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Acquired Idiopathic Stiffness after Contemporary Total Knee Arthroplasty: Incidence, Risk Factors, and Results over 25 Years

Aaron R. Owen, M.D.[1], **Meagan E. Tibbo, M.D.**[1], **Andre J. van Wijnen, Ph.D.**[1,2], **Mark W. Pagnano, M.D.**[1], **Daniel J. Berry, M.D.**[1], **Matthew P. Abdel, M.D.**[1,*]

[1]Department of Orthopedic Surgery, Mayo Clinic, 200 First Street S.W., Rochester, MN 55905

[2]Department of Biochemistry and Molecular Biology, Mayo Clinic, 200 First Street S.W., Rochester, MN 55905

Abstract

Background: Acquired idiopathic stiffness (AIS) remains a common failure mode of contemporary TKAs. The current study investigated the incidence of AIS and manipulation under anesthesia (MUA) at a single institution over time, determined outcomes of MUAs, and identified risk factors associated with AIS and MUA.

Methods: We identified 9,771 patients (12,735 knees) who underwent primary TKAs with cemented, modular metal-backed, posterior-stabilized implants from 2000 – 2016 using our institutional total joint registry. Mean age was 68 years, 57% were female, and mean BMI was 33 kg/m^2. Demographic, surgical, and comorbidity data were investigated via univariate Cox proportional hazard models and fit to an adjusted multivariate model to access risk for AIS and MUA. Mean follow-up was 7 years.

Results: During the study period, 456 knees (3.6%) developed AIS and 336 knees (2.6%) underwent MUA. Range of motion (ROM) increased a mean of 34° after the MUA; however, ROM for patients treated with MUA was inferior to patients without AIS at final follow-up (102° vs. 116°, $p<0.0001$). Significant risk factors included younger age (HR 2.3, $p<0.001$), increased tourniquet time (HR 1.01, $p<0.001$), general anesthesia (HR 1.3, $p=0.007$), and diabetes (HR 1.5, $p=0.001$).

Discussion: Acquired idiopathic stiffness has continued to have an important adverse impact on the outcomes of a subset of patients undergoing primary TKAs. When utilized, MUA improved mean ROM by 34°, but patients treated with MUA still had decreased ROM compared to patients without AIS. Importantly, we identified several significant risk factors associated with AIS and subsequent MUA.

Keywords

Arthrofibrosis; Contracture; Stiffness; Manipulation Under Anesthesia (MUA); Range of Motion (ROM)

[*]Corresponding author and requests for reprints author (Matthew P. Abdel, M.D.): abdel.matthew@mayo.edu.

INTRODUCTION

Despite advancements in surgical technique, implant design, and perioperative management strategies such as pain control and mitigation of blood loss, acquired idiopathic stiffness (AIS) continues to be one of the most common complication following primary total knee arthroplasty (TKA) affecting approximately 4% of patients.[1–4] Initial management of patients with AIS includes physical therapy and manipulation under anesthesia (MUA).[5, 6] Unfortunately, some recalcitrant cases go on to more involved procedures including operative lysis of scar tissue (either arthroscopic or open) or revision arthroplasty to reduce pain and restore knee function.[5, 7]

Acquired idiopathic stiffness development likely constitutes host and perioperative factors.[4, 8, 9] While some risk factors such as limited preoperative motion, prior knee surgery, and suboptimal rehabilitative efforts have been consistently reported as increasing the risk of AIS, other patient factors (e.g. age and sex) and comorbidities (e.g. diabetes) have been associated inconsistently.[4–6, 8, 10–12] As the projected incidence of TKA procedures continues to rise, a greater understanding of the incidence and risk factors associated with this complication is desirable.[13–15]

The aims of the current study were to investigate the incidence of AIS and subsequent need for MUA at a single institution over time, describe the outcomes of MUA, and determine the risk factors associated with both AIS and need for MUA.

PATIENTS AND METHODS

Patients

A retrospective review of patients undergoing primary TKA from 1990 to 2016 was performed using our institutional total joint registry.[16] Patients included had undergone primary TKA with cemented, modular metal-backed, posterior-stabilized components, and all patellae were resurfaced. Primary TKAs performed for neoplastic causes were excluded. Patients were divided into contemporary (2000 – 2016) and historical (1990 – 1999) cohorts. The contemporary cohort was utilized to determine study outcomes, while the historical cohort was used only for a longitudinal comparison of the incidences of AIS and MUA, respectively. Institutional review board approval was obtained prior to initiation of the study.

During the contemporary study period, 9,771 patients (12,735 knees) met inclusion criteria. Within 2 years of the primary TKA, 236 patients died, 173 patients were revised, and 270 (3%) patients had less than 2 years of follow-up and were considered lost to follow-up. Among the remaining 9,092 patients, mean follow-up was 7 years (range, 2 – 20 years). Mean age was 68 years (range, 19 – 96 years), 57% were female, and mean body mass index (BMI) was 33 kg/m^2 (range, 14 – 69 kg/m^2). The three most frequent indications for primary TKA were osteoarthritis (88%), post-traumatic arthritis (10%), and arthritis associated with rheumatologic diseases (1.4%) (Table 1). Prior knee surgery was reported in 2,495 cases (20%). The three most commonly reported prior knee surgeries were meniscectomy in 713 cases (29%), open debridement for non-infectious indications in 531 cases (21%), and arthroscopic debridement in 512 cases (21%).

Total knee systems utilized included: Press Fit Condylar (P.F.C.) Sigma fixed-bearing (DePuy-Synthes; Warsaw, Indiana) in 6,007 TKAs (47%), Triathlon (Stryker; Mahwah, New Jersey) in 3,032 TKAs (24%), NexGen (Zimmer-Biomet; Warsaw, Indiana) in 1,503 TKAs (12%), P.F.C. Sigma Rotating Platform (DePuy-Synthes) in 1,116 TKAs (9%), Attune (DePuy-Synthes) in 459 TKAs (4%), Persona (Zimmer- Biomet) in 418 TKAs (3%), Genesis II (Smith & Nephew; Memphis, Tennessee) in 88 TKAs (1%), iBalance (Arthrex; Naples, Florida) in 60 TKAs (<1%), Vanguard (Zimmer- Biomet) in 39 TKAs (<1%), and Empowr (DJO Global; Dallas, Texas) in 13 TKAs (<1%).

Knee Society scores (KSSs) were obtained preoperatively and at 3 months, 2 years, 5 years, and every 5 years postoperatively thereafter per our institutional protocol. Acquired idiopathic stiffness was defined as arc of motion ≤ 90° persisting for ≥ 12 weeks as determined at clinical follow up within 1 year of the index TKAs or as motion ≤ 90° requiring MUA prior to 12 weeks.[4] Patients with pre-existing limitations of motion ≤ 90° were not characterized as having AIS. To provide a longitudinal comparison of AIS and MUA rates, the incidence of AIS and MUA were determined in the same manner for patients in the preceding decade of 1990 to 1999 at our institution. Patients that did not meet AIS criteria were considered the control cohort.

Statistical Analysis

Statistical analysis was performed using Statistical Analysis System (SAS) version 9.2 (SAS Institute Inc.; Cary, North Carolina). Group characteristics including the 17 variables that comprise the Charlson Comorbidity Index (CCI) were collected. Severity and age-weighted CCI was computed for each patient.[17] Categorical variables were summarized as counts and percentages. Continuous variables were summarized as means and standard deviations. Continuous variables were analyzed with unpaired Student's t-tests. Categorical variables were analyzed with Chi-square tests. Individual associations between baseline characteristics of interest and AIS development were investigated by fitting several univariate Cox proportional hazards models. Hazard ratios (HRs) pertaining to time were evaluated at 1-minute increments for tourniquet and operative times. A select combination of these variables was chosen via best subset selection and used to fit an adjusted multivariate model containing the following variables: age, sex, BMI, unilateral versus bilateral TKA, prior knee surgery, smoking status, primary underlying diagnosis, tourniquet time, operative time, anesthesia type, hypertension, diabetes, peripheral vascular disease, moderate/severe liver disease, and metastatic solid tumor. This survival analysis process was repeated for MUA within 1 year as the event of interest, the selected multivariate model for which contained many of the same variables as for the AIS outcome. The only difference was that moderate/severe renal disease was included as a factor in the model for MUA, while moderate/severe liver disease and metastatic solid tumor were not used. The potential for multicollinearity between the selected variables was assessed with the variance inflation factor (VIF), and no evidence of serious multicollinearity was found with all VIF values less than 3. Significance was set at $p < 0.05$.

RESULTS

Incidence of AIS and MUA

From 2000 to 2016, 456 of 12,735 knees (3.6%) developed AIS. In the preceding decade (1990 – 1999), 129 of 3,141 knees (4.1%) were affected. There was no difference in the incidence of AIS between the contemporary and historical cohorts (p=0.16). MUA was utilized in 336 of 12,735 TKAs (2.6%) from 2000 to 2016. In the decade prior (1990 – 1999), MUA was performed in 89 of 3141 TKAs (2.8%). There was no difference in the incidence of MUA between the contemporary and historical cohorts (p=0.54).

Preoperatively, patients who went on to develop AIS had a small and non-clinically relevant reduction in ROM compared to patients that did not go on to develop AIS (104° ± 17° vs. 108° ± 16°, respectively; p=0.01). Postoperatively, patients diagnosed with AIS demonstrated decreased ROM compared to those without AIS at most recent follow-up (100° ± 20° vs. 116° ± 12°, respectively; p<0.0001).

The KSSs in patients who developed AIS increased from 39 ± 19 preoperatively to 79 ± 18 postoperatively (p<0.0001) and from 40 ± 19 preoperatively to 86 ± 12 postoperatively (p<0.0001) in patients without AIS. The KSSs for patients with AIS were inferior to those without at most recent follow-up (p<0.0001).

There was no difference in the preoperative range of motion among patients with AIS treated with MUA compared to those with AIS not treated with MUA (105° ± 17° vs. 102° ± 17°, p=0.10). For patients treated with MUA, mean pre-MUA ROM was 67° ± 16° which improved a to a mean of 102° ± 19° at most recent follow-up. Range of motion for patients treated with MUA was inferior to that of controls at final follow-up (102° ± 19° vs. 116° ± 12°, respectively; p<0.0001). MUA was performed at a mean of 6 weeks (range, 1 – 32 weeks) postoperatively. A second MUA was utilized in 16 patients at a mean of 5 weeks following the first intervention (range, 1 – 15 weeks). Mean ROM prior to the second MUA was 68° ± 21° and ROM at most recent follow-up was 105° ± 11° in this subset of patients. Likewise, ROM among patients treated with a second MUA was inferior to that of controls at final follow-up (105° ± 11° vs. 116° ± 12°, respectively; p<0.0001). Overall, MUA was successful in restoring the arc of motion to ≥ 90° in 295 of 336 patients (88%). For the entire MUA cohort, KSSs improved from a mean of 41 ± 20 preoperatively to a mean of 79 ± 19 postoperatively (p <0.0001). Similar to those with AIS, the KSSs for patients who were treated with an MUA were inferior to those not treated with an MUA (79 ± 19 vs. 85 ± 12, respectively; p<0.0001). There were no complications such as periprosthetic fractures or extensor mechanism disruptions associated with any MUAs.

Of the 336 patients who underwent an MUA, four patients later were treated with a revision TKA for AIS at a mean of 2 years after the primary TKA (range, 0.5 – 5 years). There were two modular revisions combined with a lysis of adhesions (LOA), whereas the other two patients had non-modular revisions and a LOA, including one femoral component revision, and one both component revision. At final follow-up, the mean ROM in these four patients treated with a revision TKA was 80° (range, 60° – 90°).

Univariate Analysis

Demographics, intraoperative factors, and comorbidities were compared among patients with and without AIS by univariate cox hazard analysis. The risk of AIS development was associated with a number of factors (Table 2). Patient factors associated with an increased risk of AIS included younger age at time of primary TKA (HR 2.5; 95% confidence interval (CI) 2.0 – 3.0; p<0.001), smoking (HR 1.7; 95% CI 1.2 – 2.4; p=0.004), and a history of prior knee surgery (HR 1.6; 95% CI 1.4 – 2.0; p<0.001). Additionally, risk of AIS development was associated with intraoperative variables including longer tourniquet times (p<0.001) and longer operative time (p<0.001). Of the operative factors evaluated, administration of general anesthesia was associated with greatest risk for AIS (HR 1.5; 95% CI 1.2 – 1.8; p<0.001). Patients with increased medical complexity, as evident by CCI score, were associated with reduced risk of AIS development (p<0.001) (Table 2).

Univariate analysis demonstrated that the risk of MUA was associated with many of the same risk factors as AIS including smoking at the time of primary TKA (p=0.04), longer tourniquet time (p<0.001), longer operative time (p=0.005), and utilization of general anesthesia (p<0.001). The largest unadjusted risk for MUA was younger age (HR 2.8; 95% CI 2.2 – 3.5; p<0.001) (Table 3). Patients with increasing CCI were associated with reduced risk of MUA (p<0.0001) (Table 3).

Multivariate Analysis

Multivariate analysis was performed to account for confounding biases (Table 2). Following these adjustments, current smoking and prior knee surgery were no longer associated with AIS. Younger age (p<0.001), post-traumatic arthritis (p=0.04), general anesthesia (p=0.007), and diabetes (HR 1.5; 95% CI 1.2 – 2.0; p=0.001) were found to be independent risk factors for AIS in the multivariate model. Reduced risk of AIS was associated with lower BMI (HR 0.80; 95% CI 0.64 – 0.99; p=0.04) and diagnosis of hypertension (HR 0.76; 95% CI 0.62 – 0.97; p=0.03) (Figure 1).

Multivariate analysis also was performed to account for confounding biases regarding risk of MUA (Table 3). Following adjustments, need for MUA was associated with increased tourniquet time (p<0.001), younger age (p<0.001), and a diagnosis of diabetes (HR 1.5; 95% CI 1.1 – 2.0; p=0.01). Reduced risk was associated with lower BMI (HR 0.74; 95% CI 0.57 – 0.95; p=0.02), hypertension (HR 0.74; 95% CI: 0.57 – 0.97; p=0.03), and moderate to severe renal disease (HR 0.6; 95% CI 0.35 – 0.97; p=0.03) (Figure 2).

DISCUSSION

AIS is a disabling and common complication following primary TKA.[8] Despite advances in contemporary TKAs, the pathogenesis, risk factors, and true incidence of AIS are not fully understood. In a high volume, academic practice, we found the incidence of AIS and subsequent need for MUA following primary TKA has remained relatively unchanged over the past 25 years with incidences in contemporary practice of 3.6% and 2.8%, respectively.

Our group has previously used the term AIS and defined it as an arc of motion ≤ 90° that persists beyond 12 weeks post-operatively as measured by goniometer at clinical follow-up

in patients without prior limitations in knee range of motion.[4] Using this definition, we report the incidence of AIS to be 3.6% of primary TKAs in our contemporary cohort and 4.1% in our historical cohort. Historically, “postoperative stiffness” has been defined by a variety of measures including the maximum flexion, arc of motion, as well as the degree of flexion contracture observed.[12, 18, 19] These differences have led to discrepancies in the reported incidence of AIS with values ranging from < 1% to 38%.[4, 12] Notably, a recent meta-analysis demonstrated the aggregate incidence of AIS to be approximately 4% which is comparable to our institution’s incidence over the previous three decades.[4]

The incidence of MUA has been reported to range from 0.5% – 10% in both historical and contemporary primary TKA cohorts.[6, 11, 20–22] To date, to our knowledge, no study has evaluated the incidence of MUA over time at a single institution. At our institution from 1990 – 2016, MUA was offered to patients with AIS who failed to improve with conservative management following primary TKAs. Utilizing this indication, the incidence of MUA was 2.6% in our contemporary cohort and 2.8% in the historical cohort.

Similar to previous reports, the current study demonstrated significant improvement in ROM after MUA.[23] While MUA was effective in restoring ROM to > 90° in the majority of patients, mean ROM in patients requiring MUA remained inferior to others at long-term follow-up.[24–26] Additionally, although patients who were treated with MUA demonstrated significant improvements in KSSs, these scores were inferior to patients not treated with an MUA.[27]

The pathogenesis of AIS and subsequent need for MUA is multifactorial and incompletely understood. Regarding host-specific variables, our study identified younger age, BMI < 30 mg/kg^2, smoking, diabetes, and lower CCI as significant risk factors for AIS and MUA. These risk factors are consistent with previous individual reports, but the first time these were comprehensively identified from a single data source.[11, 26, 28]

Interestingly, reduced risk of AIS as well as MUA was associated with both increasing number of comorbidities as well as individual diagnoses such as hypertension, history of myocardial infarction, peripheral vascular disease, congestive heart failure, renal disease and rheumatologic disease (Table 2). This observation may be related to the anti-myofibroblastogenesis impacts of medications these patients take for their co-morbidities combined with the fact that some of these patients are low demand and simply cannot tolerate an incremental reoperation and/or revision.[29, 30] Translational work has attempted to elucidate the role of pharmacologic agents utilized to treat the comorbidities and their effect on excessive fibrotic tissue development.[30–35] However, to date the usage of these medications in the clinical space have been limited.[36, 37] Furthermore, investigation into the medical and perioperative management of these patients may identify factors modulating the pathogenesis of disease. Likewise, stratification of patients based on comorbidity status may provide insights into patients’ predisposition to AIS.

In addition to host-specific variables, our study identified surgical factors that increased the risk of AIS and MUA including utilization of general anesthesia and increased tourniquet time. Many investigations have shown the benefits of neuraxial anesthesia in regards to

perioperative pain control and achievement of postoperative milestones (e.g. time to mobilization and hospital discharge).[38, 39] Similarly, tourniquet utilization has been reported in some but not all previous studies to result in increased postoperative pain, early reductions in postoperative knee ROM, and quadriceps strength after TKA.[40–42] It is also possible that these findings are associations and not related to causation; use of general anesthesia and longer tourniquet times may have been proxies for case complexity.

There are limitations to the current study. Foremost, radiographs were not reviewed. Instead, a contemporary cohort of patients with similar prostheses was analyzed to determine the incidence of AIS and MUA at our institution. Moreover, there were patients with flexion less than 90° who refused or were not recommended to have MUA, which altered the incidence and results of the intervention. Finally, multiple surgeons participated in the study. Although this introduced variability in terms of surgical technique and implant utilization, it increases the generalizability and allowed nearly 10,000 patients to be analyzed.

In conclusion, the incidence of AIS (3.6%) and MUA (2.6%) following primary TKA at our institution has remained stable over the past 25 years. Although MUA resulted in improved motion in a majority of patients by a mean of 34°, motion and clinical outcomes at final follow-up were inferior to those unaffected by AIS. Continued investigation into the multiple intrinsic (i.e. genetic) and extrinsic (i.e. surgical technique and implant design) factors that contribute to AIS may reduce the incidence of this problematic complication and promote preventative strategies of care.

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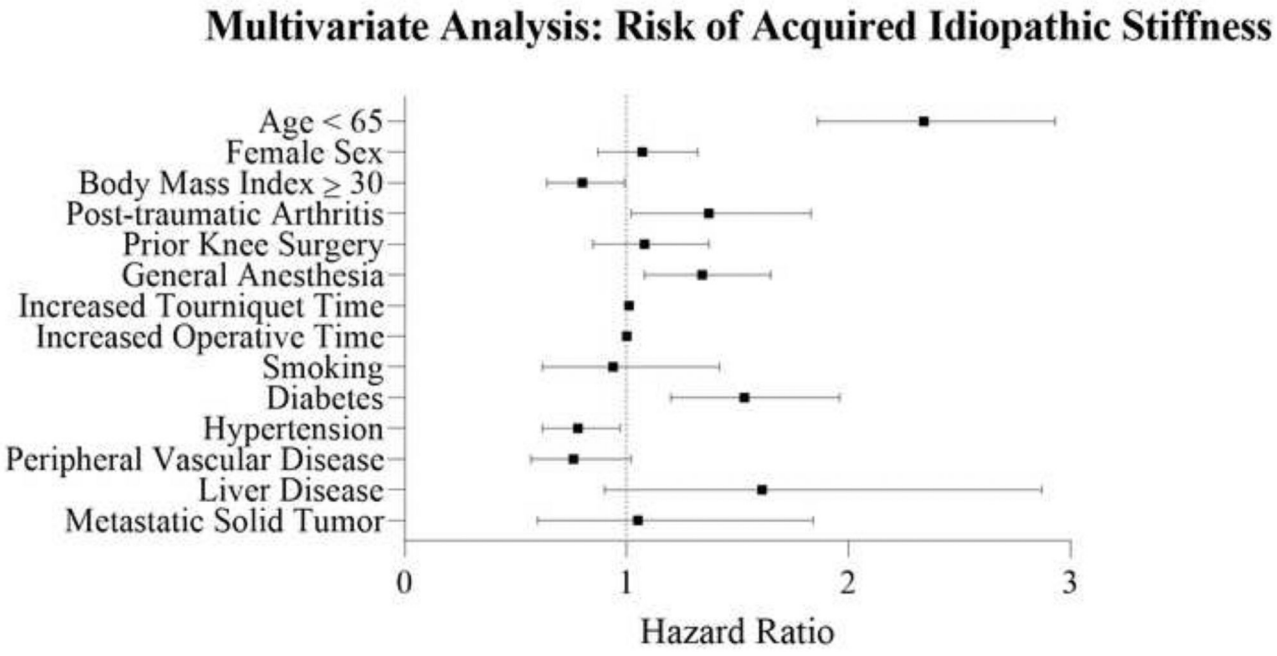

Figure 1.

Forest plot demonstrating the hazard ratios and confidence intervals of patient demographics, surgical characteristics, and comorbidities associated with risk of acquired idiopathic stiffness as determined by multivariate analysis.

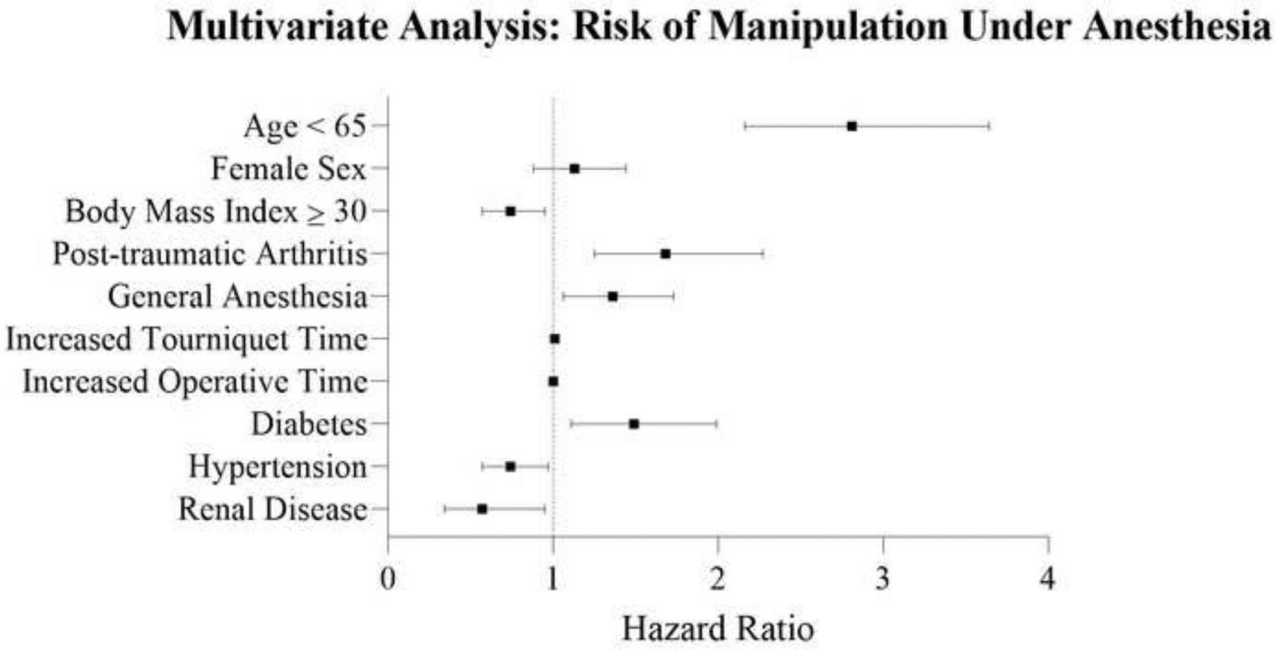

Figure 2.

Forest plot demonstrating the hazard ratios and confidence intervals of patient demographics, surgical characteristics, and comorbidities associated with manipulation under anesthesia as determined by multivariate analysis.

Table 1.

Study cohort demographics

Variables	AIS (n=456)	No AIS (n=12,279)
Age at TKA (years), mean (SD)	62 (11)	68 (10)
BMI (kg/m^2), mean (SD)	32 (6)	33 (7)
Female, No. (%)	261 (57)	7035 (58)
Indication for TKA, No. (%)		
Osteoarthritis	362 (7981.5)	10851 (88.4)
Post-traumatic arthritis	83 (18)	1185 (9.6)
Rheumatoid arthritis	3 (1)	180 (1.5)
Other	8 (2)	67 (0.5)
Manipulation under anesthesia, No. (%)	336 (74)	0 (0)
Death within 2 years, No. (%)	5 (1)	231 (2)
Lost to follow-up before 2 years, No. (%)	14 (3)	298 (2)
Follow-up (years), mean	7	7

*AIS = acquired idiopathic stiffness; SD = standard deviation; BMI = body mass index; TKA = total knee arthroplasty

Table 2.

Univariate and multivariate analysis of variables associated with acquired idiopathic stiffness

Variable	Unadjusted HR	95% CI	p-value	Adjusted HR	95% CI	p-value
Patient Characteristics						
Sex						
Female	1.00	0.83 – 1.21	0.99	1.07	0.87 – 1.32	0.53
Male (reference)						
Age						
< 65 years	2.46	2.04 – 2.96	<0.001	2.34	1.86 – 2.93	<0.001
≥ 65 years (reference)						
Body mass index						
≥ 30 kg/m^2	0.93	0.77 – 1.12	0.43	0.80	0.64 – 0.99	0.04
< 30 kg/m^2 (reference)						
Indication for TKA						
Post-traumatic arthritis	2.09	1.65 – 2.66	<0.001	1.37	1.02 – 1.83	0.04
Osteoarthritis (reference)						
Smoking status						
Current	1.67	1.18 – 2.36	0.004	0.94	0.62 – 1.42	0.76
Never (reference)						
Prior knee surgery						
Yes	1.64	1.35 – 1.99	<0.001	1.08	0.85 – 1.37	0.53
No (reference)						
Surgical Characteristics						
Unilateral or Bilateral TKAs						
Simultaneous bilateral	0.66	0.46 – 0.96	0.03	0.78	0.70 – 0.88	<0.001
Staged bilateral	0.45	0.33 – 0.61	<0.001	–	–	–
Unilateral (reference)						
Anesthesia						
General	1.47	1.22 – 1.77	<0.001	1.34	1.08 – 1.65	0.007
Neuraxial (reference)						
Tourniquet time, min	1.01	1.01 – 1.01	<0.001	1.01	1.00 – 1.01	<0.001

Variable	Unadjusted HR	95% CI	p-value	Adjusted HR	95% CI	p-value
Operative time, min	1.00	1.00 – 1.00	<0.001	1.00	1.00 – 1.00	0.76
Comorbidities[^]						
Diabetes	1.17	0.94 – 1.45	0.17	1.53	1.20 – 1.96	0.001
Hypertension	0.57	0.47 – 0.69	<0.001	0.78	0.62 – 0.97	0.03
Peripheral vascular disease	0.60	0.46 – 0.77	<0.001	0.76	0.57 – 1.02	0.07
Liver disease[†]	1.29	0.73 – 2.29	0.38	1.61	0.90 – 2.87	0.11
Metastatic solid tumor	0.77	0.45 – 1.31	0.33	1.05	0.60 – 1.84	0.86
Congestive heart failure	0.61	0.42 – 0.88	0.01	–	–	–
Renal disease[†]	0.64	0.45 – 0.91	0.01	–	–	–
Rheumatologic disease	0.82	0.59 – 1.14	0.24	–	–	–
Myocardial infarct	0.75	0.51 – 1.09	0.13	–	–	–
Other cancer	0.84	0.66 – 1.07	0.15	–	–	–
Cerebrovascular disease	0.79	0.58 – 1.06	0.12	–	–	–
Dementia	0.66	0.34 – 1.28	0.22	–	–	–
Chronic pulmonary disease	0.99	0.80 – 1.22	0.90	–	–	–
Mild liver disease	1.14	0.85 – 1.51	0.39	–	–	–
Diabetes with organ damage	0.93	0.63 – 1.36	0.70	–	–	–
Hemiplegia	0.79	0.37 – 1.65	0.52	–	–	–
Ulcer	0.82	0.57 – 1.17	0.27	–	–	–
CCI	0.45	0.37 – 0.54	<0.001	–	–	–

[*] HR = Hazard Ratio; CI = Confidence Interval; TKA = Total Knee Arthroplasty; CCI = Charlson Comorbidity Index

[^] Absence of disease served as reference for comorbidity data

[†] Moderate or severe disease

Table 3.

Univariate and multivariate analysis of patient variables associated with need for manipulation under anesthesia

Variable	Unadjusted HR	95% CI	p-value	Adjusted HR	95% CI	p-value
Patient Characteristics						
Sex						
Female	1.06	0.85 – 1.31	0.63	1.13	0.88 – 1.44	0.34
Male (reference)						
Age						
< 65 years	2.79	2.24 – 3.47	<0.001	2.81	2.16 – 3.64	<0.001
≥ 65 years (reference)						
Body mass index						
≥ 30 kg/m2	0.88	0.71 – 1.09	0.23	0.74	0.57 – 0.95	0.02
< 30 kg/m^2 (reference)						
Indication for TKA						
Post-traumatic arthritis	2.69	2.08 – 3.48	<0.001	1.68	1.25 – 2.27	<0.001
Osteoarthritis (reference)						
Smoking status						
Current	1.54	1.01 – 2.34	0.04	–	–	–
Never (reference)						
Prior knee surgery						
Yes	1.79	1.44 – 2.24	<0.001	–	–	–
No (reference)						
Surgical Characteristics						
Unilateral or Bilateral TKAs						
Simultaneous bilateral	0.66	0.46 – 0.96	0.03	0.78	0.70 – 0.88	<0.001
Staged bilateral	0.45	0.33 – 0.61	<0.001	–	–	–
Unilateral (reference)						
Anesthesia						
General	1.49	1.20 – 1.85	<0.001	1.36	1.06 – 1.73	0.02
Neuraxial (reference)						
Tourniquet time, min	1.01	1.01 – 1.01	<0.001	1.01	1.00 – 1.01	<0.001

Variable	Unadjusted HR	95% CI	p-value	Adjusted HR	95% CI	p-value
Operative time, min	1.00	1.00 – 1.00	0.005	1.00	1.00 – 1.00	0.55
Comorbidities[^]						
Diabetes	1.10	0.88 – 1.42	0.49	1.49	1.11 – 1.99	0.01
Hypertension	0.51	0.41 – 0.63	<0.001	0.74	0.57 – 0.97	0.03
Renal disease[†]	0.43	0.26 – 0.69	0.001	0.57	0.34 – 0.95	0.03
Peripheral vascular disease	0.60	0.44 – 0.81	0.001	–	–	–
Liver disease[†]	1.46	0.78 – 2.73	0.24	–	–	–
Metastatic solid tumor	0.90	0.50 – 1.59	0.71	–	–	–
Congestive heart failure	0.49	0.30 – 0.78	0.003	–	–	–
Rheumatologic disease	0.75	0.50 – 1.12	0.16	–	–	–
Myocardial infarct	0.67	0.43 – 1.06	0.09	–	–	–
Other cancer	0.80	0.60 – 1.06	0.12	–	–	–
Cerebrovascular disease	0.72	0.50 – 1.04	0.08	–	–	–
Dementia	0.58	0.26 – 1.30	0.19	–	–	–
Chronic pulmonary disease	0.91	0.71 – 1.16	0.44	–	–	–
Mild liver disease	1.13	0.81 – 1.57	0.49	–	–	–
Diabetes with organ damage	0.90	0.57 – 1.41	0.63	–	–	–
Ulcer	0.83	0.55 – 1.26	0.38	–	–	–
CCI	0.40	0.32 – 0.49	<0.001	–	–	–

[*] HR = Hazard Ratio; CI = Confidence Interval; TKA = Total Knee Arthroplasty; CCI = Charlson Comorbidity Index

[^] Absence of disease served as reference for comorbidity data

[†] Moderate or severe disease