in vivo *38*: 2981-2989 (2024)
doi:10.21873/invivo.13781

Gout Risk After Total Knee Arthroplasty: A Propensity-score-matched Cohort Study

SHIU-JAU CHEN[1,2], ZONG-HAN LIN[3], YUN-FENG LI[4], YU-CHIAO KU[4], CHIEN-YING LEE[5,6], YU-LUN WU[7,8], HUI-CHIN CHANG[4,9,10] and SHUO-YAN GAU[5,11,12]

[1]*Department of Neurosurgery, Mackay Memorial Hospital, Taipei, Taiwan, R.O.C.;*
[2]*Department of Medicine, Mackay Medical College, New Taipei City, Taiwan, R.O.C.;*
[3]*Department of Medical Education and Research, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan, R.O.C.;*
[4]*School of Medicine, Chung Shan Medical University, Taichung, Taiwan, R.O.C.;*
[5]*Department of Pharmacology, Chung Shan Medical University, Taichung, Taiwan, R.O.C.;*
[6]*Department of Pharmacy, Chung Shan Medical University Hospital, Taichung, Taiwan, R.O.C.;*
[7]*Department of Neurosurgery, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan, R.O.C.;*
[8]*School of Medicine, College of Medicine, National Sun Yat-sen University, Kaohsiung, Taiwan, R.O.C.;*
[9]*Evidence-based Medicine Center, Chung Shan Medical University Hospital, Taichung, Taiwan, R.O.C.;*
[10]*Library, Chung Shan Medical University Hospital, Taichung, Taiwan, R.O.C.;*
[11]*Department and Graduate Institute of Business Administration, National Taiwan University, Taipei, Taiwan, R.O.C.;*
[12]*Department of Orthopedics Department, Chi-Mei Medical Center, Tainan, Taiwan, R.O.C.*

Abstract. *Background/Aim: Gout, characterized by acute inflammatory symptoms and monosodium urate crystal deposits in joints, is prevalent among males and the elderly. Total knee arthroplasty (TKA) is a common treatment for knee osteoarthritis (OA), but its impact on the risk of developing gout is unclear. This study examined the risk of gout in patients undergoing TKA. Patients and Methods: Utilizing the TriNetX research network, a retrospective cohort study was conducted on OA patients without prior gout. The TKA cohort was compared to a non-TKA control group using propensity score matching to balance covariates. The primary outcome was the incidence of gout over a five-year follow-up period. Results: The study included 38,834 matched pairs of TKA and non-TKA patients. TKA patients had a 15.6% higher risk of developing gout (HR=1.156; 95%CI=1.042-1.284) compared to controls. Sensitivity analyses confirmed the increased risk across various models and follow-up durations. Conclusion: TKA is associated with a higher risk of developing gout, particularly in females and older adults. Clinicians should monitor and manage gout risk in TKA patients, emphasizing preventive measures and early intervention. Further research is needed to understand the underlying mechanisms and improve patient care post-TKA.*

Correspondence to: Hui-Chin Chang, MLS, Evidence-based Medicine Center, Chung Shan Medical University Hospital, No. 110, Sec. 1, Jianguo N. Rd., South District, Taichung City 40201, Taiwan, R.O.C. E-mail: changhc01@gmail.com

Key Words: Gout, total knee arthroplasty, real-world study, epidemiology.

Gout is a common disease characterized by acute inflammatory symptoms and monosodium urate crystals deposited in joints and tissues (1). The incidence of gout is higher in male and elderly individuals (2). Several risk factors for developing gout have been identified, including hyperuricemia, alcohol consumption, metabolic syndrome, and diet (1). In terms of the pharmacological treatment, non-steroidal anti-inflammatory drugs (NSAIDs), colchicine, and corticosteroids could be considered (3). Therefore, patients with gout often face higher direct and indirect costs, which may impact their economic condition and daily life (4).

In the current aging society, osteoarthritis (OA) is becoming increasingly common in clinical practice. Therefore, total knee arthroplasty (TKA) is often applied as an essential surgery process for patient with knee OA (5). TKA can help patients relieve pain, improve function, and even reduce treatment costs (6). Nevertheless, the poor outcomes and comorbidities after TKA have not been completely demonstrated in recent studies. Gout, as an

inflammatory condition that frequently affects joint structures, has been linked to TKA in several studies. Patients with gout who undergo TKA may face a higher risk of comorbidities, such as cardiac arrest, hematoma, infection, and capsulitis, as well as increased surgery and care costs (7). Moreover, patients with a history of gout may have an increased risk of being diagnosed with acute gout diagnosis after TKA (8). Obviously, the relationship between gout and TKA should be substantially valued in clinical practice. However, the literature on the occurrence of gout after TKA in OA patients without a prior diagnosis of gout remains incomplete. Therefore, in this cohort study, we aimed to clarify the risk of gout in patients who have undergone TKA.

Patients and Methods

TriNetX, a network of over 120 healthcare organizations, provides anonymized medical records for large-scale epidemiological research (9-12). In the current study, we utilized TriNetX and chose the US Collaborative Network as our primary source of analysis, containing data from over 65 Healthcare organizations (HCOs) located exclusively within the USA. The TriNetX database was previously approved by the Western Institutional Review Board (Western IRB). The subsequent determination regarding the de-identification process attested on December 2020 replaced the need of Western IRB approval in TriNetX studies. Ethical approval was not required for the study involving humans in accordance with the local legislation and institutional requirements.

For the current retrospective cohort study, we used data from individuals who were recruited between 2015 and 2017. Study individuals were characterized according to two conditions: a diagnosis of OA indicated in the TriNetX system and no gout in the medical history. Exclusion criteria included individuals who had died either before or after the index date, as well as those younger than eighteen years. Another exclusion criterion was cancer in the medical history. The TKA cohort comprised patients who underwent TKA during the enrollment period. The control cohort comprised patients with OA but who have not undergone any form of TKA surgery. The propensity score-matching method was applied to minimize confounding by indication. This method produces a control group that closely resembles the treatment group across various characteristics. Matching was performed based on criteria, such as age, sex, race, body mass index (BMI), comorbidities, medication use, laboratory values, socioeconomic factors, and healthcare utilization (Table I and Table II). The outcome of interest in the study was the development of gout. We also performed several additional analyses to evaluate internal validity. These analyses involved variations in matching criteria, duration of follow-up and subgroups of participants.

Statistical analyses. We used the analytics function built into the TriNetX platform to analyze the data. We compared the baseline characteristics between the groups using an standardized mean difference (SMD) statistic. If the SMD >0.1, we considered the difference to be statistically significant. We calculated hazard ratios to assess the risk of developing gout. The obtained hazard ratios were evaluated for their statistical significance based on their 95% confidence intervals.

Results

Baseline characteristics. After excluding patients who were under 18 years old, deceased, or had gout and cancer before or on the index day, the TKA group consisted of 38,834 patients, and the non-TKA control group comprised 2,134,981 patients. Following this, using 1:1 propensity score matching, both the TKA and control groups included 38,834 patients each (Figure 1). Patients in TKA group had a higher proportion of alcohol dependence, substance use, and co-medication use (thiazides and related diuretics, chlorthalidone, and cyclosporine) compared to the control group. Following the matching process, we found no statistically significant differences between the TKA group and the control group, in baseline characteristics, such as age, sex, ethnicity, body mass index, and healthcare utilization patterns (Table I).

Gout risk in TKA patients. The cumulative incidence of gout in the TKA cohort increased over time within the five-year follow-up period (Figure 2). The control cohort also showed an upward trend in gout incidence; however, the incidence remained lower than that of the TKA cohort. The analysis showed a statistically significant difference between the two groups (p-value<0.01). Individuals who underwent TKA had a 15.6% higher risk of developing gout compared to the control group (HR=1.156; 95%CI=1.042-1.284).

Sensitivity analyses. Compared to the control group, a significantly elevated risk of gout was observed in the TKA cohort across various models and conditions (Table III). In the analysis with different matching covariates, the hazard ratio was 1.288 (95%CI=1.198-1.383) in the crude model, 1.244 (95%CI=1.118-1.384) when adjusted for age, sex, comorbidities, and race, and 1.178 (95%CI=1.061-1.309) when adjusted for age, sex, race, and comedications. For different wash-out periods, the hazard ratio was 1.135 (95%CI=1.016-1.267) for a 12-month period, 1.146 (95%CI=1.017-1.293) for a 24-month period, and 1.150 (95%CI=1.006-1.315) for a 36-month period. When considering different follow-up times, the hazard ratio was 1.135 (95%CI=1.035-1.246) for an 8-year period, 1.156 (95%CI=1.061-1.258) for a 10-year period, and 1.119 (95%CI=1.018-1.229) for a 12-year period. These findings remained consistent across different covariate-matching models, wash-out periods, and follow-up times.

Stratification analysis. The stratification analysis of gout in TKA patients presents the hazard ratios for subgroups during the 5-year follow up, based on sex and age (Table IV). Women who underwent TKA had a 38.1% greater risk of gout compared to the control group, and this risk was also elevated (25.7%) for those aged 65 or older who had TKA surgery. These findings were statistically significant.

Table I. *Baseline characteristics*.

	Before matching			After matching[a]		
	TKA cohort (n=38,834)	Control cohort (n=2,134,981)	SMD	TKA cohort (n=38,834)	Control cohort (n=38,834)	SMD
Age at index						
Mean±SD	63.6±10.1	59.2±14.2	**0.36**	63.6±10.1	63.7±10.3	0.01
Sex						
Male	14,205 (36.6)	783,385 (36.7)	0.00	14,205 (36.6)	14,276 (36.8)	0.00
Female	24,357 (62.7)	1,251,730 (58.6)	0.08	24,357 (62.7)	24,299 (62.6)	0.00
Race, n (%)						
White	28,206 (72.6)	1,431,246 (67.0)	**0.12**	28,206 (72.6)	28,313 (72.9)	0.01
Black or African American	4,134 (10.6)	267,564 (12.5)	0.06	4,134 (10.6)	4,200 (10.8)	0.01
Asian	1,086 (2.8)	49,541(2.3)	0.03	1,086 (2.8)	1,104 (2.8)	0.00
American Indian or Alaska Native	158 (0.4)	6,943(0.3)	0.01	158 (0.4)	136 (0.4)	0.01
Native Hawaiian or Other Pacific Islander	315 (0.8)	6,902 (0.3)	0.06	315 (0.8)	330 (0.9)	0.00
Socioeconomic status						
Socioeconomic/psychosocial circumstances problem	190 (0.5)	16,701 (0.8)	0.04	190 (0.5)	135 (0.3)	0.02
Lifestyle						
Alcohol dependence, smoking and substance use	1,964 (5.1)	141,034 (6.6)	0.07	1,964 (5.1)	1,823 (4.7)	0.02
Comorbidities						
Hypertension	10,188 (26.2)	459,053 (21.5)	**0.11**	10,188 (26.2)	10,231 (26.3)	0.00
Diabetes mellitus	3,527 (9.1)	189,952 (8.9)	0.01	3,527 (9.1)	3,500 (9.0)	0.00
Hyperlipidemia	6,040 (15.6)	275,479 (12.9)	0.08	6,040 (15.6)	6,014 (15.5)	0.00
Hyperuricemia	10 (0.0)	727 (0.0)	0.00	10 (0.0)	10 (0.0)	0.00
Co-medications						
Aspirin	6,415 (16.5)	193,939 (9.1)	**0.22**	6,415 (16.5)	6,373 (16.4)	0.00
Thiazides and related diuretics	5,303 (13.7)	170,354 (8.0)	**0.18**	5,303 (13.7)	5,230 (13.5)	0.01
Chlorthalidone	238 (0.6)	9,971 (0.5)	0.02	238 (0.6)	195 (0.5)	0.01
Cyclosporine	184 (0.5)	7,687 (0.4)	0.02	184 (0.5)	133 (0.3)	0.02
Medical Utilization Status						
Ambulatory visit	25,912 (66.7)	1,258,602 (59.0)	**0.16**	25,912 (66.7)	25,827 (66.5)	0.00
Laboratory data						
BMI, n (%)						
≥25 (kg/m^2)	7,836 (20.2)	305,039 (14.3)	**0.16**	7,836 (20.2)	7,638 (19.7)	0.01
Urate, n (%)						
≥10 (mg/dl)	36 (0.1)	1,353 (0.1)	0.01	36 (0.1)	16 (0.0)	0.02

Bold font represents a standardized mean difference (SMD) was more than 0.1. TKA: Total knee arthroplasty; BMI: body mass index. [a]Propensity score matching was presented with the covariates of age at index, sex, race, body mass index, status of comorbidities (including diabetes mellitus, hypertension, hyperlipidemia, hyperuricemia), status of comedication use (chlorothiazide, chlorthalidone, aspirin, cyclosporine), lab data (C-reactive protein, urate), problems related to housing and economic circumstances, individuals with potential health hazards related to socioeconomic and psychosocial circumstances, and medical utilization status.

Discussion

In this study, we conducted a retrospective cohort analysis using data from a large U.S. electronic health records database to examine the incidence of gout in patients with severe OA who underwent TKA compared to those who did not undergo TKA. Our findings revealed a significantly higher incidence of gout among patients who received TKA. Specifically, the hazard ratio for gout in the TKA group was 1.288 (95%CI=1.198-1.383), indicating a nearly 29% increased risk of developing gout post-operatively. This association persisted across various subgroups, including different sex and age categories, with notable increases in risk observed particularly among female patients and those aged 65 years and older.

In the United States, the incidence and prevalence of gout have been rising steadily in recent years (13, 14). Data suggest a substantial rise in gout prevalence within the United States, with estimates ranging from under 3 million to over 8 million affected individuals (15, 16). Another study described a continuous increase in prevalence from 2011 to 2018, with the most recent prevalence estimated at 5.1%, affecting approximately 12 million individuals (17).

Table II. *Utilized definitions of study population, covariates and outcome events.*

Description	Adopted codes[a]
Study population	
Osteoarthritis	ICD-10-CM: M15-M19
Procedures	
Total knee replacement	ICD-10-PCS[b]: 0SRD0JZ, 0SRC0JZ, 0SRW0JZ, 0SRV0JZ, 0SRU0JZ, 0SRT0JZ, 0SRD07Z, 0SRD0KZ, 0SRU07Z, 0SRU0KZ, 0SRW07Z, 0SRW0KZ, 0SRC0KZ, 0SRT07Z, 0SRT0KZ, 0SRV0KZ
Confounding factors and comorbidities	
Neoplasms	ICD-10-CM: C00-D49
Diabetes mellitus	ICD-10-CM: E08-E13
Hypertension	ICD-10-CM: I10
Hyperlipidemia	ICD-10-CM: E78.5
Hyperuricemia	ICD-10-CM: E79.0
Mental and behavioral disorders due to psychoactive substance use	ICD-10-CM: F10-F19
Persons with potential health hazards related to socioeconomic and psychosocial circumstances	ICD-10-CM: Z55-Z65
Medications	
Aspirin	RxNorm:1191
Thiazides and related diuretics	VA:CV701
Chlorthalidone	RxNorm:2409
Cyclosporine	RxNorm:3008
Outcomes	
Gout	ICD-10-CM: M10

[a]ICD-10-CM: International Classification of Diseases, Tenth Revision, Clinical Modification. [b]ICD-10-PCS: International Classification of Diseases, Tenth Revision, Procedure Coding System.

Gout typically presents as acute inflammatory arthritis (gout flares) characterized by intense pain affecting lower extremity joints (1, 18). Severe gout flares can lead to significant limitations in the use of the affected area and difficulty walking (19). Gout attacks often provide clues for doctors to diagnose the condition. These attacks typically affect a single joint, most commonly in the lower leg. In particular, gout frequently targets the joint at the base of the big toe (known as podagra) (1). Identified risk factors for gout include age (2), sex (15, 20), race (2), and genetic predispositions (2, 21). Male patients are 2 to 4 times more likely to develop gout compared to female patients (15, 20). Metabolic diseases are also considered risk and precipitating factors for gout, including hyperuricemia (1), hypertension (22), metabolic syndrome (23), and even local anatomical factors that may predispose individual joints to gouty inflammation. These include elevated local urate concentration (24), repeated microtrauma to joints, pre-existing degenerative changes, or lower temperatures in distal sites of limbs that were circulated less efficiently (25). Existing OA, particularly in the small joints of the fingers (Heberden's and Bouchard's nodes), might increase the risk of gout attacks in these locations (26). Furthermore, hospitalization itself is known to be a factor that can trigger gout flares. Retrospective studies have identified predictors of gout flares in hospitalized patients, including trauma and surgery (27). Also, regarding the association between gout attack and hyperuricemia, it is believed to involve a two-step process. First, high levels of uric acid in the blood (hyperuricemia) lead to the formation of sharp urate crystals in joints. Second, the body launches an intense inflammatory response to these crystals, causing the characteristic pain and swelling of a gout attack (28).

Reports have documented cases of crystalline arthritis occurring at the prosthetic joint site several years after TKA (29, 30). Previous studies have indicated that patients undergoing TKA may present with symptoms, such as joint swelling, pain accompanied by joint dysfunction, and even systemic fever. Gout flares can be easily confused with septic arthritis at first. This is because common blood tests, like white blood cell count, sedimentation rate, and C-reactive protein, can be increased in both conditions (29). In this case, differentiating periprosthetic crystalline arthritis from acute septic arthritis at initial presentation can be challenging, and even experienced physicians may make incorrect diagnoses (31). Therefore, synovial fluid aspiration plays a crucial role in diagnosing joint swelling and pain in patients with a history of prosthetic joint replacement (32).

Diagnosing periprosthetic joint infection (PJI) can be challenging due to the lack of standardized definitions.

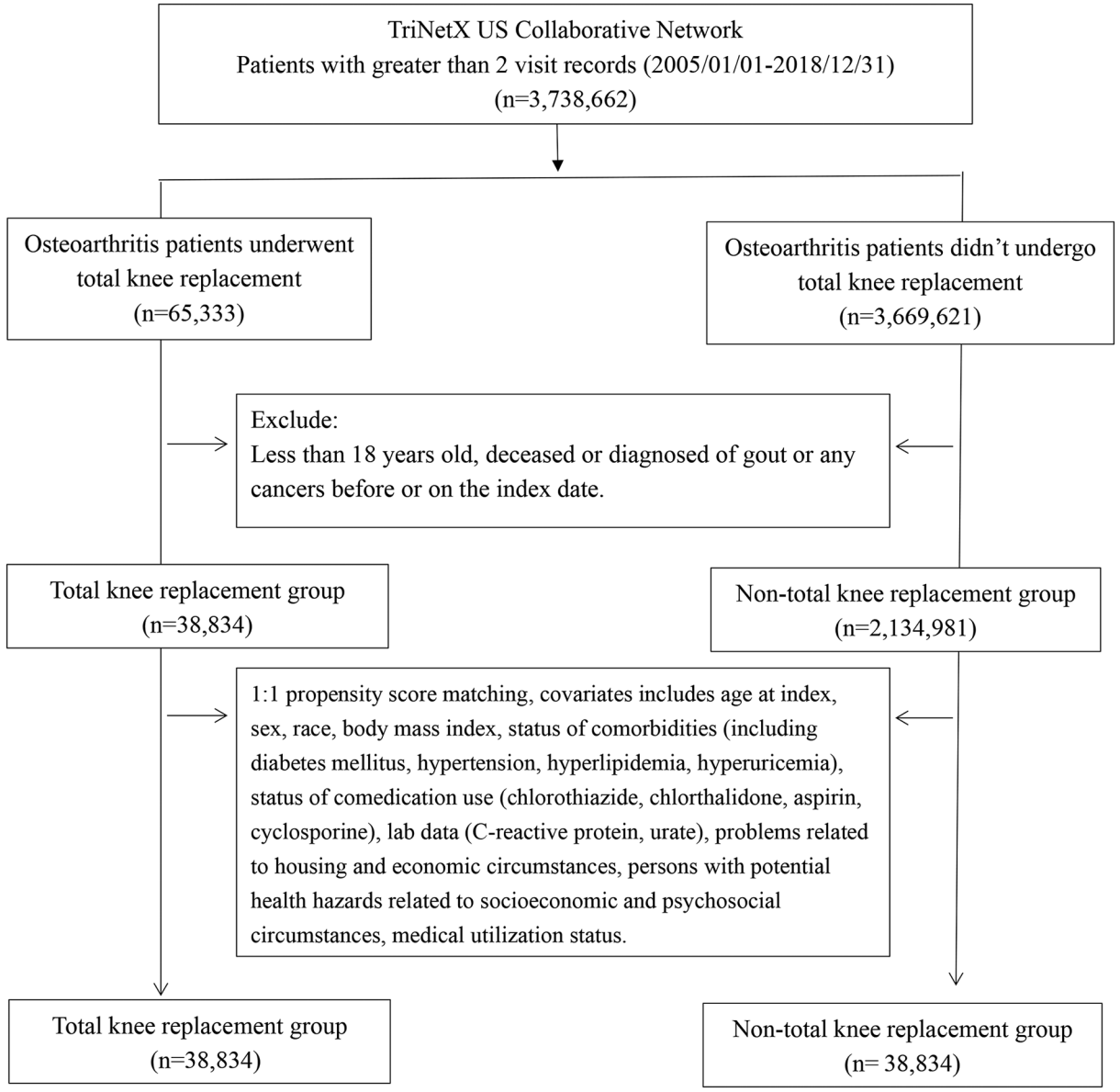

Figure 1. *Patient selection process*.

Various diagnostic criteria have been proposed in the academic community, including the 2021 European Bone and Joint Infection Society (EBJIS) criteria (33), the 2018 International Consensus Meeting (ICM) criteria (34), and the 2013 Infectious Disease Society of America guidelines (35). The latest diagnostic criteria for periprosthetic joint infection (PJI) suggested by the EBJIS indicate that a definitive PJI diagnosis is established if any of the following are present: a sinus tract with communication to the joint or prosthesis, synovial fluid cytology showing a leukocyte count greater than 3,000 cells/µl or a percentage of polymorphonuclear cells greater than 80%, or visible microorganisms on high-power field examination, among other criteria. The EBJIS criteria have demonstrated the highest consistency and sensitivity between preoperative classification and final diagnosis (36). However, there is no consensus on the optimal treatment for periprosthetic crystalline arthritis. Treatment options reported in the literature (37) include non-surgical medical therapy, arthroscopic irrigation, open irrigation procedures and change of the polyethylene insert, and open washout procedures, and first-stage revision surgery (38).

Despite the increasing number of case reports indicating that gout may be a rare complication of TKA, there is still a significant lack of comprehensive studies addressing this

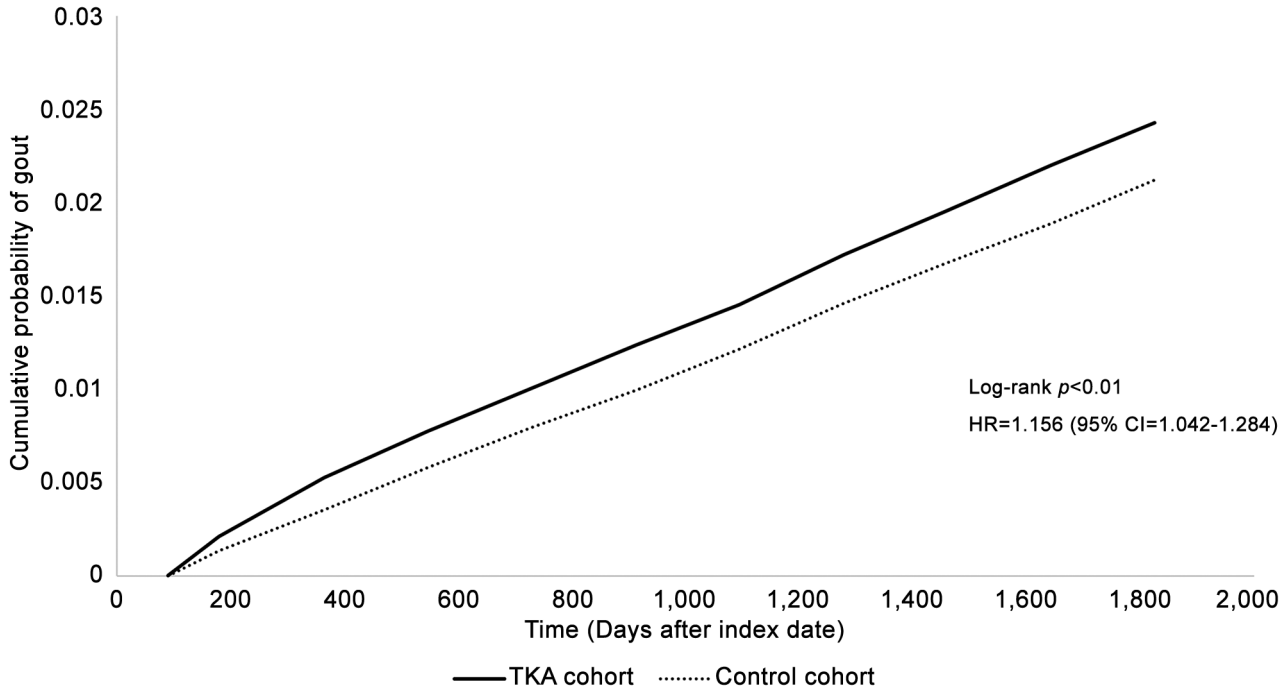

Figure 2. *Kaplan-Meier plot of 5-year follow-up period.*

Table III. *Hazard ratio of gout with 95% confidence interval under various models.*

Various matching covariates	Model 1[a]	Model 2[b]	Model 3[c]
Non-TKA controls	1.00	1.00	1.00
TKA patients	1.288 (1.198,1.383)	1.244 (1.118,1.384)	1.178 (1.061,1.309)
Various wash-out periods	Model 1[d]	Model 2[e]	Model 3[f]
Non-TKA controls	1.00	1.00	1.00
TKA patients	1.135 (1.016,1.267)	1.146 (1.017,1.293)	1.150 (1.006,1.315)
Various follow-up times	Model 1[g]	Model 2[h]	Model 3[i]
Non-TKA controls	1.00	1.00	1.00
TKA patients	1.135 (1.035,1.246)	1.156 (1.061,1.258)	1.119 (1.018,1.229)

TKA: Total knee arthroplasty. Propensity score matching was presented with the covariates of age at index, sex, race, body mass index, status of comorbidities (including diabetes mellitus, hypertension, hyperlipidemia, hyperuricemia), status of comedication use (chlorothiazide, chlorthalidone, aspirin, cyclosporine), lab data (C-reactive protein, urate), problems related to housing and economic circumstances, individuals with potential health hazards related to socioeconomic and psychosocial circumstances, and medical utilization status. [a]Crude model without performing propensity score matching. [b]Covariates of propensity score matching includes age at index, sex, comorbidities and race. [c]Covariates of propensity score matching includes age at index, sex, race and comedications. [d]Wash-out period was set as 12 months in this model. Incident gout occurred within 12 months were not calculated as outcome events. [e]Wash-out period was set as 24 months in this model. Incident gout occurred within 24 months were not calculated as outcome events. [f]Wash-out period was set as 36 months in this model. Incident gout occurred within 36 months were not calculated as outcome events. [g]Follow-up period was set as 8 years in this model. [h]Follow-up period was set as 10 years in this model. [i]Follow-up period was set as 12 years in this model.

issue. Prior research has not definitively explored the link between TKA and the risk of gout after surgery. This study fills this gap by analyzing a large group of TKA patients from a robust, multi-center database. Our findings revealed an increased risk of gout in individuals who underwent TKA compared to those who did not. Additionally, previous

Table IV. *Stratification analysis of gout risk in total knee arthroplasty (TKA) patients in 5-year follow-up.*

Subgroups	Cases occurring new-onset gout		HR (95%CI)[a]
	TKA cohort No. of outcome event (%)	Control cohort No. of outcome event (%)	
Sex			
Male	414 (2.9)	374 (2.6)	1.089 (0.947,1.252)
Female	347 (1.4)	247 (1.0)	1.381 (1.173,1.626)
Age at index date			
18-64 years old	79 (1.3)	76 (1.2)	1.030 (0.752,1.411)
≥65 years old	686 (2.1)	540 (1.7)	1.257 (1.123,1.407)

[a]Propensity score matching was presented with the covariates of age at index, sex, race, body mass index, status of comorbidities (including diabetes mellitus, hypertension, hyperlipidemia, hyperuricemia), status of comedication use (chlorothiazide, chlorthalidone, aspirin, cyclosporine), lab data (C-reactive protein, urate), problems related to housing and economic circumstances, individuals with potential health hazards related to socioeconomic and psychosocial circumstances, and medical utilization status.

Mendelian randomization studies have confirmed the absence of a bidirectional causal relationship between OA, urate levels, and gout (39). Given these findings, TKA should be considered a risk factor for gout. Clinicians should be aware of the importance of monitoring and managing gout risk in TKA patients postoperatively and should implement preventive measures for high-risk individuals, such as women and elderly patients, including dietary adjustments and prophylactic medications.

Our study analyzes a large, global database to examine the link between TKA and gout risk. We employed various methods including subgroup analyses, propensity score matching, and adjustments for confounding factors to strengthen our findings. However, this retrospective study has inherent limitations due to its design and data sources. First, we relied on ICD-10-CM codes to identify patients and assess outcomes, which may lead to potential misdiagnosis and misclassification, as in many database-derived retrospective studies (40, 41). Second, there is a potential imbalance between the severity of OA in the two groups. Patients who underwent TKA likely had more severe OA compared to those who did not. However, existing research suggests that there is no clear two-way cause-and-effect relationship between OA and gout. Third, even with matching of the TKA and non-TKA groups, there is still a chance that some unknown factors (confounding variables) might influence the observed association between TKA and gout risk. Fourth, while our study population within the US reflects diverse ethnicities, it is unclear whether the observed connection between TKA and gout risk applies equally to Asian or European populations, which could lead to potential bias in generalizability. Fifth, due to the lack of information regarding the composition of knee prosthesis materials, we could not analyze gout risk based on different materials. Sixth, we could not observe the location of gout occurrences through medical records. Lastly, our study alone cannot elucidate the complex mechanisms underlying the increased risk of gout post-TKA, necessitating further research to uncover this association.

Our study found that patients undergoing TKA are at a higher risk of developing gout. We aim to raise awareness among clinicians about the potential for crystalline arthropathy following total joint replacement surgery. It is crucial to assess for crystalline arthropathy before treating presumed periprosthetic joint infections to avoid misdiagnosis and ensure appropriate patient management. Additionally, postoperative management of gout risk should be a priority. We also anticipate more prospective studies to confirm the causal relationship between TKA and gout risk, investigate the biological mechanisms of gout development post-TKA, and explore how different types of TKA surgeries and postoperative management strategies affect gout incidence. Identifying the optimal treatment approach for this patient population is essential.

Funding

None.

Conflicts of Interest

The Authors have no conflicts of interest in relation to this study.

Authors' Contributions

All the Authors were involved in drafting or revising the article and approved of the submitted version. Study conception and design: Lin ZH, Chang HC, Li YF, Ku YC, Lee CY, Wu YL, Chen SJ, and Gau SY. Data acquisition: Chang HC and Gau SY. Data analysis and demonstration: Chang HC, and Gau SY. Original draft preparation: Lin ZH, Chang HC, Li YF, Ku YC, Lee CY, Wu YL, Chen SJ, and Gau SY.

References

1 Dalbeth N, Gosling AL, Gaffo A, Abhishek A: Gout. Lancet 397(10287): 1843-1855, 2021. DOI: 10.1016/S0140-6736(21)00569-9

2 Kuo CF, Grainge MJ, Zhang W, Doherty M: Global epidemiology of gout: prevalence, incidence and risk factors. Nat Reviews Rheumatol 11(11): 649-662, 2015. DOI: 10.1038/nrrheum.2015.91

3 Roddy E, Doherty M: Treatment of hyperuricaemia and gout. Clin Med (Lond) 13(4): 400-403, 2013. DOI: 10.7861/clinmedicine.13-4-400

4 Rai SK, Burns LC, De Vera MA, Haji A, Giustini D, Choi HK: The economic burden of gout: A systematic review. Semin Arthritis Rheum 45(1): 75-80, 2015. DOI: 10.1016/j.semarthrit.2015.02.004

5 Gademan MG, Hofstede SN, Vliet Vlieland TP, Nelissen RG, Marang-van de Mheen PJ: Indication criteria for total hip or knee arthroplasty in osteoarthritis: a state-of-the-science overview. BMC Musculoskelet Disord 17(1): 463, 2016. DOI: 10.1186/s12891-016-1325-z

6 Carr AJ, Robertsson O, Graves S, Price AJ, Arden NK, Judge A, Beard DJ: Knee replacement. Lancet 379(9823): 1331-1340, 2012. DOI: 10.1016/S0140-6736(11)60752-6

7 Rosas S, Zuskov A, Luo TD, Roche MW, Emory CL, Plate JF: Gout as a predictor of total knee arthroplasty outcomes and costs. J Knee Surg 35(04): 362-366, 2022. DOI: 10.1055/s-0040-1715098

8 Cole MW, Collins LK, Wilder JH, Ross BJ, Hawkins BJ, Sherman WF: The effects of gout following total knee arthroplasty: a retrospective analysis. J Arthroplasty 38(8): 1499-1503, 2023. DOI: 10.1016/j.arth.2023.01.064

9 Lin ZH, Chang HC, Wu YL, Gau SY: Increased risk of new-onset rheumatoid arthritis among osteoarthritis patients received total knee arthroplasty: a global federated health network analysis. Int J Med Sci 21(6): 994-1002, 2024. DOI: 10.7150/ijms.93457

10 Gau SY, Lo SW, Chen SJ, Liao WC, Tsai RY, Su YJ, Chang HC, Li CP: New-onset fibromyalgia after total knee replacement in patients with osteoarthritis: a propensity-score-matched cohort study in the United States. In Vivo 38(4): 1957-1964, 2024. DOI: 10.21873/invivo.13652

11 Chang HC, Wu CL, Chiu TM, Liao WC, Gau SY: Risk of osteoarthritis in patients with hidradenitis suppurativa: a global federated health network analysis. Front Immunol 14: 1285560, 2023. DOI: 10.3389/fimmu.2023.1285560

12 Li CP, Lo SW, Tsai RY, Chang HC, Gau SY: New-onset hidradenitis suppurativa in psoriasis patients: a multi-center, retrospective cohort study. Life (Basel) 14(6): 730, 2024. DOI: 10.3390/life14060730

13 Choi H: Epidemiology of crystal arthropathy. Rheum Dis Clin North Am 32(2): 255-273, 2006. DOI: 10.1016/j.rdc.2006.03.002

14 Smith E, Hoy D, Cross M, Merriman TR, Vos T, Buchbinder R, Woolf A, March L: The global burden of gout: estimates from the Global Burden of Disease 2010 study. Ann Rheum Dis 73(8): 1470-1476, 2014. DOI: 10.1136/annrheumdis-2013-204647

15 Chen-Xu M, Yokose C, Rai SK, Pillinger MH, Choi HK: Contemporary prevalence of gout and hyperuricemia in the United States and decadal trends: The National Health and Nutrition Examination Survey, 2007-2016. Arthritis Rheumatol 71(6): 991-999, 2019. DOI: 10.1002/art.40807

16 Kramer HM, Curhan G: The association between gout and nephrolithiasis: The National Health and Nutrition Examination Survey III, 1988-1994. Am J Kidney Dis 40(1): 37-42, 2002. DOI: 10.1053/ajkd.2002.33911

17 Yokose C, McCormick N, Lu N, Tanikella S, Lin K, Joshi AD, Raffield LM, Warner E, Merriman T, Hsu J, Saag K, Zhang Y, Choi HK: Trends in prevalence of gout among US Asian adults, 2011-2018. JAMA Netw Open 6(4): e239501, 2023. DOI: 10.1001/jamanetworkopen.2023.9501

18 Taylor WJ, Fransen J, Jansen TL, Dalbeth N, Schumacher HR, Brown M, Louthrenoo W, Vazquez-Mellado J, Eliseev M, McCarthy G, Stamp LK, Perez-Ruiz F, Sivera F, Ea HK, Gerritsen M, Scire C, Cavagna L, Lin C, Chou YY, Tausche AK, Vargas-Santos AB, Janssen M, Chen JH, Slot O, Cimmino MA, Uhlig T, Neogi T: Study for updated gout classification criteria: identification of features to classify gout. Arthritis Care Res (Hoboken) 67(9): 1304-1315, 2015. DOI: 10.1002/acr.22585

19 Gaffo AL, Schumacher HR, Saag KG, Taylor WJ, Dinnella J, Outman R, Chen L, Dalbeth N, Sivera F, Vázquez-Mellado J, Chou CT, Zeng X, Perez-Ruiz F, Kowalski SC, Goldenstein-Schainberg C, Chen L, Bardin T, Singh JA: Developing a provisional definition of flare in patients with established gout. Arthritis Rheum 64(5): 1508-1517, 2012. DOI: 10.1002/art.33483

20 Zobbe K, Prieto-Alhambra D, Cordtz R, Højgaard P, Hindrup JS, Kristensen LE, Dreyer L: Secular trends in the incidence and prevalence of gout in Denmark from 1995 to 2015: a nationwide register-based study. Rheumatology (Oxford) 58(5): 836-839, 2019. DOI: 10.1093/rheumatology/key390

21 Köttgen A, Albrecht E, Teumer A, Vitart V, Krumsiek J, Hundertmark C, Pistis G, Ruggiero D, O'Seaghdha CM, Haller T, Yang Q, Tanaka T, Johnson AD, Kutalik Z, Smith AV, Shi J, Struchalin M, Middelberg RP, Brown MJ, Gaffo AL, Pirastu N, Li G, Hayward C, Zemunik T, Huffman J, Yengo L, Zhao JH, Demirkan A, Feitosa MF, Liu X, Malerba G, Lopez LM, van der Harst P, Li X, Kleber ME, Hicks AA, Nolte IM, Johansson A, Murgia F, Wild SH, Bakker SJ, Peden JF, Dehghan A, Steri M, Tenesa A, Lagou V, Salo P, Mangino M, Rose LM, Lehtimäki T, Woodward OM, Okada Y, Tin A, Müller C, Oldmeadow C, Putku M, Czamara D, Kraft P, Frogheri L, Thun GA, Grotevendt A, Gislason GK, Harris TB, Launer LJ, McArdle P, Shuldiner AR, Boerwinkle E, Coresh J, Schmidt H, Schallert M, Martin NG, Montgomery GW, Kubo M, Nakamura Y, Tanaka T, Munroe PB, Samani NJ, Jacobs DR Jr, Liu K, D'Adamo P, Ulivi S, Rotter JI, Psaty BM, Vollenweider P, Waeber G, Campbell S, Devuyst O, Navarro P, Kolcic I, Hastie N, Balkau B, Froguel P, Esko T, Salumets A, Khaw KT, Langenberg C, Wareham NJ, Isaacs A, Kraja A, Zhang Q, Wild PS, Scott RJ, Holliday EG, Org E, Viigimaa M, Bandinelli S, Metter JE, Lupo A, Trabetti E, Sorice R, Döring A, Lattka E, Strauch K, Theis F, Waldenberger M, Wichmann HE, Davies G, Gow AJ, Bruinenberg M, LifeLines Cohort Study, Stolk RP, Kooner JS, Zhang W, Winkelmann BR, Boehm BO, Lucae S, Penninx BW, Smit JH, Curhan G, Mudgal P, Plenge RM, Portas L, Persico I, Kirin M, Wilson JF, Mateo Leach I, van Gilst WH, Goel A, Ongen H, Hofman A, Rivadeneira F, Uitterlinden AG, Imboden M, von Eckardstein A, Cucca F, Nagaraja R, Piras MG, Nauck M, Schurmann C, Budde K, Ernst F, Farrington SM, Theodoratou E, Prokopenko I, Stumvoll M, Jula A, Perola M, Salomaa V, Shin SY, Spector TD, Sala C, Ridker PM, Kähönen M, Viikari J, Hengstenberg C, Nelson CP, CARDIoGRAM Consortium, DIAGRAM Consortium, ICBP Consortium, MAGIC Consortium, Meschia JF, Nalls MA, Sharma P,

Singleton AB, Kamatani N, Zeller T, Burnier M, Attia J, Laan M, Klopp N, Hillege HL, Kloiber S, Choi H, Pirastu M, Tore S, Probst-Hensch NM, Völzke H, Gudnason V, Parsa A, Schmidt R, Whitfield JB, Fornage M, Gasparini P, Siscovick DS, Polašek O, Campbell H, Rudan I, Bouatia-Naji N, Metspalu A, Loos RJ, van Duijn CM, Borecki IB, Ferrucci L, Gambaro G, Deary IJ, Wolffenbuttel BH, Chambers JC, März W, Pramstaller PP, Snieder H, Gyllensten U, Wright AF, Navis G, Watkins H, Witteman JC, Sanna S, Schipf S, Dunlop MG, Tönjes A, Ripatti S, Soranzo N, Toniolo D, Chasman DI, Raitakari O, Kao WH, Ciullo M, Fox CS, Caulfield M, Bochud M, Gieger C: Genome-wide association analyses identify 18 new loci associated with serum urate concentrations. Nat Genet 45(2): 145-154, 2013. DOI: 10.1038/ng.2500

22 McAdams-DeMarco MA, Maynard JW, Baer AN, Coresh J: Hypertension and the risk of incident gout in a population-based study: the atherosclerosis risk in communities cohort. J Clin Hypertens (Greenwich) 14(10): 675-679, 2012. DOI: 10.1111/j.1751-7176.2012.00674.x

23 Rho YH, Choi SJ, Lee YH, Ji JD, Choi KM, Baik SH, Chung SH, Kim CG, Choe JY, Lee SW, Chung WT, Song GG: The prevalence of metabolic syndrome in patients with gout: a multicenter study. J Korean Med Sci 20(6): 1029-1033, 2005. DOI: 10.3346/jkms.2005.20.6.1029

24 Simkin PA: The pathogenesis of podagra. Ann Intern Med 86(2): 230, 1977. DOI: 10.7326/0003-4819-86-2-230

25 McCarty DJ: Gout without hyperuricemia. JAMA 271(4): 302, 1994. DOI: 10.1001/jama.1994.03510280064034

26 Lally EV, Zimmermann B, Ho G Jr, Kaplan SR: Urate-mediated inflammation in nodal osteoarthritis: clinical and roentgenographic correlations. Arthritis Rheum 32(1): 86-90, 1989. DOI: 10.1002/anr.1780320115

27 Jatuworapruk K, Grainger R, Dalbeth N, Taylor WJ: Development of a prediction model for inpatient gout flares in people with comorbid gout. Ann Rheum Dis 79(3): 418-423, 2020. DOI: 10.1136/annrheumdis-2019-216277

28 Ichida K, Matsuo H, Takada T, Nakayama A, Murakami K, Shimizu T, Yamanashi Y, Kasuga H, Nakashima H, Nakamura T, Takada Y, Kawamura Y, Inoue H, Okada C, Utsumi Y, Ikebuchi Y, Ito K, Nakamura M, Shinohara Y, Hosoyamada M, Sakurai Y, Shinomiya N, Hosoya T, Suzuki H: Decreased extra-renal urate excretion is a common cause of hyperuricemia. Nat Commun 3: 764, 2012. DOI: 10.1038/ncomms1756

29 Green AM, Gemayel A, Silberg E: Crystalline-induced arthropathy following total knee replacement. Cureus 13(8): e17619, 2021. DOI: 10.7759/cureus.17619

30 Yahia SA, Zeller V, Desplaces N, Chazerain P, Lhotellier L, Marmor S, Ziza JM: Crystal-induced arthritis after arthroplasty: 7 cases. Joint Bone Spine 83(5): 559-562, 2016. DOI: 10.1016/j.jbspin.2016.01.006

31 Mika A, Gilbert W, Martin JR, Polkowski G: Diagnosis dilemma, culture-negative periprosthetic hip infection *versus* acute gouty arthritis: a case report. JBJS Case Connect 13(2), 2023. DOI: 10.2106/JBJS.CC.23.00023

32 Huffman N, Pasqualini I, Surace P, Molloy RM, Piuzzi NS, Deren ME: Diagnosis, treatment, and outcomes of crystalline arthropathy in the setting of total knee arthroplasty: a critical analysis review. JBJS Rev 11(12), 2023. DOI: 10.2106/JBJS.RVW.23.00163

33 McNally M, Sousa R, Wouthuyzen-Bakker M, Chen AF, Soriano A, Vogely HC, Clauss M, Higuera CA, Trebše R: The EBJIS definition of periprosthetic joint infection. Bone Joint J 103-B(1): 18-25, 2021. DOI: 10.1302/0301-620X.103B1.BJJ-2020-1381.R1

34 Parvizi J, Tan TL, Goswami K, Higuera C, Della Valle C, Chen AF, Shohat N: The 2018 definition of periprosthetic hip and knee infection: an evidence-based and validated criteria. J Arthroplasty 33(5): 1309-1314.e2, 2018. DOI: 10.1016/j.arth.2018.02.078

35 Osmon DR, Berbari EF, Berendt AR, Lew D, Zimmerli W, Steckelberg JM, Rao N, Hanssen A, Wilson WR, Infectious Diseases Society of America. Diagnosis and management of prosthetic joint infection: clinical practice guidelines by the Infectious Diseases Society of America. Clin Infect Dis 56(1): e1-e25, 2013. DOI: 10.1093/cid/cis803

36 Sousa R, Ribau A, Alfaro P, Burch MA, Ploegmakers J, McNally M, Clauss M, Wouthuyzen-Bakker M, Soriano A: The European Bone and Joint Infection Society definition of periprosthetic joint infection is meaningful in clinical practice: a multicentric validation study with comparison with previous definitions. Acta Orthop 94: 8-18, 2023. DOI: 10.2340/17453674.2023.5670

37 Khalfaoui MY, Yassa R: Crystal arthropathy following knee arthroplasty: a review of the literature. Int J Orthop 2(5): 411-417, 2015. DOI: 10.17554/j.issn.2311-5106.2015.02.113

38 Archibeck MJ, Rosenberg AG, Sheinkop MB, Berger RA, Jacobs JJ: Gout-induced arthropathy after total knee arthroplasty: a report of two cases. Clin Orthop Relat Res (392): 377-382, 2001. DOI: 10.1097/00003086-200111000-00049

39 Chen D, Xu H, Sun L, Li Y, Wang T, Li Y: Assessing causality between osteoarthritis with urate levels and gout: a bidirectional Mendelian randomization study. Osteoarthritis Cartilage 30(4): 551-558, 2022. DOI: 10.1016/j.joca.2021.12.001

40 Huang KH, Lee CH, Cheng YD, Gau SY, Tsai TH, Chung NJ, Lee CY: Correlation between long-term use of metformin and incidence of NAFLD among patients with type 2 diabetes mellitus: A real-world cohort study. Front Endocrinol (Lausanne) 13: 1027484, 2022. DOI: 10.3389/fendo.2022.1027484

41 Huang SC, Gau SY, Huang JY, Wu WJ, Wei JC: Increased risk of hypothyroidism in people with asthma: evidence from a real-world population-based study. J Clin Med 11(10): 2776, 2022. DOI: 10.3390/jcm11102776

Received July 29, 2024
Revised August 12, 2024
Accepted August 17, 2024