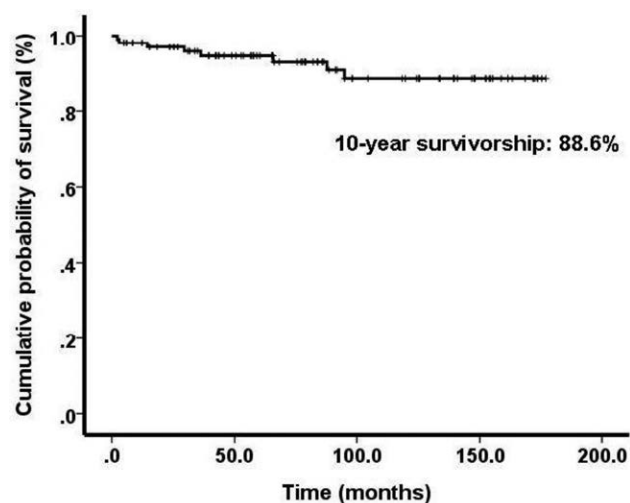


Fig. 2 The Kaplan-Meier survivorship curve depicting the 10-y survival rate of 88.6%.

Table 2**Comparisons between unilateral, staged-bilateral, and simultaneous-bilateral TKR**

	Unilateral (n = 46 ^a)	Staged (n = 16)			Simultaneous (n = 11 ^a)	<i>p</i> ¹	<i>p</i> ²
		1st	2nd	Total			
Hemophilia A	39 (84.8)			13 (81.3)	9 (81.8)	0.919	
Age							
Median	32.1 (17.3–55.7)	32.9 (23.7–49.8)	37.3 (26.5–54.9)		30.0 (24.5–49.7)		
≤30	18 (39.1)	8 (50)	6 (37.5)		6 (54.5)	0.711	
>30	28 (60.9)	8 (50)	10 (62.5)		5 (45.5)		
Era						0.202	
Before 2004	23 (50.0)	11 (68.8)	6 (37.5)		6 (54.5)		
After 2004	23 (50.0)	5 (31.2)	10 (62.5)		5 (45.5)		
Hospitalization days	15 (7–32)	12.5 (6–30)	11 (7–36)	23.5 (14–53)	15 (9–20)	0.703	0.001
Factor usage (USD)	43 543 (93–258 785)	41 805 (7245–86 816)	47 912 (17 131–255 125)	93 878 (34 250–328 633)	54 737 (18 008–126 482)	0.091	0.044
Transfusion amount	4 (0–38)	2 (0–12)	2 (0–14)	3 (0–26)	8 (2–16)	0.287	0.183
Admission cost (USD)	48 326 (4165–262 619)	46 427 (11 515–96 956)	52 574 (21 636–262 011)	101 932 (43 067–345 933)	61 587 (26 159–134 497)	0.096	0.023
Failure	7 (15.2)			1 (6.3)	0 (0)	0.188	1.000

¹*P*: simultaneous vs. unilateral vs. staged 1st vs. staged 2nd. ²*P*: Simultaneous vs. staged 1st + 2nd.

TKR = total knee replacement; USD = United States Dollar.

^aOne patient with inhibitor was excluded from this analysis in both the single and bilateral TKR groups.

surgical type, costs of the prescribed coagulation factors, coagulation factor usage of 12 months before surgery and at 1 to 6 and 7 to 18 months after surgery, transfusion amounts, length of hospital stay, and total costs of hospitalization were extracted and categorized.

2.3. Statistical analysis

The data from NHIRD was managed using the Microsoft SQL Server 2008 R2. SPSS statistical software, version 20.0, for Windows (SPSS Inc., Chicago, IL, USA) was used to perform all the analyses. The prosthesis-failure-free survival was plotted by the Kaplan-Meier method. Comparisons among unilateral TKR, staged-bilateral TKR, and simultaneous-bilateral TKR were conducted by the ANOVA test, chi-square test, or Student's *t* test. The mean daily factor usage before and after TKR was examined using the paired Student's *t* test. Two-tailed *p* < 0.05 was considered to be significant.

3. RESULTS

During the period between 1995 and 2011, 996 hemophilia patients were registered in the NHIRD of Taiwan. Among these patients, 103 primary TKR surgeries were performed on 75 patients (7.5%) with severe hemophilic arthropathy (Fig. 1). Sixty-three patients were diagnosed with hemophilia A and the remaining 12 with hemophilia B. Hemophilia patients with factor VIII inhibitor or HIV were not enrolled in the study. Unilateral TKR surgery was performed on 47 patients, whereas 28 patients received bilateral TKR, including 12 simultaneous TKR and 16 staged TKR in two consecutive admissions (Table 1).

The mean age of the patients was 32.3 years (range, 17.3–55.7 years) at the time of index surgery, and the mean follow-up duration was 77.9 months (range, 2.3–176.8 months). The mean hospital stay was 14 days (range, 6–36 days). Among the 103 TKR implants, 8 (8.5%) were revised, removed, or converted to a knee arthrodesis at a mean duration of 32.8 months (range, 2.3–95 months) after surgeries. Four cases were derived from aseptic loosening, and 4 were caused by infections. The 10-year prosthesis survivorship was 88.6% (Fig. 2).

We further analyzed the amount of coagulation factors used before and after TKR. Table 3 demonstrates that the

mean daily consumption of coagulation factor was 235.7 units (range, 0–2884.3) before the surgery in all hemophilic patients, which increased significantly during the first 6 months after TKR (364.9 units; *p* = 0.002) but later decreased to 202.1 units after 18 months of surgery (*p* = 0.633). No significant difference in the daily factor consumption was noted in hemophilic patients before and 18 months after the TKR. Regarding the difference between the two types of hemophilia, less amount of coagulation factor was postoperatively prescribed for patients with hemophilia B than that in hemophilia A in 18 months after TKR (205.9 vs. 178.4 U/day, respectively; Table 3).

To evaluate the cost-effectiveness of TKR surgeries performed on hemophilic patients, the direct costs of factor supplement, total admission costs, length of hospital stay, and packed red blood cells (PRBC) transfusion for the surgeries of simultaneous-bilateral TKR were compared with that of unilateral TKR and staged-bilateral TKR surgeries (Table 2; Fig. 3). For patients receiving unilateral TKR surgery, the mean length of hospital stay was 15 days (range, 7–32 days) and the mean cost of factor supplement was United States Dollar (USD) 43 543. An average of four packed red blood cells units was transfused (range, 0–38 U), and the mean total admission cost was USD 48 326 (range, USD 4165–262 619).

Table 3**Comparison of mean daily factor usage before and after surgery**

	Preoperative ^a		Postoperative	
	Mean	Interval, mo	Mean	<i>p</i>
All (n = 75)	235.7 (0–2884.3)	1	280.8 (0–3973.6)	0.067
		6	364.9 (0–4584.9)	0.002
		18	202.1 (0–1671.9)	0.633
Haemophilia	235.6 (0–2884.3)	1	277.9 (0–3973.6)	0.162
A (n = 63)		6	363.2 (0–4584.9)	0.007
		18	205.9 (0–1671.9)	0.806
Haemophilia	413.5 (17.3–615.4)	1	323.5 (0–2313.0)	0.155
B (n = 12)		6	410.9 (22.5–1278.3)	0.064
		18	178.4 (0–710.1)	0.323

^aMean daily factor usage of 12 mo before surgery.

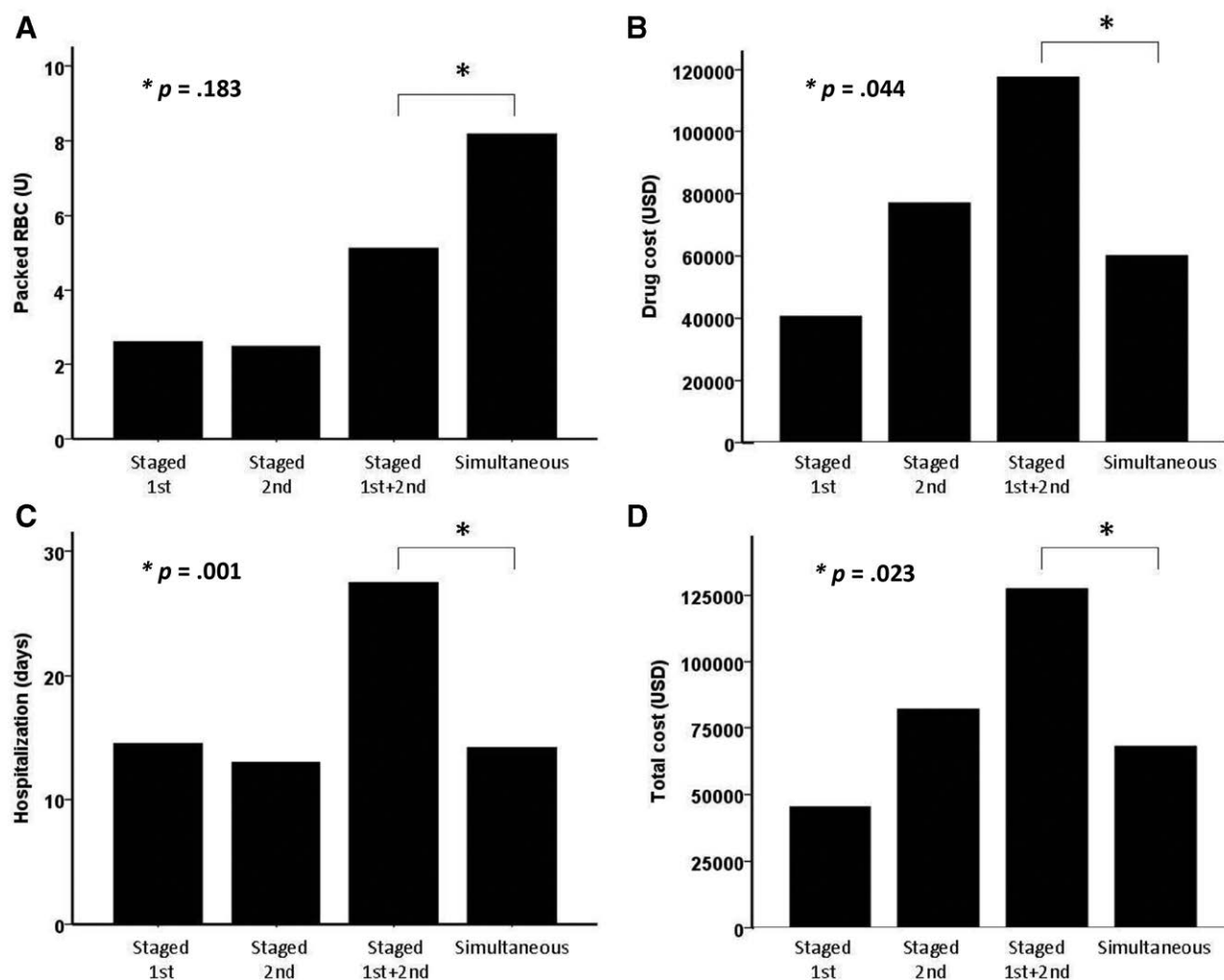


Fig. 3 Comparison of staged-bilateral total knee replacement for hemophilia patients with the simultaneous group showing that the latter had significantly lower drug cost (B), shorter hospitalization stay (C), lower total cost (D), and more blood transfusion unit (A). RBC = red blood cells; USD = United States Dollar.

Regarding the bilateral TKRs, the mean length of hospital stay was 15 days (range, 9–20 days) in patients receiving simultaneous-bilateral TKR, and the cumulative hospital stay was 23.5 days (range, 14–53 days) for subjects receiving staged-bilateral TKR surgery ($p = 0.001$). In addition, the mean expenses of factor supplement cost were USD 54 737 (range, USD 18 008–126 482) and USD 93 878 (range, USD 34 250–328 633) for simultaneous and staged TKRs, respectively ($p = 0.044$). In comparison with staged-bilateral TKRs, simultaneous procedures exhibited significantly reduced mean total admission cost by a difference of USD 40 336 (USD 101 923 vs. 61 587; $p = 0.023$; Fig. 3).

4. DISCUSSION

The incidence of TKR performed on patients with hemophilic arthropathy is much lower than that for treating other types of knee arthritis due to its low prevalence in the general population. General orthopedic surgeons need to gather their prior treatment experiences from the results of large population-based studies. To the best of our knowledge, previous reports related to TKR surgery for end-stage hemophilia arthropathy are limited to single-institute experiences.^{7,10–18} This study elucidated the current status of TKR surgeries performed on patients

with hemophilia by using the Taiwanese nationwide population data. Seventy-five subjects out of 996 hemophilia patients (7.5%) received the TKR surgery within the 14 studied years in Taiwan. For patients with advanced hemophilic arthropathy requiring TKR treatment, we concluded that the current surgery rate was lower than expected. It is well known that TKR surgeries operated on hemophilic patients demand more complicated techniques in association with higher rates of complications as compared with that for the general population. The underlying risks arising from factors such as bleeding, deep infection, and early prosthetic failures give rise to more difficult issues for both orthopedic surgeons and patients.

In this study, we reported a revision- or removal-free, 10-year prosthesis survival rate of 88.6% in Taiwan. This result is comparable to the results of previous studies^{8,10} on hemophilia patients receiving TKR surgeries, but it showed lower than the rates of 90% to 97% obtained from 10 to 15 years of follow-up among the general population receiving TKR. To achieve better prognosis, including lower incidences of complications, better physical function, and improved pain relief, enhanced surgical techniques and multidisciplinary management are recommended.

In addition to improved postoperative pain relief and knee function, it was reported that TKR surgery exhibits advantage to decrease bleeding for hemophilic patients with end-stage arthropathy. Bae et al reported that the median preoperative

consumption of coagulation factor was 4837 units/month, which significantly decreased to 1500 units/month at the end of the first year after TKR surgery.¹⁷ In this study, however, no significant difference in the amount of factor consumption was noted among hemophilia patients between the period before and after TKR. However, further analysis on hemophilia subtypes revealed that patients with hemophilia B received much lesser factor supplement 18 months after TKR than patients with hemophilia A (178.4 vs. 413.5 U/day; Table 3).

In the general population, simultaneous-bilateral TKR surgeries exhibited advantage in cost reduction accompanied with an equivalent rate of complications with that of staged-bilateral TKR surgeries.^{19–22} However, in patients with severe hemophilia, bilateral involvements of knee arthropathy are frequent, and TKR is indicated for both bilateral knees. Concerning perioperative bleeding, higher rate of complications and limited experience in hemophilic patients, most orthopedic surgeons prefer staged-bilateral TKR instead of simultaneous-bilateral TKR in hemophilic patients with bilateral severe knee arthropathy. It has been reported that, as compared with staged-bilateral TKR, the simultaneous-bilateral TKR showed advantages in less consumption of factors as a consequence of significantly reduced cost of hospitalization in hemophilia patients with bilateral severe knee arthropathy.^{22,23} In our nationwide study, 28 patients underwent bilateral TKRs, including 12 simultaneous-bilateral TKRs and 16 staged-bilateral TKRs. In agreement with results reported by Thes et al, patients receiving simultaneous-bilateral TKR surgeries showed significant reduction in their cumulative hospital stay, factor consumption, and total cost, whereas the prosthesis failure rate and PRBC transfusion amount were comparable with those of staged-bilateral TKR surgeries (Table 2). The expensive cost of coagulation factor consumption in hemophilia patients has been always a major concern in the management of hemophilia patients with arthroplasty. Analysis on cost-effectiveness revealed that the expense of factors supplement accounted for >88.9% of the costs accrued in our study. Further study indicates that, in comparison with staged-bilateral TKRs, simultaneously bilateral TKRs saved exceeded up to 40 345 USD in the mean admission cost (USD 101 932 vs. 61 587) in hemophilic patients receiving bilateral TKR.

In conclusion, based on our nationwide study, we found the prevalence of TKA for hemophilia patients in Taiwan was around 7.5% with mean age at surgery of 32.3 years. The mean hospital stay was 15 days, the cost of factor supplement was mean USD 43 543, and admission cost was 48 326 USD. The mean daily factor usage was decreased from 235.7 units preoperatively to 202.1 units postoperatively. The failure rate was 8.5% at mean 32.8 months (range, 2.3–95), and the 10-year prosthesis survivorship was 88.6%. In addition, in comparison with the staged-bilateral TKRs, the simultaneous procedures significantly reduced the mean total cost from USD 101 923 to 61 587 ($p = 0.023$). Therefore, simultaneously bilateral TKR is a safe and cost-effective procedure in hemophilic patients with bilateral severe knee arthropathy. However, this procedure should be performed by the experienced orthopedic surgeon with a special team, which is also experienced in the comprehensive care of hemophilic patients.

REFERENCES

- Rodriguez-Merchan EC. Musculoskeletal complications of hemophilia. *HSS J* 2010;6:37–42.
- Vanderhave KL, Caird MS, Hake M, Hensinger RN, Urquhart AG, Silva S, et al. Musculoskeletal care of the hemophiliac patient. *J Am Acad Orthop Surg* 2012;20:553–63.
- Rodriguez-Merchan EC. Prevention of the musculoskeletal complications of hemophilia. *Adv Prev Med* 2012;2012:201271.
- Moore MF, Tobase P, Allen DD. Meta-analysis: outcomes of total knee arthroplasty in the haemophilia population. *Haemophilia* 2016;22:e275–85.
- Post M, Telfer MC. Surgery in hemophilic patients. *J Bone Joint Surg Am* 1975;57:1136–45.
- Marmor L. Total knee replacement in hemophilia. *Clin Orthop Relat Res* 1977;125:192–5.
- Zingg PO, Fucentese SF, Lutz W, Brand B, Mamisch N, Koch PP. Haemophilic knee arthropathy: long-term outcome after total knee replacement. *Knee Surg Sports Traumatol Arthrosc* 2012;20:2465–70.
- Westberg M, Paus AC, Holme PA, Tjønnfjord GE. Haemophilic arthropathy: long-term outcomes in 107 primary total knee arthroplasties. *Knee* 2014;21:147–50.
- Innocenti M, Civinini R, Carulli C, Villano M, Linari S, Morfini M. A modular total knee arthroplasty in haemophilic arthropathy. *Knee* 2007;14:264–8.
- Panotopoulos J, Ay C, Trieb K, Schuh R, Windhager R, Wanivenhaus HA. Outcome of total knee arthroplasty in hemophilic arthropathy. *J Arthroplasty* 2014;29:749–52.
- Jenkins PJ, Ekrol I, Lawson GM. Total knee replacement in patients with haemophilia: the Scottish experience. *Scott Med J* 2013;58:223–7.
- Wang K, Street A, Dowrick A, Liew S. Clinical outcomes and patient satisfaction following total joint replacement in haemophilia—23-year experience in knees, hips and elbows. *Haemophilia* 2012;18:86–93.
- Uprichard J, Adamidou D, Goddard NJ, Mann HA, Yee TT. Factor IX replacement to cover total knee replacement surgery in haemophilia B: a single-centre experience, 2000–2010. *Haemophilia* 2012;18:46–9.
- Goddard NJ, Mann HA, Lee CA. Total knee replacement in patients with end-stage haemophilic arthropathy: 25-year results. *J Bone Joint Surg Br* 2010;92:1085–9.
- Chiang CC, Chen PQ, Shen MC, Tsai W. Total knee arthroplasty for severe haemophilic arthropathy: long-term experience in Taiwan. *Haemophilia* 2008;14:828–34.
- Rodriguez-Merchan EC. Total knee replacement in haemophilic arthropathy. *J Bone Joint Surg Br* 2007;89:186–8.
- Bae DK, Yoon KH, Kim HS, Song SJ. Total knee arthroplasty in hemophilic arthropathy of the knee. *J Arthroplasty* 2005;20:664–8.
- Sheth DS, Oldfield D, Ambrose C, Clyburn T. Total knee arthroplasty in hemophilic arthropathy. *J Arthroplasty* 2004;19:56–60.
- Lin AC, Chao E, Yang CM, Wen HC, Ma HL, Lu TC. Costs of staged versus simultaneous bilateral total knee arthroplasty: a population-based study of the Taiwanese National Health Insurance Database. *J Orthop Surg Res* 2014;9:59.
- Odum SM, Troyer JL, Kelly MP, Dedini RD, Bozic KJ. A cost-utility analysis comparing the cost-effectiveness of simultaneous and staged bilateral total knee arthroplasty. *J Bone Joint Surg Am* 2013;95:1441–9.
- Reuben JD, Meyers SJ, Cox DD, Elliott M, Watson M, Shim SD. Cost comparison between bilateral simultaneous, staged, and unilateral total joint arthroplasty. *J Arthroplasty* 1998;13:172–9.
- Thès A, Molina V, Lambert T. Simultaneous bilateral total knee arthroplasty in severe hemophilia: a retrospective cost-effectiveness analysis. *Orthop Traumatol Surg Res* 2015;101:147–50.
- Mortazavi SMJ, Haghpanah B, Ebrahiminasab MM, Baghdadi T, Hantoshzadeh R, Toogeh G. Simultaneous bilateral total knee arthroplasty in patients with haemophilia: a safe and cost-effective procedure? *Haemophilia* 2016;22:303–7.