



■ ARTHROPLASTY

The association of preoperative blood markers with postoperative readmissions following arthroplasty

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Aims

While preoperative bloodwork is routinely ordered, its value in determining which patients are at risk of postoperative readmission following total knee arthroplasty (TKA) and total hip arthroplasty (THA) is unclear. The objective of this study was to determine which routinely ordered preoperative blood markers have the strongest association with acute hospital readmission for patients undergoing elective TKA and THA.

Methods

Two population-based retrospective cohorts were assembled for all adult primary elective TKA (n = 137,969) and THA (n = 78,532) patients between 2011 to 2018 across 678 North American hospitals using the American College of Surgeons National Quality Improvement Programme (ACS-NSQIP) registry. Six routinely ordered preoperative blood markers - albumin, haematocrit, platelet count, white blood cell count (WBC), estimated glomerular filtration rate (eGFR), and sodium level - were queried. The association between preoperative blood marker values and all-cause readmission within 30 days of surgery was compared using univariable analysis and multivariable logistic regression adjusted for relevant patient and treatment factors.

Results

The mean TKA age was 66.6 years (SD 9.6) with 62% being females (n = 85,163/137,969), while in the THA cohort the mean age was 64.7 years (SD 11.4) with 54% being female (n = 42,637/78,532). In both cohorts, preoperative hypoalbuminemia (< 35 g/l) was associated with a 1.5- and 1.8-times increased odds of 30-day readmission following TKA and THA, respectively. In TKA patients, decreased eGFR demonstrated the strongest association with acute readmission with a standardized odds ratio of 0.75 per two standard deviations increase (p < 0.0001).

Conclusion

In this population level cohort analysis of arthroplasty patients, low albumin demonstrated the strongest association with acute readmission in comparison to five other commonly ordered preoperative blood markers. Identification and optimization of preoperative hypoalbuminemia could help healthcare providers recognize and address at-risk patients undergoing TKA and THA. This is the most comprehensive and rigorous examination of the association between preoperative blood markers and readmission for TKA and THA patients to date.

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Introduction

More than 650,000 total knee arthroplasties (TKAs) and 450,000 total hip arthroplasties (THAs) are performed in the USA annually, with these numbers expected to increase to 3.5 million annually by 2030.¹⁻³ Between 2.4% to 4.6% of arthroplasty patients are

readmitted to hospital within the first 30 days as a result of an acute complication, leading to increased patient morbidity as well as additional personal and hospital costs.⁴⁻⁶ This becomes increasingly prudent as more hospitals move towards episode of care bundled funding models for arthroplasty, whereby

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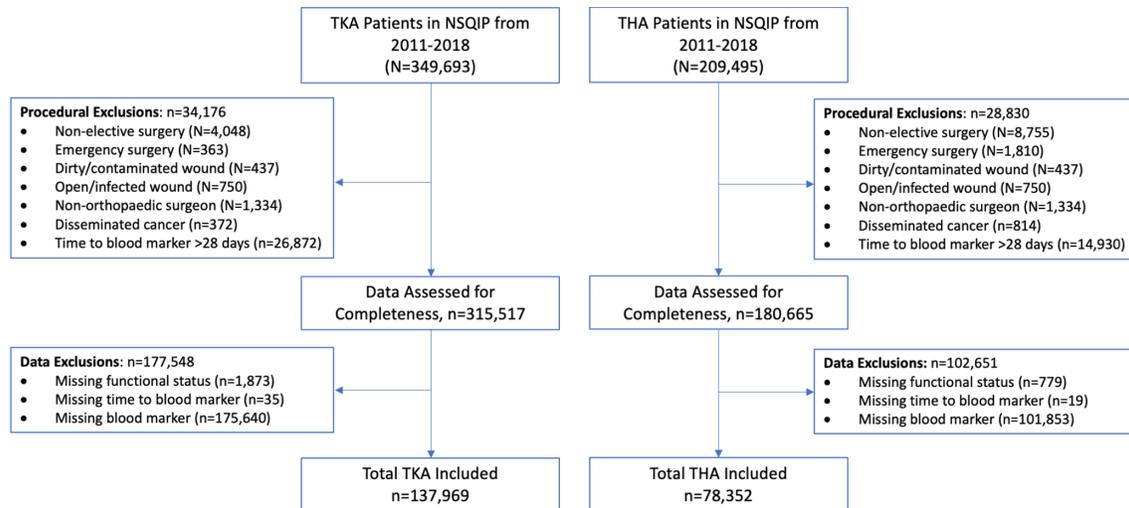


Fig. 1

Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)³⁰ diagram of cohort assembly for total knee arthroplasty (TKA) and total hip arthroplasty (THA) patients. NSQIP, National Quality Improvement Programme.

hospitals and providers are responsible for acute readmission care costs.^{7,8}

Previous studies have identified various factors that are associated with a higher risk of postoperative morbidity following arthroplasty, including advanced age,⁹⁻¹¹ male sex,^{12,13} previous myocardial infarction (MI), liver or renal disease,^{14,15} and a higher American Society of Anesthesiologists (ASA) classification.^{16,17} However, some of these patient factors are non-modifiable, limiting the opportunity for preoperative interventions to lower postoperative risks. Schroer et al⁷ examined a series of modifiable risk factors in arthroplasty patients and determined that anaemia, malnutrition, obesity, diabetic control, narcotic use, and tobacco use were all associated with adverse outcomes and increased healthcare expenditure.

Patients undergoing elective TKA or THA routinely have preoperative bloodwork drawn, though the value of these tests in the arthroplasty population has been called into question.¹⁸ The purpose of this study was to determine which commonly ordered preoperative blood markers, as prospectively collected by the American College of Surgeons National Surgical Quality Improvement Programme (ACS-NSQIP) registry, are most associated with acute hospital re-admissions following primary elective unilateral TKA and THA for osteoarthritis (OA).

Methods

Study design and data source. A population-based, retrospective cohort study of patients undergoing primary TKA or THA in North America was conducted using the ACS-NSQIP registry. ACS-NSQIP is a prospective collected and audited registry with over 678 hospitals in North America, whereby patients undergoing common surgical procedures are identified and followed for 30 days postoperatively.^{19,20} Audited coders review inpatient and

outpatient records to track the occurrence of complications. The accuracy and reproducibility of ACS-NSQIP coding has been previously reported on in several surgical sub-specialties including orthopaedics.²¹⁻²⁹

Study patients and cohort assembly. Two retrospective cohorts composed of all adult patients (aged > 18 years) who underwent a primary elective unilateral TKA or THA for OA at an ACS-NSQIP affiliated hospital in North America between 2011 and 2018 inclusive were created using appropriate Current Procedural Terminology (CPT) codes (Supplementary Material). We excluded all cases that were bilateral, nonelective, indicated for infectious, traumatic, pathological, or oncological diagnosis, patients with systemic sepsis or disseminated cancer, revision procedures, cases performed by nonorthopaedic primary surgeons, and those who were missing one or more of the six preoperative blood markers routinely collected (albumin, haematocrit, platelets, WBC, eGFR, and sodium) (Figure 1).³⁰

Following the application of inclusion and exclusion criteria, the THA and TKA cohorts were further split into 2011 to 2016 arthroplasty patients and 2017 to 2018 arthroplasty patients inclusive. The 2011 to 2016 cohorts were used as the development cohorts, while the 2017 to 2018 cohorts were used as validation cohorts for the purpose of a temporal external validation of association findings.

Preoperative blood markers. The ACS-NSQIP database records ten commonly ordered preoperative blood markers, of which six were selected a priori given their use in practice and potential association with arthroplasty outcomes and included in our analysis as covariates of interest: albumin,⁷ haematocrit,³¹ platelets,³² sodium,³³ and white blood cells (WBCs).³⁴ Estimated globular filtration rate was derived using creatinine, age, sex, and race.³⁵

Table I. Summary of patients.

Variable	TKA cohort (2011 to 2018) n = 137,969	THA cohort (2011 to 2018) n = 78,532
Mean age, yrs (SD)	66.6 (9.6)	64.7 (11.4)
Female sex, n (%)	85,163 (61.7)	42,637 (54.3)
Race, n (%)		
White	109,179 (79.1)	64,370 (82.0)
Black	10,939 (7.9)	6,478 (8.3)
Other	17,851 (12.9)	7,684 (9.7)
Independent functional status	136,484 (98.9)	77,241 (98.4)
Mean BMI, kg/m ² (SD)	33.2 (6.8)	30.4 (6.3)
Smoker, n (%)	11,766 (8.5)	10,392 (13.2)
CHF, n (%)	442 (0.3)	259 (0.3)
COPD, n (%)	5143 (3.7)	3,181 (4.1)
Diabetes, n (%)	25,660 (18.6)	9,673 (12.3)
Dialysis, n (%)	262 (0.2)	157 (0.2)
Hypertension, n (%)	91,673 (66.4)	44,953 (57.2)
Steroid use, n (%)	5,487 (4.0)	3,152 (4.0)
Bleeding disorder, n (%)	3,111 (2.3)	1,620 (2.1)
Dyspnea, n (%)	8,387 (6.1)	3,730 (4.8)
ASA grade, n (%)		
I/II	67,731 (49.1)	44,494 (56.7)
III/IV	70,238 (50.9)	34,038 (43.3)
Anaesthesia type, n (%)		
General	70,317 (51.0)	43,515 (55.4)
Neuraxial	67,652 (49.0)	35,017 (44.6)
Mean operation length, mins (SD)	92.4 (33.6)	92.5 (38.4)
Mean length of stay, days (SD)	2.6 (2.4)	2.2 (1.4)
Discharge destination, n (%)		
Home	106,562 (77.2)	63,529 (80.9)
Other	31,407 (22.8)	15,003 (19.1)

ASA, American Society of Anesthesiologists; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; SD, standard deviation; THA, total hip arthroplasty; TKA, total knee arthroplasty.

For this purpose, we assumed all elective patients undergoing arthroplasty were in a steady state at the time of preoperative blood collection. All blood markers were required to have been collected within 30 days prior to surgery. Normal ranges for these blood markers are defined in Supplementary Material 2.

Covariates. Covariates for inclusion in our multivariable analysis were identified a priori based on known confounders, variables known to influence outcomes in arthroplasty patients, and those deemed clinically relevant. Patient factors included age,⁹⁻¹¹ sex,^{12,13} race,³⁶ BMI,³⁷ baseline functional status (as per ACS-NSQIP definitions: independent, partially dependent, or totally dependent),⁴ comorbidities (congestive heart failure (CHF),

Table II. Preoperative laboratory results.

Preoperative blood marker	TKA cohort (2011 to 2018) n = 137,969	THA cohort (2011 to 2018) n = 78,532
Albumin		
Mean albumin g/l (SD)	41.1 (0.37)	41.5 (0.39)
Low (0 to 34 g/l), n (%)	5,253 (3.8)	2,658 (3.4)
Normal (35+ g/l), n (%)	132,716 (96.2)	75,874 (96.6)
HCT		
Mean HCT L/L (SD)	41.0 (4.1)	41.2 (4.2)
Low (Male < 45 L/L, Female < 37 L/L), n (%)	43,239 (31.3)	28,020 (35.7)
Normal, n (%)	94,730 (68.7)	50,512 (64.3)
Platelets		
Mean platelets 10 ⁹ /l (SD)	245.0 (66.6)	248.5 (67.7)
Low (0 to 139 × 10 ⁹ /l), n (%)	4,248 (3.1)	2,142 (2.7)
Normal (140+ × 10 ⁹ /l), n (%)	133,721 (96.9)	76,390 (97.3)
WBC		
Mean WBC 10 ⁹ /l (SD)	7.0 (2.1)	7.0 (2.3)
Low/Normal (0 to 11 × 10 ⁹ /l), n (%)	133,222 (96.6)	75,592 (96.3)
High (12+ × 10 ⁹ /l), n (%)	4,747 (3.4)	2,940 (3.7)
eGFR		
Mean eGFR, ml/min/1.73 m ² (SD)	82.2 (24.4)	84.7 (25.4)
Severe (< 30 ml/min/1.73 m ²), n (%)	1,022 (0.7)	574 (0.7)
Mild/Moderate (30 to 89 ml/min/1.73 m ²), n (%)	102,066 (66.7)	49,073 (62.5)
Normal (≥ 90 ml/min/1.73 m ²), n (%)	44,881 (32.5)	28,885 (36.8)
Sodium		
Mean sodium, mmol/l (SD)	139.8 (2.8)	139.7 (2.8)
Low (< 135 mmol/l), n (%)	4,808 (3.5)	3,173 (4.0)
Normal (135 to 147 mmol/l), n (%)	132,889 (96.3)	75,222 (95.8)
High (≥ 148 mmol/l), n (%)	272 (0.2)	137 (0.2)

eGFR, estimate glomerular filtration rate; HCT, hematocrit; preop, preoperative; SD, standard deviation; THA, total hip arthroplasty; TKA, total knee arthroplasty; WBC, white blood cell count.

chronic obstructive pulmonary disorder (COPD), diabetes, bleeding disorder, chronic renal failure requiring dialysis, hypertension requiring medication, current steroid use for chronic condition(s), and active smoking within one year of index surgery),^{14,15,19} and American Society of Anesthesiologists (ASA) class.^{16,17} Perioperative and treatment factors included: anaesthesia type,³⁸ operation length, hospital length of stay,³⁶ and discharge destination.³⁶ Missing values for age and BMI were imputed via multiple imputation.³⁹

Outcome. Our primary outcome was acute hospital readmission, defined as within 30 days of index arthroplasty surgery. The ACS-NSQIP database captures any cause readmission within 30 days of surgery at any hospital, neither limited to the institution at which surgery was performed nor ACS-NSQIP participating hospitals.

Table III. Univariable association of continuous blood marker results with acute readmission in development and validation.

TKA Variable	Development (2011 to 2016)		Validation (2017 to 2018)		THA Development (2011 to 2016)		Validation (2017 to 2018)	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Patients, n	82,810		55,159		46,889		31,643	
Readmissions, n (%)	2,635 (3.2)		1,748 (3.2)		1,623 (3.5)		1,102 (3.5)	
Albumin	0.69 (0.64 to 0.74)	< 0.0001	0.64 (0.59 to 0.70)	< 0.0001	0.64 (0.58 to 0.70)	< 0.0001	0.55 (0.49 to 0.61)	< 0.001
HCT	0.79 (0.73 to 0.85)	< 0.0001	0.70 (0.64 to 0.77)	< 0.0001	0.75 (0.69 to 0.83)	< 0.0001	0.56 (0.50 to 0.62)	< 0.0001
Platelets	0.84 (0.77 to 0.91)	< 0.0001	0.81 (0.73 to 0.89)	< 0.0001	0.98 (0.89 to 1.08)	0.6835	0.98 (0.87 to 1.10)	0.6927
WBC	1.20 (1.13 to 1.28)	< 0.0001	1.22 (1.12 to 1.32)	< 0.0001	1.19 (1.11 to 1.29)	< 0.0001	1.33 (1.21 to 1.46)	< 0.0001
eGFR	0.62 (0.56 to 0.67)	< 0.0001	0.60 (0.54 to 0.66)	< 0.0001	0.81 (0.72 to 0.90)	< 0.0001	0.65 (0.57 to 0.74)	< 0.0001
Sodium	0.86 (0.80 to 0.93)	< 0.0001	0.83 (0.76 to 0.91)	< 0.0001	0.91 (0.82 to 1.00)	0.0502	0.84 (0.75 to 0.94)	0.0032

Odds ratios are standardized to demonstrate odds adjustment per two standard deviation incremental increase in each variable, allowing for magnitude comparison between variables. Odds ratios are unadjusted. Variables are considered statistically significant if $p < 0.0005$ is maintained across both development and validation cohorts. CI, confidence interval; eGFR, estimated glomerular filtration rate; HCT, haematocrit; OR, odds ratio; THA, total hip arthroplasty; TKA, total knee arthroplasty; WBC, white blood cell count.

Statistical analysis. Descriptive statistics were calculated for each blood marker and covariate as appropriate. Unadjusted associations between variables and readmission were assessed using univariable logistic regression and Pearson's chi-squared tests as appropriate. Multivariable logistic regression modelling was performed on the development cohorts to evaluate the independent association of each blood marker with acute readmission while controlling for the aforementioned a priori selected covariates. We used univariable models to determine the unadjusted association of blood markers with readmission, and multivariable models adjusted for relevant covariates were used to determine the independent association of the blood markers with readmission. We estimated odds ratios (ORs) and 95% confidence intervals (CIs) for included covariates, expressed per two standard deviations change for continuous blood marker data.⁴⁰ This was done to allow for comparison of the magnitude of effect across included continuous and binary variables on the odds of readmission independent of their respective scales.⁴⁰ Secondly, blood markers were categorized based on clinical cut-offs (Supplementary Material 2) and our multivariable models were again applied to produce ORs and 95% CIs for the influence of abnormally high or low blood marker values on acute readmission.

Statistical significance was set conservatively at a two-sided $p < 0.0005$ using Bonferroni correction to account for multiplicity of testing of the six covariates of interest in development and validation cohorts as either continuous or categorical variables, corresponding to 96 statistical tests. All statistical work was calculated using SAS Software, version 9.4 (SAS Institute, USA).

Validation. Results from statistical analyses within the development cohorts were compared to results following the same analyses in the 2017 to 2018 validation cohorts. This was done to examine the results using a temporal-based validation in an effort to lessen the likelihood of type 1 error. Variables that maintained statistical

significance through both cohorts were considered to influence acute readmission.

Results

We identified a total of 137,969 TKA patients (mean age 66.6 years (SD 9.6); 62% female, BMI 33.2 kg/m² (SD 6.8)) and 78,532 THA patients (mean age 64.7 years (SD 11.4), 54% female, BMI 30.4 kg/m² (SD 6.3)) that underwent an elective unilateral arthroplasty from 2011 to 2018 with complete blood marker profiles (Figure 1). A comparison of included patients to those who were excluded for not having a full set of blood markers is presented in Supplementary Material 3. On average, patients who were missing one or more blood marker values were slightly younger and healthier preoperatively, with a lower prevalence of comorbidities in comparison to those included in our analysis.

Overall, the vast majority of included patients in both cohorts were functionally independent at baseline and the most common comorbidities were hypertension requiring medication, diabetes, and smoking, which is in keeping with previous studies (Table I).^{14,41}

With regards to baseline blood markers, 111,130 TKA patients (80.6%) and 62,701 THA patients (79.8%) had at least one blood marker abnormality; the most common abnormalities in both cohorts were low eGFR, anemia, hypoalbuminemia, and hyponatremia (Table II). The acute readmission rate was 3.2% ($n = 4,383$) for all TKA patients and 3.5% ($n = 2,725$) for all THA patients.

Univariable analysis – total knee arthroplasty. Our univariable analysis demonstrated that all six preoperative blood markers were significantly associated with acute readmission following TKA in both the development and validation cohorts when analyzed as continuous variables ($p < 0.0001$) (Table III). When standardized per two standard deviations increase, albumin (OR 0.69, 95% CI 0.64 to 0.74) and eGFR (OR 0.62, 95% CI 0.56 to 0.67) demonstrated the strongest associations with acute readmission. The association between blood

Table IV. Univariable association of blood marker results categorized by clinically relevant cutoffs and acute readmission.

Preoperative blood marker	TKA				THA			
	Development (2011 to 2016)		Validation (2017 to 2018)		Development (2011 to 2016)		Validation (2017 to 2018)	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Albumin, g/l								
Low (0 to 34)	1.88 (1.60 to 2.20)	< 0.0001	2.43 (2.05 to 2.89)	< 0.0001	2.01 (1.63 to 2.48)	< 0.0001	2.59 (2.26 to 2.96)	< 0.0001
Normal (35+)	Ref.		Ref.		Ref.		Ref.	
Haematocrit, l/l								
Low (M: < 45, F: < 37)	1.48 (1.37 to 1.61)	< 0.0001	1.57 (1.42 to 1.73)	< 0.0001	1.18 (1.07 to 1.31)	0.0011	1.45 (1.28 to 1.60)	< 0.0001
Normal	Ref.		Ref.		Ref.		Ref.	
Platelets, 10⁹/l								
Low (0 to 139)	1.59 (1.33 to 1.91)	< 0.0001	1.83 (1.47 to 2.28)	< 0.0001	1.73 (1.35 to 2.20)	< 0.0001	1.65 (1.23 to 2.22)	0.0007
Normal (140+)	Ref.		Ref.		Ref.		Ref.	
WBC, 10⁹/l								
Low/Normal (0 to 11)	Ref.		Ref.		Ref.		Ref.	
High (12+)	1.37 (1.14 to 1.65)	< 0.0001	1.45 (1.16 to 1.82)	0.0012	1.67 (1.35 to 2.07)	< 0.0001	1.67 (1.30 to 2.16)	< 0.0001
eGFR, ml/min/1.73m²								
Severe (< 30)	3.32 (2.50 to 4.42)	< 0.0001	3.99 (2.78 to 5.72)	< 0.0001	2.30 (1.50 to 3.51)	< 0.0001	3.99 (2.60 to 6.13)	< 0.0001
Mild/Mod. (30 to 89)	1.25 (1.15 to 1.37)		1.34 (1.21 to 1.50)		1.09 (0.98 to 1.21)		1.34 (0.17 to 1.53)	
Normal (≥ 90)	Ref.		Ref.		Ref.		Ref.	
Sodium, mmol/l								
Low (< 135)	1.56 (1.32 to 1.85)	< 0.0001	1.39 (1.10 to 1.76)	0.0199	1.35 (1.08 to 1.68)	< 0.0001	1.67 (1.26 to 2.15)	0.0004
Normal (135 to 147)	Ref.		Ref.		Ref.		Ref.	
High (≥ 148)	1.14 (0.51 to 2.59)		0.61 (0.15 to 2.48)		3.94 (1.96 to 7.92)		0.93 (0.23 to 3.81)	

Odds ratios (OR) are unadjusted. Variables are considered statistically significant if $p < 0.0005$ is maintained across both development and validation cohorts. CI, confidence interval; eGFR, estimated glomerular filtration rate; Mod, moderate; N/A, not applicable; Ref, reference category; THA, total hip arthroplasty; TKA, total knee arthroplasty; WBC, white blood cell count.

Table V. Multivariable regression of the association between continuous blood marker results and acute readmission.

Variable	TKA				THA			
	Development (2011 to 2016)		Validation (2017 to 2018)		Development (2011 to 2016)		Validation (2017 to 2018)	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Patients, n	82,810		55,159		46,889		31,643	
Readmissions, n (%)	2,635 (3.2)		1,748 (3.2)		1,623 (3.5)		1,102 (3.5)	
Albumin	0.82 (0.76 to 0.88)	< 0.0001	0.80 (0.73 to 0.88)	< 0.0001	0.82 (0.74 to 0.91)	< 0.0001	0.78 (0.69 to 0.89)	< 0.0001
HCT	0.86 (0.80 to 0.94)	0.0005	0.81 (0.73 to 0.89)	< 0.0001	0.89 (0.80 to 0.99)	0.0258	0.70 (0.62 to 0.89)	< 0.0001
Platelets	0.93 (0.85 to 1.01)	0.0688	0.89 (0.89 to 0.98)	0.0242	1.00 (0.90 to 1.10)	0.9404	0.98 (0.86 to 1.11)	0.7156
WBC	1.13 (1.05 to 1.21)	0.0008	1.14 (1.04 to 1.25)	0.0054	1.09 (1.01 to 1.17)	0.0281	1.18 (1.06 to 1.32)	0.0027
eGFR	0.75 (0.69 to 0.83)	< 0.0001	0.78 (0.71 to 0.87)	< 0.0001	1.00 (0.90 to 1.11)	0.9371	0.96 (0.84 to 1.09)	0.4929
Sodium	0.90 (0.83 to 0.97)	0.0057	0.88 (0.80 to 0.96)	0.0063	0.98 (0.88 to 1.08)	0.6214	0.93 (0.83 to 1.05)	0.2568

Odds ratios are standardized to demonstrate odds adjustment per two standard deviation incremental increase in each variable, allowing for magnitude comparison between variables. Odds ratios are adjusted for the patient and treatment factors listed in Table I – adjusted odds ratios for these variables are presented in Supplementary Material 4. Variables are considered statistically significant if $p < 0.0005$ is maintained across both development and validation cohorts. CI, confidence interval; eGFR, estimated glomerular filtration rate; HCT, haematocrit; OR, odds ratio; WBC, white blood cell count.

markers and readmission ($p < 0.0005$) was maintained for all variables except WBC and sodium, when the variables were analyzed using clinically relevant cut-offs to compare normal versus abnormal on a categorical basis (Table IV). This analysis demonstrated that those with severe renal impairment (eGFR < 30) had a 3.32-times increase in their odds of readmission in comparison to normal (95% CI 2.50 to 4.42; $p < 0.0001$). Similarly, patients with hypoalbuminemia had 1.88-times greater odds of readmission in comparison to those with normal albumin values (95% CI 1.60 to 2.20; $p < 0.0001$). **Multivariable analysis – total knee arthroplasty.** Our multivariable analysis to determine the independent

association of preoperative blood markers with odds of acute readmission after adjustment for relevant patient and treatment covariates demonstrated that lower preoperative albumin, haemoglobin, sodium, WBC, and eGFR were all significantly associated with increased rates of readmission in both the development and external validation cohorts (Table V). When analyzed as a continuous variable, per two standard deviations increase in preoperative albumin, the OR for acute readmission was 0.82 (95% CI 0.76 to 0.88; $p < 0.0001$) in TKA patients. Translated clinically, TKA patients with preoperative hypoalbuminemia (< 35 g/l) had a 1.4-times greater odds of readmission in comparison to those with normal

Table VI. Multivariable regression of the association of blood marker results categorized by clinically relevant cutoffs and acute readmission.

Preoperative blood marker	TKA				THA			
	Development (2011 to 2016)		Validation (2017 to 2018)		Development (2011 to 2016)		Validation (2017 to 2018)	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Albumin								
Low (0 to 34)	1.40 (1.19 to 1.65)	< 0.001	1.77 (1.48 to 2.12)	< 0.001	1.39 (1.12 to 1.73)	0.0029	1.53 (1.20 to 1.93)	< 0.001
Normal (35+)	Ref.		Ref.		Ref.		Ref.	
Haematocrit								
Low (M: < 45, F: < 37)	1.17 (1.06 to 1.28)	0.0016	1.25 (1.11 to 1.41)	< 0.001	1.04 (0.92 to 1.18)	0.4910	1.39 (1.20 to 1.62)	< 0.001
Normal	Ref.		Ref.		Ref.		Ref.	
Platelets								
Low (0 to 139)	1.14 (0.94 to 1.37)	0.1787	1.31 (1.04 to 1.64)	0.0227	1.35 (1.05 to 1.74)	0.0199	1.19 (0.87 to 1.62)	0.2780
Normal (140+)	Ref.		Ref.		Ref.		Ref.	
WBC								
Low/Normal (0 to 11)	Ref.		Ref.		Ref.		Ref.	
High (12+)	1.16 (0.96 to 1.40)	0.1313	1.18 (0.93 to 1.48)	0.1676	1.32 (1.06 to 1.64)	0.0123	1.24 (0.95 to 1.61)	0.1176
eGFR								
Severe (< 30)	2.00 (1.45 to 2.76)	< 0.001	1.62 (1.04 to 2.50)	< 0.001	1.38 (0.86 to 2.21)	0.5106	1.32 (0.75 to 2.30)	0.1364
Mild/Mod. (30 to 89)	1.13 (1.21 (1.08 to 1.36)		0.94 (0.84 to 1.05)		1.10 (0.96 to 1.27)	
Normal (≥ 90)	Ref.		Ref.		Ref.		Ref.	
Sodium								
Low (< 135)	1.39 (1.17 to 1.65)	< 0.001	1.17 (0.91 to 1.49)	0.1642	1.14 (0.91 to 1.43)	0.6907	1.29 (0.99 to 1.68)	0.0506
Normal (135 to 147)	Ref.		Ref.		Ref.		Ref.	
High (≥ 148)	1.06 (0.46 to 2.40)		0.56 (0.14 to 2.30)		3.67 (1.80 to 7.49)		0.75 (0.18 to 3.12)	

Odds ratios are adjusted for previously listed covariates in Table I. Variables are considered statistically significant if $p < 0.0005$ is maintained across both development and validation cohorts.

CI, confidence interval; eGFR, estimated glomerular filtration rate; Mod, moderate; OR, odds ratio; Ref, reference category; THA, total hip arthroplasty; TKA, total knee arthroplasty; WBC, white blood cell count.

preoperative values (95% CI 1.19 to 1.65; $p < 0.0001$) (Table VI). These findings were replicated with similar values and maintained statistical significance in our validation cohorts. Preoperative eGFR and haematocrit were significantly associated with the odds of readmission when analyzed as a continuous variables in both the development and validation cohorts (Table V), however when clinically relevant cut-offs were applied for categorical analysis, no significant association was demonstrated (Table VI). Preoperative platelet count, WBC, and sodium were not associated with acute readmission.

Univariable analysis – total hip arthroplasty. Our univariable analysis demonstrated that albumin, haematocrit, WBC, and eGFR were significantly associated with acute readmission following THA in both the development and validation cohorts when analyzed as continuous variables ($p < 0.0001$) (Table III). Platelets and sodium were not associated with readmission. When standardized per two standard deviations increase, albumin (OR 0.64, 95% CI 0.58 to 0.70) and haematocrit (OR 0.75, 95% CI 0.69 to 0.83) demonstrated the strongest associations with acute readmission. When analyzed categorically (Table IV), patients with hypoalbuminemia had 2.01-times greater odds of readmission (95% CI 1.63 to 2.48; $p < 0.0001$). The association between haematocrit and acute readmission did not maintain significance when analyzed categorically, as those with anaemia (haematocrit < 45 for men, < 37 for women)

and those without. THA patients with severe renal impairment had a 2.30-times increase in their odds of readmission in comparison to those with normal eGFR (95% CI 1.50 to 3.51; $p < 0.0001$).

Multivariable analysis – total hip arthroplasty. In the THA cohort specifically, lower albumin was the only preoperative blood marker to produce statistically significant results in both the development and validation cohorts when analyzed either continuously or with clinically relevant cut-offs (Tables V and VI). For each two standard deviations increase in preoperative albumin, the OR for acute readmission was 0.82 (95% CI 0.74 to 0.91; $p < 0.0001$) for THA patients. Preoperative haematocrit, platelets, WBC, eGFR, and sodium levels did not prove to significantly influence the odds of acute readmission. Independent associations for non-laboratory covariates and acute readmission are shown in Supplementary Material 4.

Discussion

Using health-administrated data in the ACS-NSQIP registry, we identified 137,969 patients who underwent an elective unilateral primary TKA and 78,532 patients who underwent an elective unilateral primary THA between 2011 and 2018, and analyzed their risk for acute hospital readmission based on six routinely ordered preoperative blood markers. To our knowledge, this is the only study to examine the association

of each of these blood markers with hospital readmission. With over 137,000 TKA patients and 78,000 THA patients identified, 3.2% and 3.5% experienced a hospital readmission within 30 days of their elective arthroplasty surgery. Overall, preoperative albumin was strongly associated with readmission for both TKA and THA patients in univariable and multivariable analysis, while haematocrit and eGFR also demonstrated association with readmission in both univariable and multivariable analyses in TKA patients.

Few studies have investigated the relationship between preoperative blood markers and readmission in the arthroplasty population. Very recently, several of these studies have highlighted the association of hypoalbuminemia and malnutrition in postoperative complication rates, with increased odds of postoperative medical complication, surgical site infection, intensive care unit transfer, and readmission following arthroplasty.^{7,42–48} In this regard, our study's findings are consistent with these previous studies, which provide a possible avenue for perioperative intervention. A 2019 comparative observational study by Shroer et al⁴⁹ demonstrated significantly lower rates of readmission in malnourished arthroplasty patients treated with perioperative nutritional intervention compared with controls. Similar findings have been demonstrated in hip fracture patients.⁵⁰ While no randomized trials in orthopaedic patients have been performed on nutritional intervention, a recent large scale trial in general internal medicine demonstrated improved survival and clinical outcomes in hospitalized patients at nutritional risk with individualized nutritional support.⁵¹ Taken together, the mounting body of evidence for the association of malnutrition and preoperative hypoalbuminemia with postoperative arthroplasty outcomes suggests that albumin has utility as a preoperative marker to identify patients who are at greater odds of postoperative readmission, and suggests an avenue for intervention.

Previous studies performed on THA patients,^{52,53} and on combined arthroplasty patients,⁵⁴ have demonstrated increased odds of postoperative complications, mortality, and surgical site infection in patients with preoperative anaemia. While our study similarly found increased odds of readmission in the TKA population with low HCT, these results were not seen in the THA cohort after adjustment for relevant covariates. Similarly, previously literature has demonstrated decreased eGFR and/or elevated creatinine are associated with significantly higher postoperative DVT, MI, readmission, and mortality in arthroplasty patients.^{35,55–58} In our study, decreased eGFR was associated with increased odds of acute readmission in the elective TKA population, but these results were not replicated in the THA cohort after covariate adjustment.

The pre-specification of development and validation cohorts with temporal validation of initial findings using both continuous and clinically relevant cut-offs, the conservative α adjustment for significance, and the use of a large database from over 650 hospitals strengthens the external validity of our study and the clinical applicability of our findings in comparison to previous published work. Furthermore, our use of both multivariable and univariable models allows for better understanding of the blood markers' independent association with readmission, as well as the unadjusted change in odds if a patient presents with a particular laboratory derangement. However, despite its strengths, this study has several limitations. First, this is a retrospective study using a registry which is highly dependent on coder validity. However, the NSQIP database and its coding practices are audited, demonstrate an interobserver reliability of 98.4%, and have demonstrated high accuracy of reported outcomes and complications when cross-referenced with other databases.⁵⁹ The > 700 hospitals who participate in NSQIP do so voluntarily. Accordingly, it is possible that the characteristics of patients and outcomes differ between hospitals that participate in NSQIP and those that do not. However, studies investigating these potential discrepancies have not demonstrated a meaningful difference.⁶⁰ The NSQIP database includes follow-up for only 30 days postoperatively, and there is no indication from this study as to longer-term outcomes or patient-reported outcome measures and satisfaction. The metric of morbidity used in this study – 30-day readmission – while very relevant given hospital funding and healthcare cost implications, may not accurately capture all specific postoperative complications, as those that happened during initial hospital stay or those that were managed as an outpatient would not be captured in this surrogate outcome. It would also include patients admitted to hospital for another reason which may not have been related to their arthroplasty during the 30-day period. However, under most bundled payment care models, the hospitals would still be responsible for the costs of readmission in this time window, regardless of cause.^{61–64} Furthermore, we are unable to comment on the aetiologies of blood marker derangement and whether they were a result of comorbid chronic conditions. Finally, because we included only patients with a full set of preoperative blood markers to maintain consistency across our statistical analysis, this cohort represents a sicker, more comorbid arthroplasty population as shown in Supplementary Material 3. Clinicians may be less likely to order preoperative investigations on patients without comorbid conditions, introducing an element of selection bias.

In summary, in this population-level large cohort analysis of arthroplasty patients, albumin demonstrated

the strongest association with acute readmission in comparison to five other commonly ordered preoperative blood markers. Identification and optimization of preoperative hypoalbuminemia could help healthcare providers recognize and address at-risk patients undergoing elective TKA and THA, though further studies are needed in this regard.



Take home message

- In this retrospective cohort study of 216,501 patients, preoperative lower albumin proved to have the greatest impact on the odds of readmission in comparison to five other commonly ordered preoperative blood tests in both total hip arthroplasty (THA) and total knee arthroplasty (TKA) patients.
- Identification and optimization of preoperative hypoalbuminemia could help healthcare providers recognize and address at-risk patients undergoing elective TKA and THA.

Supplementary material



A list of Current Procedural Terminology Codes used for patient identification; normal ranges of blood markers examined in this paper; characteristics of excluded patients; and independent associations for non-laboratory covariates with acute readmission.

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