Research Article

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Sickle cell disease and readmissions rates after lower extremity arthroplasty: a multistate analysis 2007–2014

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Aim: To compare readmission rates between patients with sickle cell disease (SCD) and non-sickle cell disease undergoing total hip and knee arthroplasty (THA and TKA). **Methods:** Identified adult patients who underwent THA or TKA from 2007 to 2014 in California, Florida, New York, Maryland and Kentucky using a multistate database. Outcomes were 30- and 90-day readmission rates, mortality, complications, length of stay and hospital charges. Logistic regression models were used for analysis. **Results:** Compared with non-sickle cell disease patients following TKA and THA, SCD patients had higher odds of 30- (odds ratio [OR]: 3.79) and 90-day readmissions (OR: 4.15), mortality (OR: 6.54), more complications, longer length of stay, and higher total charges. **Conclusion:** Following TKA and THA, SCD is associated with higher readmissions and worse outcomes.

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Keywords: hematology • observational research • outcomes research

Background

Sickle cell disease (SCD) is a genetic disorder of hemoglobin polymerization where rigid sickle-shaped hemoglobin is formed under hypoxia-related stress. Major consequences stemming from sickling of erythrocytes include extravascular hemolytic anemia, microvascular obstructions and thrombosis, which result in organ infarction and vaso-occlusive pain crises [1]. Patients with SCD inherit two homozygous hemoglobin S genes, or less commonly, a compound of hemoglobin S gene and another form of thalassemia in the other gene. In USA, the estimated incidence of sickle cell trait (SCT) is 15.5 cases per 1000 live births of all races, with the highest being 73.1 cases per 1000 births in black newborns [2]. A significantly higher risk of having SCD has been shown in non-Hispanic blacks compared with non-Hispanic whites [2,3]. In 2005, the mean total medical expenditure for children with SCD and Medicaid insurance was $11,075, compared with $14,722 for privately insured patients [4]. These expenditures are more than sixfold and tenfold higher than children of the same age group without SCD, which are $1706 for Medicaid insurance and $1293 for private insurance [5].

Osteonecrosis of the femoral head (ONFH) is a common complication in SCD patients. In a California cohort study, Adesina *et al.* showed that 23% of SCD patients underwent total hip arthroplasty (THA) at a median age of 36 years due to ONFH [6]. The SCD patients also have increased risks for osteonecrosis of the knee and a younger median age for total knee arthroplasty (TKA) [7]. Numerous studies have shown that having SCD is associated with more adverse perioperative outcomes in patients undergoing THA and TKA, including increased postoperational complications, length of stay (LOS), and total hospital charges [8–11]. However, many of these studies are outdated or have limited sample size (Table 1). Since 2008, the Centers for Medicare and Medicaid Services have mandated

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Table 1. Literature review of total hip and total knee arthroplasty postoperative outcomes by sickle cell disease status.

Procedure	Study, journal title, year	Data source (hospitals, states, dataset)	Data collection (years)	Sample size (N)	Outcomes reported	Limitations of prior studies	Ref.
THA	Adesina *et al.*, *Blood Adv.*, 2017	California's Office of Statewide Planning and Development discharge databases	1991–2013	Total 6237 patients with SCD	30- and 90-day readmission rate posthip replacement surgery among SCD patients with ONFH	– Single state, only examined readmissions of the subgroup with ONFH – No comparison with non-SCD patients	[6]
Uncemented HA	Ilyas *et al.*, *J. Arthroplasty*, 2018	King Faisal Specialist Hospital and Research Center, (Saudi Arabia)	2000–2012	Total 101 patients (133 hips)	Pain scores, range of motion, function, 10-year survivorship and some complications	– No control group, single site in Saudi Arabia and small sample size – Does not examine readmissions, in-hospital mortality, LOS and total hospital charges	[34]
THA and TKA	Perfetti *et al.*, *J. Arthroplasty*, 2015	NIS	1998–2010	THA patients: 3532 with SCD and 2,653,653 without SCD. The TKA patients: 724 with SCD and 5,660,896 without SCD	LOS, total hospital charges, perioperative complications	– Outdated data – The NIS does not provide readmission outcomes – Did not examine in-hospital mortality	[11]
TKA, hysterectomy and appendectomy	Kamble *et al.*, *Am. J. Hematol.*, 2010	NIS	2002–2006	Hysterectomy: 118 SCD and 85,073 non-SCD discharges. Appendectomy: 69 SCD and 24,802 non-SCD discharges. Knee replacement: 62 SCD and 14,517 non-SCD discharges	LOS and inpatient costs	– Outdated data – The NIS does not provide readmission outcomes – Did not examine THA	[35]
Hip replacement and cholecystectomy	Dinan *et al.*, *Am. J. Hematol.*, 2009	NIS	2002–2005	Cholecystectomy: 118,187 non-SCD discharges and 887 SCD discharges. Hip replacement: 69,670 non-SCD discharges and 321 SCD discharges	Inpatient costs, LOS and in-hospital mortality	– Outdated data – The NIS does not provide readmission outcomes – Did not examine postoperative complications – Did not examine TKA	[8]

Search term:
([knee replacement] OR [knee arthroplasty] OR [hip replacement] OR [hip arthroplasty] OR [total joint replacement] OR [total joint arthroplasty] OR [81.51] OR [81.54]) AND ([sickle cell] OR [sickle cell anemia] OR [sickle cell disease] OR [sickle cell thalassemia] OR [hemoglobin SC disease]) AND ([mortality] OR [complications] OR [morbidity] OR [patient readmission] OR [readmission] OR [length of stay] OR [resource utilization] OR [utilization] OR [outcomes] OR [total charges])
ASES: American shoulder and elbow surgeon; LOS: Length of stay; HA: Hip arthroplasty; NIS: Nationwide inpatient sample; ONFH: Osteonecrosis of the femoral head; SCD: Sickle cell disease; THA: Total hip arthroplasty; TKA: Total knee arthroplasty.

Table 1. Literature review of total hip and total knee arthroplasty postoperative outcomes by sickle cell disease status (cont.).

Procedure	Study, journal title, year	Data source (hospitals, states, dataset)	Data collection (years)	Sample size (N)	Outcomes reported	Limitations of prior studies	Ref.
THA	Hernigou *et al.*, *Clin. Orthop. Relat. Res.*, 2008	Chirurgie Orthopedique et Traumatologique, Hôpital Henri Mondor, University Paris XII	1980–2000	244 consecutive patients (312 THAs) with SCD and osteonecrosis	Long-term pain relief, function and complications	– Outdated data, small sample and single site – Did not examine readmission, in-hospital mortality, LOS and hospital charges	[36]
Revision THA	Kalacý *et al.*, *ASM*, 2007	Mustafa Kemal University Faculty of Medicine Hatay Turkey and Faculty of Medicine Çukurova University Balcali Adana Turkey	1988–1999	Ten patients with SCD who had revision THA	LOS, blood loss, operative time, re-revision and complications	– Outdated data, small sample and single site in Turkey – Population is limited to those who had revision THA – Did not examine readmission, in-hospital mortality and hospital charges	[37]
Shoulder arthroplasty	Lau *et al.*, *JSES*, 2007	Adult sickle cell clinic of Washington University, (St Louis, MO, USA)	1994–2005	Eight patients with SCD and avascular necrosis who had shoulder arthroplasty	ASES, pain and activities of daily living scores and complications	– Outdated data, small sample and single site – Did not examine TKA and THA	[38]
Total hip replacement	Al-Mousawi *et al.*, *Int. Orthop.*, 2002	Salmanyia Medical Centre, (Bahrain)	1984–1995	Total 35 total hip replacement arthroplasties in 28 patients	Operation duration, intraoperative blood loss, intravenous fluid, LOS	– Outdated data, small sample and single site in Bahrain – Did not examine TKA – Did not examine readmission, in-hospital mortality and hospital charges	[39]

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Table 1. Literature review of total hip and total knee arthroplasty postoperative outcomes by sickle cell disease status (cont.).

Procedure	Study, journal title, year	Data source (hospitals, states, dataset)	Data collection (years)	Sample size (N)	Outcomes reported	Limitations of prior studies	Ref.
THA	Moran *et al.*, *Clin. Orthop. Relat. Res.*, 1993	The Hospital for Special Surgery, NY, USA	1973–1988	Total 22 arthroplasties in 14 patients with endstage osteonecrosis of femoral head secondary to sickle cell hemoglobinopathy	Mortality, failure vs surviving arthroplasties, revisions, complications	– Outdated data, small sample and single site. – Did not examine TKA – Did not examine readmission, LOS and hospital charges	[40]
THA	Acurio and Friedman, *J. Bone Joint Surg. Br.*, 1992	Medical University of South Carolina	1970–1986	Total 25 hip arthroplasties in 25 patients with sickle-cell hemoglobinopathy and osteonecrosis	Revisions, complication rate and infection rate	– Outdated data, small sample and single site – Did not examine TKA – Did not examine readmission, LOS and hospital charges	[41]
THA	Clarke *et al.*, *J. Bone Joint Surg. Br.*, 1989	Johns Hopkins University	1978–1988	Total 27 hips of patients who had sickle cell anemia with avascular necrosis of the femoral head	Revisions, operation durations, blood loss	– Outdated data, small sample and single site – Did not examine TKA – Did not examine readmission, LOS and hospital charges	[42]
THA	Bishop *et al.*, *J. Bone Joint Surg. Am.*, 1988	Grady Memorial Hospital, (Atlanta, Georgia)	1974–1984	Total 11 patients with primary 13 THAs total	Infections, revisions, pain	– Outdated data, small sample and single site – Did not examine TKA – Did not examine readmission, LOS and hospital charges	[43]
Total hip replacement, cholecystectomy and splenectomy	Adam *et al.*, *Am. J. Med.*, 2008	Duke University, Durham (NC, USA); University of North Carolina, Chapel Hill (NC, USA); and Emory University, Atlanta (GA, USA); East Carolina University, Greenville (NC, USA) and the Carolinas Medical Center, Charlotte (NC, USA)	2002–2007	Total 509 unrelated adult patients	Surgery frequency across age and obstetrical history/o	– Outdated data, small sample and sites limited to southeast USA – Did not examine – Did not examine readmission, LOS, in-hospital mortality and hospital charges	[44]

Search term:
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ASES: American shoulder and elbow surgeon; LOS: Length of stay; HA: Hip arthroplasty; NIS: Nationwide inpatient sample; ONFH: Osteonecrosis of the femoral head; SCD: Sickle cell disease; THA: Total hip arthroplasty; TKA: Total knee arthroplasty.

Table 1. Literature review of total hip and total knee arthroplasty postoperative outcomes by sickle cell disease status (cont.).

Procedure	Study, journal title, year	Data source (hospitals, states, dataset)	Data collection (years)	Sample size (N)	Outcomes reported	Limitations of prior studies	Ref.
Simultaneous bilateral THA	Ilyas and Moreau, *J. Arthroplasty*, 2002	King Faisal Specialist Hospital and RC, Riyadh, (Saudi Arabia)	1990–1998	Total 18 consecutive patients (36 hips) with SCD	Procedure time, blood loss, complications and pain, function and range of motion scores	– Outdated data, small sample and single site in Saudi Arabia – Did not examine TKA – Did not examine readmission, LOS, in-hospital mortality, & hospital charges.	[45]
Orthopedic procedures (including hip replacement)	Vichinsky *et al.*, *Am. J. Hematol*, 1999	26 centers	1988–1993	Total 118 SCD patients, 138 surgeries	Complications	– Outdated data and small sample size – Did not examine TKA – Did not examine readmission, LOS and hospital charges	[46]
Uncemented bipolar hip replacements	Sanjay and Moreau, *Int. Orthop.*, 1996	King Faisal Specialist Hospital and Research Centre, (Saudi Arabia)	1987–1992	Total 26 uncemented bipolar hip replacements for avascular necrosis of the femoral head due to sickle cell disease	Harris hip scores and complications	– Outdated data, single site in Saudi Arabia and small sample size – Did not examine TKA – Did not examine readmission, LOS and hospital charges	[47]

Search term:
([knee replacement] OR [knee arthroplasty] OR [hip replacement] OR [hip arthroplasty] OR [total joint replacement] OR [total joint arthroplasty] OR [81.51] OR [81.54]) AND ([sickle cell] OR [sickle cell anemia] OR [sickle cell disease] OR [sickle cell thalassemia] OR [hemoglobin SC disease]) AND ([mortality] OR [complications] OR [morbidity] OR [patient readmission] OR [readmission] OR [length of stay] OR [resource utilization] OR [utilization] OR [outcomes] OR [total charges])
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reporting 30-day readmission for hip and knee replacement surgeries as an inpatient outcome quality measure [12,13]. Despite this policy, our knowledge regarding 30- and 90-day readmission rates among SCD patients after THA and TKA in a nationalwide population is limited.

Study objectives

In this study, we analyzed hospital discharge data from the State Inpatient Database (SID) from the years 2007 to 2014 in California, Florida, Kentucky, Maryland and New York. The primary goal of the study was to compare the 30- and 90-day readmission rates and adjusted odds between SCD patients and non-SCD (NSCD) patients undergoing THA and TKA. We also analyzed in-hospital mortality, LOS, total hospital charges and postoperational complications as secondary outcomes.

Study hypothesis

Our study hypothesis was that patients with SCD had higher unadjusted 30- and 90-day readmission rates and adjusted odds following TKA and THA surgeries when compared with NSCD patients. In addition, we hypothesized that SCD was associated with higher odds of in-hospital mortality, longer LOS, higher hospital charges and more postoperational complications.

Methods

Study database & population

Hospital discharge data from the SID, Healthcare Cost and Utilization Project (HCUP) and Agency for Health Research and Quality were used for this retrospective analysis, encompassing data from California from years 2007 to 2011, and Florida, Kentucky, Maryland and New York from years 2007 to 2014 [14]. Kentucky was excluded from readmissions rates analysis because these data were not available. Readmission data from Maryland were limited to 2012–2014. The SID contains data on nearly all (97%) inpatient discharges in the USA [15]. Variables abstracted for our analysis included patient demographics of age, sex, race, primary insurance payer, median household income quartile by ZIP code, patient comorbidities by present-on-admission (POA) indicators, diagnoses, procedures (TKA, THA), procedural complications, hospital and admission characteristics (state, hospital volume, emergent operation, year of operation), LOS, total hospital charges (in 2016 USD), postoperative complications and discharge disposition. Records were entered per hospital discharge. Therefore, it is possible that one patient appears more than once in the database, if they had multiple procedures performed during the same hospital stay; in this case, more than one THA or TKA procedure.

Patients $\geq$18 years, who underwent primary THA and TKA, were identified using the International Classification of Diseases, Ninth Revision, Clinical Modifications (ICD-9-CM) codes 81.51 (primary THA) and 81.54 (primary TKA). Patients with partial hip replacements (81.52), revision hip arthroplasty (81.53) or revision of knee replacement (81.55) were excluded, as were cases with more than two procedure codes from either arthroplasty and cases with both knee and hip surgeries. The SCD was identified using ICD-9-CM codes 282.41, 282.42, 282.61–282.64, 282.68 and 282.69. We used the van Walraven score, a modification of the Elixhauser comorbidity index, as a composite measure of comorbidities present on admission [16,17].

Outcomes

Our primary outcomes were the 30-day readmission rate and the 90-day readmission rate. Our secondary outcomes included surgical and postoperative complications, LOS and total hospital charges. Diagnoses which comprise each complication category were identified using ICD-9-CM codes and enumerated in Table 2. All complications were indicated as not POA in the database. We log transformed the outcome measures of LOS and total hospital charges to address non-normality. Unadjusted and adjusted analyses were conducted for the secondary outcomes between patients with and without SCD. Per HCUP requirements, data in any cell with fewer than 11 observations was masked in the results tables to protect patient confidentiality [18]. Such masking limited our reporting of diagnoses and complications with very low incidence; however, it did not inhibit any analyses.

Statistical analysis

Bivariate comparisons of baseline characteristics including patient demographics (age, gender, race, primary payer status, median household income), surgical characteristics (year, state, disposition at discharge, emergency operation, procedure type) and POA comorbidities were conducted between patients with and without SCD, combined and

Table 2. Definition of International Classification of Diseases, Ninth Revision, Clinical Modification codes for complications.

Minor complications	
Deep vein thrombosis	
451.1x	Phlebitis and thrombophlebitis of deep vessels of lower extremities
451.2x	Phlebitis and thrombophlebitis of lower extremities, unspecified
451.81	Phlebitis and thrombophlebitis of iliac vein
451.9x	Phlebitis and thrombophlebitis of unspecified site
453.2x	Other venous embolism and thrombosis of inferior vena cava
453.40	Venous embolism and thrombosis of unspecified deep vessels of lower extremity
453.41	Acute venous embolism and thrombosis of deep vessels of proximal lower extremity
453.42	Acute venous embolism and thrombosis of deep vessels of distal lower extremity
453.8x	Other venous embolism and thrombosis of other specified veins
453.9x	Other venous embolism and thrombosis of unspecified site
Other minor complication	
590.1x	Acute pyelonephritis
590.2x	Renal and perinephric abscess
590.3x	Pyeloureteritis cystica
590.8x	Other pyelonephritis or pyonephrosis, not specified as acute or chronic
590.9x	Other orthopoxvirus infections
599.0x	Urinary tract infection, site not specified
599.7x	Hematuria
995.90	Systemic inflammatory response syndrome, unspecified
995.91	Sepsis
995.92	Severe sepsis
995.93	Systemic inflammatory response syndrome due to noninfectious process without acute organ dysfunction
995.94	Systemic inflammatory response syndrome due to noninfectious process with acute organ dysfunction
996.0x	Mechanical complication of cardiac device, implant and graft
996.1x	Mechanical complication of other vascular device, implant and graft
996.2x	Mechanical complication of nervous system device, implant and graft
996.3x	Mechanical complication of genitourinary device, implant and graft
996.4x	Mechanical complication of internal orthopedic device, implant and graft
996.5x	Mechanical complication of other specified prosthetic device, implant and graft
996.6x	Infection and inflammatory reaction due to internal prosthetic device, implant and graft
996.7x	Other complications of internal (biological; synthetic) prosthetic device, implant and graft
996.8x	Complications of transplanted organ
996.9x	Complications of reattached extremity or body part
998.0x	Postoperative shock
998.1x	Hemorrhage or hematoma or seroma complicating a procedure
998.2x	Accidental puncture or laceration during a procedure, not elsewhere classified
998.3x	Disruption of wound
998.51	Infected postoperative seroma
998.59	Other postoperative infection
998.6x	Persistent postoperative fistula
998.7x	Acute reaction to foreign substance accidentally left during a procedure
998.8x	Other specified complications of procedures, not elsewhere classified
998.9x	Unspecified complication of procedure, not elsewhere classified
999.2x	Other vascular complications of medical care, not elsewhere classified
999.3x	Other infection

[†] ICD-9-CM procedure code.
CKD: Chronic kidney disease; HCUP: Healthcare Cost and Utilization Project; ICD-9-CM: International Classification of Diseases, Ninth Revision, Clinical Modification; TIA: Transient ischemic attack.

Table 2. Definition of International Classification of Diseases, Ninth Revision, Clinical Modification codes for complications (cont.).

Minor complications	
Major complications	
Renal disease	
403.01	Hypertensive chronic kidney disease, malignant, with chronic kidney disease stage V or end stage renal disease
403.11	Hypertensive chronic kidney disease, benign, with chronic kidney disease stage V or end stage renal disease
403.91	Hypertensive chronic kidney disease, unspecified, with chronic kidney disease stage V or end stage renal disease
404.02	Hypertensive heart and chronic kidney disease, malignant, without heart failure and with chronic kidney disease stage V or end stage renal disease
404.03	Hypertensive heart and chronic kidney disease, malignant, with heart failure and with chronic kidney disease stage V or end stage renal disease
404.12	Hypertensive heart and chronic kidney disease, benign, without heart failure and with chronic kidney disease stage V or end stage renal disease
404.13	Hypertensive heart and chronic kidney disease, benign, with heart failure and chronic kidney disease stage V or end stage renal disease
404.92	Hypertensive heart and chronic kidney disease, unspecified, without heart failure and with chronic kidney disease stage V or end stage renal disease
404.93	Hypertensive heart and chronic kidney disease, unspecified, with heart failure and chronic kidney disease stage V or end stage renal disease
582.xx	Chronic glomerulonephritis
583	Nephritis and nephropathy, not specified as acute or chronic
583.0x	Nephritis and nephropathy, with lesion of proliferative glomerulonephritis
583.1x	Nephritis and nephropathy, not specified as acute or chronic, with lesion of membranous glomerulonephritis
583.2x	Nephritis and nephropathy, not specified as acute or chronic, with lesion of membranoproliferative glomerulonephritis
583.4x	Nephritis and nephropathy, not specified as acute or chronic, with lesion of rapidly progressive glomerulonephritis
583.6x	Nephritis and nephropathy, not specified as acute or chronic, with lesion of renal cortical necrosis
583.7x	Nephritis and nephropathy, not specified as acute or chronic, with lesion of renal medullary necrosis
585.xx	CKD
586.xx	Renal failure, unspecified
V42.0x	Kidney replaced by transplant
V45.1x	Renal dialysis status
V56.xx	Encounter for dialysis and dialysis catheter care
In-hospital mortality - HCUP-defined measure	
Myocardial infarction	
410.xx	Acute myocardial infarction
411.81	Acute coronary occlusion without myocardial infarction
413.xx	Angina pectoris
Pneumonia	
481.xx	Pneumococcal pneumonia (*Streptococcus pneumoniae* pneumonia)
482.0x	Pneumonia due to *Klebsiella pneumoniae*
482.1x	Pneumonia due to Pseudomonas
482.2x	Pneumonia due to *H. influenzae*
482.3x	Pneumonia due to Streptococcus
482.41	Methicillin susceptible pneumonia due to *Staphylococcus aureus*
482.49	Other Staphylococcus pneumonia
482.8x	Pneumonia due to other specified bacteria
482.83	Pneumonia due to other gram-negative bacteria

†ICD-9-CM procedure code.
CKD: Chronic kidney disease; HCUP: Healthcare Cost and Utilization Project; ICD-9-CM: International Classification of Diseases, Ninth Revision, Clinical Modification; TIA: Transient ischemic attack.

Table 2. Definition of International Classification of Diseases, Ninth Revision, Clinical Modification codes for complications (cont.).

Minor complications	
482.9x	Bacterial pneumonia, unspecified
486.xx	Pneumonia, organism unspecified
997.31	Ventilator associated pneumonia
Pulmonary embolism	
415.1x	Pulmonary embolism and infarction
415.11	Latrogenic pulmonary embolism and infarction
415.12	Septic pulmonary embolism
415.19	Other pulmonary embolism and infarction
Stroke	
997.02	Latrogenic cerebrovascular infarction or hemorrhage
430.xx	Subarachnoid hemorrhage
431.xx	Intracerebral hemorrhage
432.xx	Other and unspecified intracranial hemorrhage
433.xx	Occlusion and stenosis of precerebral arteries
434.xx	Occlusion of cerebral arteries
435.xx	Transient cerebral ischemia
V12.54	Personal history of TIA and cerebral infarction without residual deficits
V17.1x	Family history of stroke (cerebrovascular)
Tachycardia	
427.0x	Paroxysmal supraventricular tachycardia
427.1x	Paroxysmal ventricular tachycardia
427.2x	Paroxysmal tachycardia, unspecified
427.3x	Atrial fibrillation and flutter
427.4x	Ventricular fibrillation and flutter
427.5x	Cardiac arrest
427.8x	Other specified cardiac dysrhythmias
427.9x	Cardiac dysrhythmia, unspecified
Cardiovascular complications	
Supraventricular arrhythmia	
427.3x	Atrial fibrillation and flutter
427.0	Paroxysmal supraventricular tachycardia
427.31	Atrial fibrillation
472.32	Atrial flutter
Myocardial infarction	
410.xx	Acute myocardial infarction
411.81	Acute coronary occlusion without myocardial infarction
413.x	Angina pectoris
Postoperative stroke	
997.02	Latrogenic cerebrovascular infarction or hemorrhage
430.xx	Subarachnoid hemorrhage
431.xx	Intracerebral hemorrhage
432.xx	Other and unspecified intracranial hemorrhage
433.xx	Occlusion and stenosis of precerebral arteries
434.xx	Occlusion of cerebral arteries
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Table 2. Definition of International Classification of Diseases, Ninth Revision, Clinical Modification codes for complications (cont.).

Minor complications	
Deep vein thrombosis	
451.1x	Phlebitis and thrombophlebitis of deep vessels of lower extremities
451.2x	Phlebitis and thrombophlebitis of lower extremities, unspecified
451.81	Phlebitis and thrombophlebitis of iliac vein
451.9x	Phlebitis and thrombophlebitis of unspecified site
453.2x	Other venous embolism and thrombosis of inferior vena cava
453.40	Venous embolism and thrombosis of unspecified deep vessels of lower extremity
453.41	Acute venous embolism and thrombosis of deep vessels of proximal lower extremity
453.42	Acute venous embolism and thrombosis of deep vessels of distal lower extremity
453.8x	Other venous embolism and thrombosis of other specified veins
453.9x	Other venous embolism and thrombosis of unspecified site
Pulmonary embolism	
415.1x	Pulmonary embolism and infarction
415.11	Latrogenic pulmonary embolism and infarction
415.12	Septic pulmonary embolism
415.19	Other pulmonary embolism and infarction
Pulmonary complications	
Pneumonia	
486.xx	Pneumonia, organism unspecified
481.xx	Pneumococcal pneumonia (*S. pneumoniae* pneumonia)
482.8x	Pneumonia due to other specified bacteria
482.3x	Pneumonia due to Streptococcus
482.9x	Bacterial pneumonia, unspecified
482.0x	Pneumonia due to *Klebsiella pneumoniae*
482.1x	Pneumonia due to Pseudomonas
482.2x	Pneumonia due to *H. influenzae*
482.41	Methicillin susceptible pneumonia due to *S. aureus*
482.49	Other Staphylococcus pneumonia
482.83	Pneumonia due to other gram-negative bacteria
997.31	Ventilator associated pneumonia
Postoperative acute respiratory insufficiency	
518.5	Postoperative acute respiratory insufficiency
Postoperative acute pneumothorax	
512.1	Postoperative acute pneumothorax
Postoperative pulmonary edema	
518.4	Postoperative pulmonary edema
Pulmonary collapse	
518.0	Pulmonary collapse
Empyema with and without fistula	
510.0	. . . with fistula
510.9	. . . without mention of fistula
Mechanical ventilation	
96.70†	Continuous invasive mechanical ventilation of unspecified duration
96.71†	Continuous invasive mechanical ventilation for less than 96 consecutive hours
96.72†	Continuous invasive mechanical ventilation for 96 consecutive hours or more
Noninvasive ventilation	
93.90†	Noninvasive mechanical ventilation

†ICD-9-CM procedure code.
CKD: Chronic kidney disease; HCUP: Healthcare Cost and Utilization Project; ICD-9-CM: International Classification of Diseases, Ninth Revision, Clinical Modification; TIA: Transient ischemic attack.

Table 2. Definition of International Classification of Diseases, Ninth Revision, Clinical Modification codes for complications (cont.).

Minor complications	
Tracheostomy	
31.1†	Temporary tracheostomy
31.2†	Permanent tracheostomy
31.29†	Other permanent tracheostomy
Infectious complications	
Sepsis/shock	
995.91	Sepsis
038	Septicemia
995.92	Severe sepsis
999.3	Other infection
998.0	Postoperative shock
Urinary tract infection	
599.0	Urinary tract infection, site not specified
590.9	Infection of kidney, unspecified
Postoperative wound infection	
998.51	Infected postoperative seroma
998.59	Other postoperative infection
Intraoperative complications	
998.2	Accidental puncture or laceration during a procedure
998.11	Hemorrhage complicating a procedure
Gastrointestinal complications	
997.4	Digestive system complications not elsewhere classified

†ICD-9-CM procedure code.
CKD: Chronic kidney disease; HCUP: Healthcare Cost and Utilization Project; ICD-9-CM: International Classification of Diseases, Ninth Revision, Clinical Modification; TIA: Transient ischemic attack.

stratified by surgery types (THA vs TKA). Emergency operations included any admission indicated as emergent, urgent or trauma center. Unadjusted rates of 30- and 90-day readmission, in-hospital mortality, and complications (categorized by system: pulmonary, cardiovascular, infectious, intraoperative, and infectious, and major and minor complications specific to SCD), as well as, estimates of log-transformed length-of-stay and total hospital charges were compared by SCD status for each surgery type (THA and TKA) [11,19]. Two-sample t-test and analysis of variance were used for continuous variables. Pearson's Chi-square and Fisher's exact test were used for categorical variables.

Generalized estimating equations were utilized to fit marginal logistic regression models to estimate effects of SCD on surgical outcomes of TKA and THA. Separate generalized estimating equations models were constructed for 30-day readmission, 90-day readmission, in-hospital mortality, major complications, minor complications, length-of-stay and total hospital charges. The models have adjusted for multiple potential confounding factors: patient age, gender, race, primary payer status, quartile of median household income as represented by home ZIP code, surgery year, state, disposition at discharge, procedure type, number of knee or hip procedures conducted in the same inpatient stay and the comorbidities using the van Walraven score, a modified measure of the Elixhauser comorbidity index. Results are reported as odds ratios (OR) and 95% CI.

Multiple sensitivity analyses were conducted to assess the robustness and consistency of findings. Multivariate models for each outcome were rerun stratified by emergent and elective surgeries, procedure type (THA and TKA) and primary payer status (Medicare, Medicaid, private insurance, uninsured and other) [12,13]. An additional stratified model was run for patients of black race only, as they are more likely to inherit SCD and historically have been shown to have poorer surgical outcomes [2]. Additional sensitivity analyses included models including a variable to indicate emergency procedures (vs elective or missing procedures, separately); models including cases only from hospitals where at least one patient with SCD was discharged with a THA or TKA procedure at any point during the study period. Therefore, we repeated models including cases only from hospitals where at least

one patient with SCD was discharged with a THA or TKA procedure each year [11–13]. An additional sensitivity analysis was done in which we removed the most statistically significant covariate determined by the Wald statistic (determined to be age in years) [19,20]. The original models were validated if the re-estimated effects of SCD were not significantly attenuated (less than 10%) and remained statistically significant in the modified models.

Model assumptions of normality and linearity were assessed graphically and statistically; goodness-of-fit tests were performed. All p-values were twosided with statistical significance at 0.05 α level. SAS version 9.4 (SAS Institute, NC, USA) was used for all statistical tests.

Results

Patient & hospital characteristics

A total of 1,422,210 procedures for patients ≥18 years old were included in our analysis during an 8-year study period from 2007 to 2014 from California (years 2007–2011), Florida, Kentucky, Maryland and New York. Among them, 35.1% were total hip arthroplasties and 64.9% were total knee arthroplasties. Total of 1000 procedures were for SCD patients, and the remainder was for NSCD patients. Of the study population, the mean age was 66.5 years (SD: 11.0 years) and 60.9% were female. Compared with NSCD patients, SCD patients were younger (SCD: 43.1 years, SD: 15.9 years vs NSCD: 66.6 years, SD: 10.9 years) and more likely to be the black race (SCD: 82.1% vs NSCD: 7.7%). We did not observe any gender difference between SCD and NSCD patients in the pooled patient population. In addition, SCD patients were more likely to have Medicaid insurance than NSCD patients (SCD: 28.0% vs NSCD: 3.4%). More SCD patients lived in areas with the lowest median household income (SCD: 38.4% vs NSCD: 19.6%), whereas NSCD patients were more likely to be in the highest median household income area (SCD: 15.3% vs NSCD: 27.2%). Surgeries for SCD patients were more likely to be emergent compared with NSCD patients (SCD: 8.7% vs NSCD: 1.5%). A much higher percentage of surgeries for SCD patients were THA compared with NSCD patients (SCD: 81.0% vs NSCD: 35.1%).

In order to avoid possible effect modification of surgery type (THA vs TKA), separate comparisons of baseline characteristic were conducted for subgroups with THA and TKA only. Table 3 shows the patient and procedural characteristics, as well as the POA comorbidities by surgery type comparing SCD patients and NSCD patients. Similar to the combined study population, among both subsets of people who had TKA only and people who had THA only, SCD patients were younger, more likely to be black than any other racial or ethnic group, living in the lowest quartile of household income and more likely to have emergent operations. We also found that SCD patients were more likely to be female compared with NSCD patients in the TKA group (SCD: 72.6% vs NSCD: 63.2%). However, gender was not significantly different between SCD and NSCD patients in the THA group.

Bivariate outcomes

Table 4 shows the results of unadjusted bivariate analyses of 30- and 90-day readmission rates, LOS, total hospital charges, mortality and postoperative complications, stratified by procedure type. In the THA only group, 17.6% of SCD patients were readmitted to a hospital within 30 days of discharge, and 34.9% readmitted within 90 days; whereas only 5.4 and 10.0% of NSCD patients were readmitted within 30 and 90 days of discharge, respectively. Similar findings were observed in the TKA only group – 15.6 and 27.4% of SCD patients were readmitted within 30 and 90 days of TKA, while only 5.0 and 9.3% of NSCD patients were readmitted at these time intervals.

For secondary outcomes, compared with NSCD patients, SCD patients were more likely to have a longer median LOS after THA and TKA (THA: 5 vs 3 days; $p < 0.0001$; TKA: 4 vs 3 days; $p < 0.0001$). In both groups, SCD patients also had higher rates of major complications (THA: 4.7 vs 3.1%; $p = 0.0069$; TKA: 5.8 vs 2.9%; $p = 0.0166$). The SCD patients also experienced more pulmonary and infectious complications when compared with NSCD patients. However, there were no statistically significant differences between SCD and NSCD in terms of cardiovascular, gastrointestinal and intraoperative complications. Additionally, in the THA group, SCD patients had higher rates of minor complications (THA: 7.5 vs 3.7 %; $p < 0.0001$) when compared with NSCD patients (Table 4). Results of individual complications which comprise the composite complication variables are listed in Supplementary Table 1, by SCD status.

In addition, total hospital charges for SCD patients undergoing THA were significantly higher than NSCD patients (SCD median: $66,444 vs NSCD: $58,355; $p < 0.0001$). In the TKA group, total hospital charges for SCD patients were higher than NSCD patients, but not statistically significantly different, which was probably due to a small number of SCD patients in the TKA group (SCD median: $57,612 vs NSCD: $54,942; Table 4).

Table 3. Demographic and present-on-admission comorbidities of patients undergoing total hip and total knee arthroplasty according to sickle cell disease status.

Characteristic	Hip			Knee		
	Sickle cell disease (%)	Nonsickle cell disease (%)	p-value	Sickle cell disease (%)	Nonsickle cell disease (%)	p-value
Total	810 (0.2)	498,907 (99.8)		190 (0)	922,303 (100)	
Age (mean, SD)	39.44 (14.57)	65.87 (12.25)	<0.0001	58.46 (11.53)	66.92 (10.14)	<0.0001
Female	478 (59)	282,645 (56.7)	0.1757	138 (72.6)	582,518 (63.2)	0.0068
Race			<0.0001			<0.0001
– White	35 (4.3)	410,621 (82.3)		17 (8.9)	708,841 (76.9)	
– Black	667 (82.3)	34,765 (7)		154 (81.1)	74,121 (8)	
– Hispanic	48 (5.9)	24,179 (4.8)		<11 (<5.8)	72,811 (7.9)	
– Other	44 (5.4)	18,503 (3.7)		<11 (<5.8)	41,953 (4.5)	
– Missing	16 (2)	10,839 (2.2)		<11 (<5.8)	24,577 (2.7)	
Year of surgery			0.0037			0.2059
– 2007	99 (12.2)	60,413 (12.1)		18 (9.5)	119,075 (12.9)	
– 2008	83 (10.2)	62,231 (12.5)		19 (10)	124,540 (13.5)	
– 2009	98 (12.1)	67,311 (13.5)		30 (15.8)	129,016 (14)	
– 2010	104 (12.8)	71,053 (14.2)		28 (14.7)	136,806 (14.8)	
– 2011	113 (14)	73,130 (14.7)		22 (11.6)	135,658 (14.7)	
– 2012	115 (14.2)	50,664 (10.2)		24 (12.6)	88,767 (9.6)	
– 2013	87 (10.7)	54,793 (11)		25 (13.2)	92,749 (10.1)	
– 2014	111 (13.7)	59,312 (11.9)		24 (12.6)	95,692 (10.4)	
Insurance			<0.0001			<0.0001
– Medicare	240 (29.6)	276,537 (55.4)		102 (53.7)	542,052 (58.8)	
– Medicaid	253 (31.2)	18,851 (3.8)		27 (14.2)	29,653 (3.2)	
– Private	264 (32.6)	186,209 (37.3)		56 (29.5)	306,151 (33.2)	
– Other	34 (4.2)	13,022 (2.6)		<11 (<5.8)	39,600 (4.3)	
– Uninsured	19 (2.3)	4288 (0.9)		0 (0.0)	4847 (0.5)	
State			<0.0001			<0.0001
– California	101 (12.5)	119,631 (24)		23 (12.1)	232,327 (25.2)	
– Florida	289 (35.7)	153,087 (30.7)		54 (28.4)	286,738 (31.1)	
– Kentucky	13 (1.6)	33,508 (6.7)		<11 (<5.8)	77,951 (8.5)	
– Maryland	143 (17.7)	41,627 (8.3)		52 (27.4)	89,456 (9.7)	
– New York	264 (32.6)	151,054 (30.3)		53 (27.9)	235,831 (25.6)	
Median household income by zipcode			<0.0001			<0.0001
– First quartile	305 (37.7)	89,250 (17.9)		79 (41.6)	188,878 (20.5)	
– Second quartile	172 (21.2)	117,543 (23.6)		41 (21.6)	231,966 (25.2)	
– Third quartile	153 (18.9)	132,174 (26.5)		35 (18.4)	246,651 (26.7)	
– Fourth quartile	128 (15.8)	149,428 (30)		25 (13.2)	237,313 (25.7)	
– Missing	52 (6.4)	10,512 (2.1)		<11 (<5.8)	17,495 (1.9)	
Emergent operation			<0.0001			<0.0001
– Emergency	85 (10.5)	17,733 (3.6)		<11 (<5.8)	3970 (0.4)	
– Nonemergent	624 (77.0)	361,318 (72.4)		165 (86.8)	685,442 (74.3)	
– Other or missing	101 (12.5)	119,856 (24.0)		<30 (<15.8)†	232,891 (25.3)	
Hospital volume			0.0531			0.0907
– First quartile	227 (28.0)	123,425 (24.7)		51 (26.8)	228,420 (24.8)	
– Second quartile	207 (25.6)	125,085 (25.1)		48 (25.3)	230,918 (25)	
– Third quartile	198 (24.4)	122,876 (24.6)		57 (30.0)	229,452 (24.9)	
– Fourth quartile	178 (22.0)	127,521 (25.6)		34 (17.9)	233,513 (25.3)	

†Masked to avoid getting the exact number of emergent procedures [13].
SD: Standard deviation.

Table 3. Demographic and present-on-admission comorbidities of patients undergoing total hip and total knee arthroplasty according to sickle cell disease status (cont.).

Characteristic	Hip			Knee		
	Sickle cell disease (%)	Nonsickle cell disease (%)	p-value	Sickle cell disease (%)	Nonsickle cell disease (%)	p-value
Elixhauser index grouped			<0.0001			<0.0001
– Less than 0	145 (17.9)	121,811 (24.4)		53 (27.9)	271,967 (29.5)	
– 0	448 (55.3)	265,373 (53.2)		72 (37.9)	466,719 (50.6)	
– 1 or more	217 (26.8)	111,723 (22.4)		65 (34.2)	183,617 (19.9)	
Elixhauser comorbidities						
– Congestive heart failure	15 (1.9)	11,151 (2.2)	0.4609	14 (7.4)	18,024 (2)	<0.0001
– Valvular disease	27 (3.3)	20,695 (4.1)	0.2452	<11 (<5.8)	34,534 (3.7)	0.6703
– Pulmonary circulation disorders	34 (4.2)	3879 (0.8)	<0.0001	<11 (<5.8)	6017 (0.7)	0.0007
– Peripheral vascular disorders	<11 (<1.4)	12,346 (2.5)	0.0015	<11 (<5.8)	19,603 (2.1)	0.6286
– Hypertension, uncomplicated	165 (20.4)	269,323 (54)	<0.0001	105 (55.3)	570,812 (61.9)	0.06
– Hypertension, complicated	34 (4.2)	22,820 (4.6)	0.6083	17 (8.9)	42,470 (4.6)	0.0043
– Paralysis	<11 (<1.4)	873 (0.2)	0.7258	<11 (<5.8)	1032 (0.1)	0.0877
– Other neurological disorders	22 (2.7)	11,463 (2.3)	0.4272	<11 (<5.8)	18,568 (2.0)	0.928
– Chronic pulmonary disease	100 (12.3)	69,845 (14)	0.1752	36 (18.9)	133,660 (14.5)	0.0811
– Diabetes, uncomplicated	30 (3.7)	63,275 (12.7)	<0.0001	38 (20.0)	174,511 (18.9)	0.7042
– Diabetes, complicated	<11 (<1.4)	5996 (1.2)	0.2287	<11 (<5.8)	16,351 (1.8)	0.4519
– Hypothyroidism	27 (3.3)	66,710 (13.4)	<0.0001	21 (11.1)	138,594 (15.0)	0.1253
– Renal failure	38 (4.7)	22,020 (4.4)	0.7006	15 (7.9)	38,880 (4.2)	0.0116
– Liver disease	24 (3.0)	5734 (1.1)	<0.0001	<11 (<5.8)	9111 (1)	0.4101
– Peptic ulcer disease excluding bleeding	0 (0.0)	91 (0)	0.7007	0 (0.0)	196 (0)	0.8407
– AIDS/HIV	<11 (<1.4)	1104 (0.2)	0.0994	0 (0.0)	333 (0)	0.7933
– Lymphoma	<11 (<1.4)	2044 (0.4)	0.861	<11 (<5.8)	2079 (0.2)	0.3819
– Metastatic cancer	0 (0.0)	1876 (0.4)	0.0804	0 (0.0)	699 (0.1)	0.7042
– Solid tumor without metastasis	<11 (<1.4)	3802 (0.8)	0.0366	<11 (<5.8)	4509 (0.5)	0.941
– Rheumatoid arthritis/collagen vascular diseases	25 (3.1)	21,039 (4.2)	0.1096	29 (15.3)	39,771 (4.3)	<0.0001
– Coagulopathy	30 (3.7)	7206 (1.4)	<0.0001	<11 (<5.8)	10,949 (1.2)	<0.0001
– Obesity	49 (6.0)	75,454 (15.1)	<0.0001	37 (19.5)	20,4376 (22.2)	0.3728
– Weight loss	<11 (<1.4)	1989 (0.4)	0.6677	<11 (<5.8)	1452 (0.2)	<0.0001
– Fluid and electrolyte disorders	34 (4.2)	16,868 (3.4)	0.199	13 (6.8)	25,057 (2.7)	0.0005
– Blood loss anemia	<11 (<1.4)	2447 (0.5)	0.0432	<11 (<5.8)	3799 (0.4)	0.168
– Deficiency anemia	78 (9.6)	37,415 (7.5)	0.0215	26 (13.7)	63,000 (6.8)	0.0002
– Alcohol abuse	<11 (<1.4)	8352 (1.7)	0.212	<11 (<5.8)	7911 (0.9)	0.2811
– Drug abuse	44 (5.4)	4339 (0.9)	<0.0001	<11 (<5.8)	4865 (0.5)	<0.0001
– Psychoses	18 (2.2)	8043 (1.6)	0.1685	<11 (<5.8)	16,021 (1.7)	0.3454
– Depression	57 (7.0)	50,688 (10.2)	0.0033	17 (8.9)	102,605 (11.1)	0.3398

†Masked to avoid getting the exact number of emergent procedures [13].
SD: Standard deviation.

Table 4. Outcome measures for patients undergoing total hip and total knee arthroplasty by sickle cell disease status.

Outcomes	Hip			Knee		
	Sickle cell disease (%)	Nonsickle cell disease (%)	p-value	Sickle cell disease (%)	Nonsickle cell disease (%)	p-value
Total	810 (0.2)	498,907 (99.8)		190 (0)	922,303 (100)	
30-day readmission	114 (17.6)	22,049 (5.4)	<0.0001	21 (15.6)	36,744 (5)	<0.0001
90-day readmission	226 (34.9)	41,138 (10)	<0.0001	37 (27.4)	68,586 (9.3)	<0.0001
Length of stay, median	5 (3; 7)	3 (3; 4)	<0.0001	4 (3; 5)	3 (3; 4)	<0.0001
Total charges, median (in 2016 USD)	66,444 (43,149; 97,326)	58,355 (39,831; 80,045)	<0.0001	57,612 (31,544; 83,730)	54,942 (35,877; 75,633)	0.4743
In-hospital mortality	<11 (<1.4)	778 (0.2)	0.5123	<11 (<5.8)	654 (0.1)	0.0185
Postoperational complications						
Cardiovascular	11 (1.4)	7273 (1.5)	0.8129	<11 (<5.8)	15,689 (1.7)	0.6666
Pulmonary	37 (4.6)	12,510 (2.5)	0.0002	16 (8.4)	23,420 (2.5)	<0.0001
Infectious	26 (3.2)	8016 (1.6)	0.0003	<11 (<5.8)	11,885 (1.3)	0.0224
Intraoperative	<11 (<1.4)	2433 (0.5)	0.3255	<11 (<5.8)	3820 (0.4)	0.8098
Gastrointestinal	<11 (<1.4)	2429 (0.5)	0.6341	<11 (<5.8)	3038 (0.3)	0.6357
Minor complication	61 (7.5)	18,650 (3.7)	<0.0001	<11 (<5.8)	27,654 (3.0)	0.0672
Major complication	38 (4.7)	15,247 (3.1)	0.0069	11 (5.8)	26,583 (2.9)	0.0166

Table 5. Risk-adjusted outcomes according to sickle cell disease status among patients undergoing total hip and total knee arthroplasty.

Outcome	Hip and knee	Hip	Knee
30-day readmission	3.79 (3.07–4.66)†	4.16 (3.27–5.30)†	2.74 (1.76–4.28)†
90-day readmission	4.15 (3.55–4.86)†	4.60 (3.82–5.53)†	2.88 (1.97–4.23)†
In-hospital mortality	6.54 (2.06–20.71)†	5.74 (1.27–26.05)§	8.72 (1.23–61.95)§
Minor complication	2.07 (1.57–2.73)†	2.34 (1.74–3.15)†	1.31 (0.60–2.85)
Major complication	2.68 (1.89–3.79)†	3.00 (2.01–4.48)†	2.08 (1.13–3.83)§
Length of stay	1.47 (1.40–1.53)†	1.52 (1.45–1.60)†	1.21 (1.13–1.28)†
Total charges in 2016 dollars	1.20 (1.16–1.24)†	1.22 (1.18–1.26)†	1.12 (1.07–1.18)†

†$p \leq 0.005$.
§$p \leq 0.05$.

Adjusted outcomes

Multivariate logistic regression models were constructed for primary and secondary outcomes while controlling for the patient (gender, age, race and ethnicity, median household incomes level and POA comorbidity index), hospital (volume and state) and surgery (year and type) characteristics (Table 5). In the pooled analysis, SCD status was associated with 279% higher odds of 30-day readmission (OR: 3.79; 95% CI: 3.07–4.66) and 315% higher odds of 90-day readmission (OR: 4.15; 95% CI: 3.55–4.86), when compared with non-SCD status. The SCD patients also had higher in-hospital mortality (OR: 6.54; 95% CI: 2.06–20.71), major complications (OR: 2.68; 95% CI: 1.89–3.79), minor complications (OR: 2.07; 95% CI: 1.57–2.73), longer LOS (OR: 1.47; 95% CI: 1.40–1.53) and higher total hospital charges (OR: 1.20; 95% CI: 1.16–1.24). Stratified models of primary outcomes by surgery group were conducted. Same patterns were found in the THA and TKA only groups: in the THA group, compared with NSCD patients, SCD patients had higher adjusted odds of 30-day readmission (OR: 4.16; 95% CI: 3.27–5.30), 90-day readmission (OR: 4.60; 95% CI: 3.82–5.53), in-hospital mortality (OR: 5.74; 95% CI: 1.27–26.05), minor complications (OR: 2.34; 95% CI: 1.74–3.15), major complications (OR: 3.00; 95% CI: 2.01–4.48), LOS (OR: 1.52; 95% CI: 1.45–1.60), and total charges (OR: 1.22; 95% CI: 1.18–1.26). For patients who had TKA, when compared with NSCD status, SCD status was associated with higher 30-day readmission (OR: 2.74; 95% CI: 1.76–4.28), 90-day readmission (OR: 2.88; 95% CI: 1.97–4.23), in-hospital mortality (OR: 8.72; 95% CI: 1.23–61.95), major complications (OR: 2.08; 95% CI: 1.13–3.83), LOS (OR: 1.21; 95% CI: 1.13–1.28) and total hospital charges (OR: 1.12; 95% CI: 1.07–1.18). However, patients with

SCD did not have significantly higher postoperative minor complications after TKA compared with those without SCD.

Because 82.1% of SCD patients in our study population are black, separate subgroup analyses were done with only black patients. Results showed higher 30-day readmission rate (OR: 3.09; 95% CI: 2.44–3.91; $p < 0.005$) and 90-day readmission rate (OR: 3.86; 95% CI: 3.26–4.57; $p < 0.005$), as well as, more major complications (OR: 1.87; 95% CI: 1.32–2.64; $p < 0.005$) and minor complications (OR: 1.82; 95% CI: 1.37–2.42; $p < 0.005$), longer LOS (OR: 1.43; 95% CI: 1.37–1.49; $p < 0.005$) and higher total cost (OR: 1.20; 95% CI: 1.16–1.24; $p < 0.005$) in the black SCD patients than in the black NSCD patients. In-hospital mortality was statistically underpowered in this subset analysis.

To further study the potential confounding effects of emergent surgery status, stratified analysis was conducted in the emergent surgery group and elective surgery group. The OR of 30- and 90-day readmissions in sickle cell patients who underwent emergent total hip and knee surgeries compared with NSCD patient are 4.21 (95% CI: 2.52–7.03), and 5.33 (95% CI: 3.51–8.10), respectively. The OR of 30- and 90-day readmissions in sickle cell patients who underwent elective total hip and knee surgeries are 3.17 (95% CI: 2.50–4.03) and 3.48 (95% CI: 2.91–4.17), respectively. When only including cases only from hospitals where at least one patient with SCD was discharged with a THA or TKA procedure at any point during the study period, the OR of 30- and 90-day readmissions in sickle cell patients compared with NSCD patients are 3.67 (95% CI: 2.98–4.53) and 4.05 (95% CI: 3.45–4.74). Results of additional sensitivity analyses in which the confounder of surgical type (elective, emergency, missing) was included as a model covariate, confirmed our main findings. Additionally, sensitivity analysis based upon removing age from the models (most significant variable based upon model's Wald statistic) in order to control for potentially unmeasured confounders did not substantially affect the estimated effect of SCD on outcomes of THA and TKA [13,19].

Discussion

In the present study, we found that between the years 2007 and 2014 patients with SCD who underwent primary TKA or THA in California, Florida, New York, Maryland and Kentucky experienced significantly worse health outcomes than patients without SCD. Patients with SCD had higher unadjusted rates and higher adjusted odds of 30- and 90-day readmission rates after both THA and TKA procedures. This adjusted result accounted for baseline demographic, procedural and hospital related factors. When compared with NSCD patients, SCD patients experienced higher unadjusted rates of major and minor complications, and longer median LOS following both THA and TKA procedures. In addition, SCD patients had higher unadjusted hospital charges after THA. Sensitivity analyses and stratified models by race, surgery type, surgical urgency confirmed the strength of the associations between SCD and the 30- and 90-day readmission rates, as well as other health outcomes following THA and TKA, showing our results to be consistent and robust. Our stratified analyses on emergent surgery status corroborated our findings and showed increased odds of 30- and 90-day readmissions in both the emergent and elective groups, suggesting that there are increased 30- and 90-day readmissions in SCD patient who underwent total hip and knee replacements independent of emergent surgery status.

These findings are consistent with previous literature reporting worse perioperative outcomes in the SCD patient population. Using the Nationwide Inpatient Sample, Dinan *et al.* found that SCD patients who had undergone cholecystectomy or hip replacement during the years 2002–2005 had longer LOS and higher hospital charges [8]. Kamble *et al.* reported similar results of higher costs and longer LOS in SCD patients who underwent hysterectomy, appendectomy and knee replacement [21]. Perfetti *et al.* showed that SCD patients who underwent THA or TKA between 1998 and 2010 had higher postoperative complications rates, longer LOS and higher hospital charges [11]. Hernigou *et al.* reported that SCD patients experienced more major medical complications after THA, including postoperative sickling crises, transfusion reactions, acute chest syndrome, deep vein thrombosis and pulmonary embolism, as well as, surgical complications, such as femoral perforation, repeat fixation of the cup, wound hematoma, peroneal nerve palsy, heterotopic ossification, wound infection, isolated acetabular wear, aseptic acetabular and femoral loosening [22].

Readmission rates have been adopted by Centers for Medicare and Medicaid Services as a quality measure for orthopedic procedures under the Hospital Readmission Reduction Program of the Affordable Care Act [23–25]. Studies suggest using readmission rates as a surrogate for the quality of inpatient and outpatient care, as well as, quality of transition of care [12,13,26].

The current study featured two lower extremity orthopedic procedural types – THA and TKA. Our analysis of readmission data in patients who underwent THA found that 17.6 and 34.9% of SCD patients were readmitted at 30- and 90-day post discharge, respectively, compared with 5.4 and 10% of NSCD patients. These results are comparable with previous findings reported in the literature. For example, in a study using California statewide data of 6237 patients, Adesina *et al.* found higher 30- and 90-day readmission rates (14 and 28%, respectively) following THA in SCD patients compared with NSCD patients. The study also identified the most common causes for unplanned readmissions, including vaso-occlusive crises, venous thromboembolism, infection and prosthesis malfunction. In addition to THA, our study found that SCD patients undergoing TKA also experienced increased 30- and 90-day readmission rates (15.6 and 27.4%, respectively) when compared with NSCD patients (5.0 and 9.3%, respectively). To the best of our understanding, no previous study has evaluated the readmission rates in this subset of patients who underwent TKA.

To our knowledge, the present study features the most up-to-date analysis of healthcare outcomes in SCD patients undergoing major lower extremity orthopedic procedures. The use of the SID from the HCUP administrative datasets allowed us to include a large number of patient records from multiple states and multiple years. Therefore, our results are widely generalizable across hospitals and primary payer types. Additionally, the large sample size enabled us to control for a wide range of potential demographic and comorbidity confounders, as well as, to conduct sophisticated sensitivity analysis to validate our regression models.

Our findings suggest that disparate health outcomes exist between SCD and NSCD patients following TKA and THA. Briefly and beyond the scope of this paper and our analysis, as SCD can have multisystem effects, preoperative assessment of anemia, cardiorespiratory disease, renal dysfunction, chronic pain and opioid use, and cerebrovascular accident could be helpful in reducing negative outcomes [27]. Studies evaluating the use of perioperative erythrocyte transfusions and types of anesthetic technique (general vs regional) have had inconsistent results [28,29]. Future research endeavors could focus on perioperative management of complications using a multidisciplinary approach.

Our study has several limitations. Although our use of POA indicators from the SID allows us to separate patients' comorbidities from complications, we have limited information on direct causes for hospital readmissions. This limits our ability to analyze the causes of readmissions at 30 and 90 days. Only 1% of our patient population had SCD, making some stratified analyses underpowered, especially when outcomes were rare. We cannot separate out the possibilities that the higher hospital charges for SCD patients, especially for THA surgeries, are due to additional precautions or increased hospital resource utilization. The accuracy of our study results depends on the validity of the HCUP dataset, which in turn relies on the completeness and correctness of clinical coding. Another limitation is that physicians may misdiagnose SCT as SCD. In a study of self-reported SCD, only 5.9% of a population studied in the southeastern USA who self-reported having SCD were confirmed genetically to have SCD [30]. However, by using a well-validated administrative dataset such as SID and ICD-9 diagnoses codes commonly used in other HCUP and sickle cell studies, the current study focuses on the evaluation of the effects of SCD in the patient population who carry a working diagnosis of SCD, as this is most often encountered by providers in the real clinical setting [14,31–33]. We believe that from a statistical perspective, the inclusion of SCT patients in the SCD group would bias the results toward the null hypothesis, suggesting an even more significantly negative impact of SCD on surgical outcomes of total hip and knee arthroplasties (as there is a mixing of effects).

In conclusion, we found that during the period from 2007 to 2014 in California, Florida, Kentucky, Maryland and New York, compared with NSCD patients who underwent TKA and THA, those with SCD had higher unadjusted risks and adjusted rates for 30- and 90-day readmissions. When compared with NSCD patients, SCD patients also had had longer median LOS, as well as, major and minor complications following TKA and THA. Additionally, we found that SCD patients had higher hospital charges after THA. Preoperative optimization and close monitoring in the intra- and postoperative periods are necessary to reduce these disparate health outcomes.

Financial & competing interests disclosure

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Summary points

- We used data from five states between 2007 and 2014 to compare health outcomes between patients with sickle cell disease (SCD) and those with nonsickle cell disease (NSCD) who underwent total hip and knee arthroplasties.
- Compared with NSCD patients, SCD patients had significantly worse health outcomes, including higher odds ratio (OR) of 30- and 90-day readmissions, in hospital mortality, major and minor complications, longer length of stay (LOS) and higher total hospital charges.
- Multivariate logistic regression models controlling for potential confounders were constructed for primary and secondary outcomes. Additional sensitivity analyses were run for admission types (emergent vs elective status), black race and hospital with experience with SCD patients.
- In patients who underwent total knee arthroplasty (TKA) or total hip arthroplasty (THA), SCD status was associated with 279% higher odds of 30-day readmission (OR: 3.79; 95% CI: 3.07–4.66) and 315% higher odds of 90-day readmission (OR: 4.15; 95% CI: 3.55–4.86), when compared with non-SCD status.
- In patients who underwent TKA or THA, SCD patients also had higher in-hospital mortality (OR: 6.54; 95% CI: 2.06–20.71), major complications (OR: 2.68; 95% CI: 1.89–3.79), minor complications (OR: 2.07; 95% CI: 1.57–2.73), longer LOS (OR: 1.47; 95% CI: 1.40–1.53) and higher total hospital charges (OR: 1.20; 95% CI: 1.16–1.24), when compared with non-SCD status.
- When stratified by surgery type (THA vs TKA), SCD status was associated with significantly worse primary and secondary outcomes in both the THA-only and the TKA-only groups, with the exception of minor complications in the TKA-only group.
- Subgroup analysis with only black patients confirm the results of higher 30- and 90-day readmission rates, major and minor complications, longer LOS, higher total cost in SCD patients independent of black race.
- Sensitivity analysis including admission types (emergent vs elective status) confirms the main findings.
- Sensitivity analysis with stratification by emergent admission types confirm the results of higher 30- and 90-day readmission rates in SCD patients, independent of emergent surgery status.

Ethical conduct

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

References

1 Kato GJ, Piel FB, Reid CD *et al.* Sickle cell disease. *Nat. Rev. Dis. Primers* 4, 18010 (2018).

2 Ojodu J, Hulihan MM, Pope SN, Grant AM. Centers for Disease Control and Prevention (CDC). Incidence of sickle cell trait – United States, 2010. *MMWR Morb. Mortal. Wkly. Rep.* 63(49), 1155–1158 (2014).

3 Niebuhr DW, Chen L, Shao S, Goldsmith J, Byrne C, Singer DE. Sickle cell trait prevalence among U.S. military service members: 1992–2012. *Mil. Med.* 182(3), e1819–e1824 (2017).

4 Mvundura M, Amendah D, Kavanagh PL, Sprinz PG, Grosse SD. Health care utilization and expenditures for privately and publicly insured children with sickle cell disease in the United States. *Pediatr. Blood Cancer* 53(4), 642–646 (2009).

5 Amendah DD, Mvundura M, Kavanagh PL, Sprinz PG, Grosse SD. Sickle cell disease-related pediatric medical expenditures in the U.S. *Am. J. Prev. Med.* 38(4 Suppl.), S550–S556 (2010).

6 Adesina O, Brunson A, Keegan THM, Wun T. Osteonecrosis of the femoral head in sickle cell disease: prevalence, comorbidities, and surgical outcomes in California. *Blood Adv.* 1(16), 1287–1295 (2017).

7 Mont MA, Marker DR, Zywiel MG, Carrino JA. Osteonecrosis of the knee and related conditions. *J. Am. Acad. Orthop. Surg.* 19(8), 482–494 (2011).

8 Dinan MA, Chou CH, Hammill BG *et al.* Outcomes of inpatients with and without sickle cell disease after high-volume surgical procedures. *Am. J. Hematol.* 84(11), 703–709 (2009).

9 Enayatollahi MA, Novack TA, Maltenfort MG, Tabatabaee RM, Chen AF, Parvizi J. In-hospital morbidity and mortality following total joint arthroplasty in patients with hemoglobinopathies. *J. Arthroplasty* 30(8), 1308–1312 (2015).

10 Jiang HJ, Weiss AJ, Barrett ML *et al.* Characteristics of hospital stays for super-utilizers by payer, 2012: statistical brief #190. In: *Healthcare Cost and Utilization Project (HCUP) Statistical Briefs*. Agency for Healthcare Research and Quality, MD, USA. (2006), www.ncbi.nlm.nih.gov/books/NBK310271/

11 Perfetti DC, Boylan MR, Naziri Q, Khanuja HS, Urban WP. Does sickle cell disease increase risk of adverse outcomes following total hip and knee arthroplasty? A nationwide database study. *J. Arthroplasty* 30(4), 547–551 (2015).

12 Arroyo NS, White RS, Gaber-Baylis LK, La M, Fisher AD, Samaru M. Racial/ethnic and socioeconomic disparities in total knee arthroplasty 30- and 90-day readmissions: a multi-payer and multistate analysis, 2007–2014. *Popul. Health Manag.* DOI: 10.1089/pop.2018.0025 (2018) (Epub ahead of print).

13 White RS, Sastow DL, Gaber-Baylis LK, Tangel V, Fisher AD, Turnbull ZA. Readmission rates and diagnoses following total hip replacement in relation to insurance payer status, race and ethnicity, and income status. *J. Racial Ethn. Health Disparities* 5(6), 1202–1214 (2018).

14 Steiner C, Elixhauser A, Schnaier J. The healthcare cost and utilization project: an overview. *Eff. Clin. Pract.* 5(3), 143–151 (2002).

15 Overview of the State Inpatient Databases (SID). (2018) www.hcup-us.ahrq.gov/sidoverview.jsp#about

16 Elixhauser A, Steiner C, Harris DR, Coffey RM. Comorbidity measures for use with administrative data. *Med. Care* 36(1), 8–27 (1998).

17 Quan H, Sundararajan V, Halfon P *et al.* Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Med. Care* 43(11), 1130–1139 (2005).

18 Requirements for Publishing Results with HCUP Data. (2018) www.hcup-us.ahrq.gov/db/publishing.jsp

19 Xu HF, White RS, Sastow DL, Andreae MH, Gaber-Baylis LK, Turnbull ZA. Medicaid insurance as primary payer predicts increased mortality after total hip replacement in the state inpatient databases of California, Florida and New York. *J. Clin. Anesth.* 43, 24–32 (2017).

20 Lin DY, Psaty BM, Kronmal RA. Assessing the sensitivity of regression results to unmeasured confounders in observational studies. *Biometrics* 54(3), 948–963 (1998).

21 Kamble S, Telen MJ, Dinan MA, Grussemeyer CA, Reed SD. Costs and length of stay for patients with and without sickle cell disease after hysterectomy, appendectomy, or knee replacement. *Am. J. Hematol.* 85(1), 79–81 (2010).

22 Hernigou P, Zilber S, Filippini P, Mathieu G, Poignard A, Galacteros F. Total THA in adult osteonecrosis related to sickle cell disease. *Clin. Orthop. Relat. Res.* 466(2), 300–308 (2008).

23 Centers for Medicare and Medicaid Services (CMS), HHS. Medicare program; hospital inpatient prospective payment systems for acute care hospitals and the long-term care hospital prospective payment system and fiscal year 2013 rates; hospitals' resident caps for graduate medical education payment purposes; quality reporting requirements for specific providers and for ambulatory surgical centers. final rule. *Fed. Regist.* 77(170), 53257–53750 (2012).

24 Centers for Medicare and Medicaid Services (CMS), HHS. Medicare program; hospital inpatient prospective payment systems for acute care hospitals and the long-term care hospital prospective payment system and Fiscal Year 2014 rates; quality reporting requirements for specific providers; hospital conditions of participation; payment policies related to patient status. Final rules. *Fed. Regist.* 78(160), 50495–51040 (2013).

25 The Patient Protection and Affordable Care Act. DC, USA. www.healthcare.gov/where-can-i-read-the-affordable-care-act/

26 Benbassat J, Taragin M. Hospital readmissions as a measure of quality of health care: advantages and limitations. *Arch. Intern. Med.* 160(8), 1074–1081 (2000).

27 O'Meara M, Davies G. Anaesthesia for patients with sickle cell disease (and other haemoglobinopathies). *Anaesth. Intensive Care Med.* 14(2), 54–56 (2013).

28 Firth PG, Head CA. Sickle cell disease and anesthesia. *Anesthesiology* 101(3), 766–785 (2004).

29 Khurmi N, Gorlin A, Misra L. Perioperative considerations for patients with sickle cell disease: a narrative review. *Can. J. Anaesth.* 64(8), 860–869 (2017).

30 Bean CJ, Hooper WC, Ellingsen D, DeBaun MR, Sonderman J, Blot WJ. Discordance between self-report and genetic confirmation of sickle cell disease status in African–American adults. *Public Health Genomics* 17(3), 169–172 (2014).

31 Brousseau DC, Owens PL, Mosso AL, Panepinto JA, Steiner CA. Acute care utilization and rehospitalizations for sickle cell disease. *JAMA* 303(13), 1288–1294 (2010).

32 Panepinto JA, Brousseau DC, Hillery CA, Scott JP. Variation in hospitalizations and hospital length of stay in children with vaso-occlusive crises in sickle cell disease. *Pediatr. Blood Cancer* 44(2), 182–186 (2005).

33 Steiner CA, Miller JL. Sickle cell disease patients in US hospitals, 2004: statistical brief #21. In: *Healthcare Cost and Utilization Project (HCUP) Statistical Briefs*. Agency for Healthcare Research and Quality(US), MD, USA. (2006) Available from: www.ncbi.nlm.nih.gov/books/NBK63489/

34 Ilyas I, Alrumaih HA, Rabbani S. Noncemented total hip arthroplasty in sickle-cell disease: long-term results. *J. Arthroplasty* 33(2), 477–481 (2018).

35 Kamble S, Telen MJ, Dinan MA, Grussemeyer CA, Reed SD. Costs and length of stay for patients with and without sickle cell disease after hysterectomy, appendectomy, or knee replacement. *Am. J. Hematol.* 85(1), 79–81 (2010).

36 Hernigou P, Zilber S, Filippini P, Mathieu G, Poignard A, Galacteros F. Total THA in adult osteonecrosis related to sickle cell disease. *Clin. Orthop. Relat. Res.* 466(2), 300–308 (2008).

37 Kalacy A, Ozkan C, Togrul E. Revision hip arthroplasty in sickle cell disease. *Ann. Saudi Med.* 27(2), 112–117 (2007).

38 Lau MW, Blinder MA, Williams K, Galatz LM. Shoulder arthroplasty in sickle cell patients with humeral head avascular necrosis. *J. Shoulder Elbow Surg.* 16(2), 129–134 (2007).

39 Al-Mousawi F, Malki A, Al-Aradi A, Al-Bagali M, Al-Sadadi A, Booz MM. Total hip replacement in sickle cell disease. *Int. Orthop.* 26(3), 157–161 (2002).

40 Moran MC, Huo MH, Garvin KL, Pellicci PM, Salvati EA. Total hip arthroplasty in sickle cell hemoglobinopathy. *Clin. Orthop. Relat. Res.* 294, 140–148 (1993).

41 Acurio MT, Friedman RJ. Hip arthroplasty in patients with sickle-cell haemoglobinopathy. *J. Bone Joint Surg. Br.* 74(3), 367–371 (1992).

42 Clarke HJ, Jinnah RH, Brooker AF, Michaelson JD. Total replacement of the hip for avascular necrosis in sickle cell disease. *J. Bone Joint Surg. Br.* 71(3), 465–470 (1989).

43 Bishop AR, Roberson JR, Eckman JR, Fleming LL. Total hip arthroplasty in patients who have sickle-cell hemoglobinopathy. *J. Bone Joint Surg. Am.* 70(6), 853–855 (1988).

44 Adam S, Jonassaint J, Kruger H *et al.* Surgical and obstetric outcomes in adults with sickle cell disease. *Am. J. Med.* 121(10), 916–921 (2008).

45 Ilyas I, Moreau P. Simultaneous bilateral total hip arthroplasty in sickle cell disease. *J. Arthroplasty* 17(4), 441–445 (2002).

46 Vichinsky EP, Neumayr LD, Haberkern C *et al.* The perioperative complication rate of orthopedic surgery in sickle cell disease: report of the National Sickle Cell Surgery Study Group. *Am. J. Hematol.* 62(3), 129–138 (1999).

47 Sanjay BK, Moreau PG. Bipolar hip replacement in sickle cell disease. *Int. Orthop.* 20(4), 222–226 (1996).