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Research Paper

Hereditary hemochromatosis is associated with increased use of joint replacement surgery: Results of a nationwide analysis

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ABSTRACT

Background: Hereditary hemochromatosis (HH) may lead to iron deposition–mediated arthropathy, causing progressive joint degeneration, necessitating replacement arthroplasty. Studies have noted an increased need for replacement arthroplasty in patients with HH. We aimed to compare the use of replacement arthroplasty and inpatient economic burden in patients with and without HH.

Methods: For our retrospective cohort study, we used the 2014 Nationwide Inpatient Sample. Patients with an *International Classification of Diseases*, Ninth Revision code for HH were included. The primary outcome was use of replacement arthroplasty; secondary outcomes were hospital length of stay, hospital costs, and total hospitalization charges. Multivariate logistic regression yielded confounder-adjusted odds ratios (ORs) and means.

Results: Of 18,250 patients with HH, 7,483 (41.0%) were women and 1,155 (6.3%) underwent replacement arthroplasty. Mean (SD) age for patients with HH and arthroplasty was 66 (18) years. The percentage of patients with HH who underwent replacement arthroplasty was higher than those without HH (3.4%; $P<.01$). On multivariate analysis, young-adult females and elderly patients with HH were more likely to undergo replacement arthroplasty compared to those without HH of the corresponding gender and age group. Mean length of stay, hospital costs, and total hospitalization charges were increased only in young adult females.

Conclusions: HH is associated with increased odds of replacement arthroplasty, particularly in the elderly, which can potentially suggest faster arthropathy progression in this age group and should raise awareness in clinicians taking care of patients with HH. Future research should identify factors mediating arthropathy progression in patients with HH.

Introduction

Hereditary hemochromatosis (HH) is an autosomal recessive disorder involving the *HFE* gene that disrupts the normal mechanisms of iron regulation, leading to increased serum iron levels that overwhelm the serum transferrin buffer and deposit in a variety of tissues, including the liver, pancreas, brain, skin, and joints, where it induces end-organ disease through oxidative damage [1]. Approximately 1 in 225 whites in the United States are homozygous for the C282Y *HFE* gene variant, with this genotype accounting for greater than 80% of the HH population [2,3]. Between 70% and 80% of individuals with HH report symptoms of arthropathy involving the metacarpophalangeal, ankle, knee, hip, or proximal interphalangeal joints by the time they reach the fifth or sixth decade of life [4,5]. Patients with HH also have an associated elevated risk of large-joint involvement, which may later necessitate joint replacement surgery [6]. Specifically, C282Y mutation carriers have been noted to have significantly higher attendance rates to rheumatology and joint replacement clinics compared to patients without the mutation [7]. As a result of progressive arthritic changes evidenced by worsening symptoms and pathologic radiographic changes, patients with HH undergo joint replacement surgeries at a rate of up to 16% [5]. Moreover, patients with HH are more likely than the general population to require multiple joint replacements, and patients homozygous for C282Y are more than 6 times as likely to require revision for noninfectious loosening of a prosthetic joint following total hip arthroplasty [5,8]. Progressive joint disease and the necessity for joint replacement surgery represent considerable morbidity and may impose a financial burden on the patient, while stressing health care resources. Prior studies aimed at determining the frequency of replacement arthroplasty in patients with HH have been

Abbreviations: aOR, adjusted odds ratio; HCUP, Healthcare Cost and Utilization Project; HH, hereditary hemochromatosis; ICD-9-CM, *International Classification of Diseases*, Ninth Revision, Clinical Modification; NIS, National (Nationwide) Inpatient Sample; OR, odds ratio.

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based on small patient populations and may not accurately represent the scope of the problem [5,9]. Therefore, the aim of our study is to determine the frequency of joint replacement within the HH population using a large national database.

Materials and methods

Study design and data source

All patients included in our retrospective cohort study were selected from the National (Nationwide) Inpatient Sample (NIS), a database developed and maintained by the Healthcare Cost and Utilization Project (HCUP), sponsored by the Agency for Healthcare Research and Quality. The NIS is the largest publically available, inpatient, all-payer database in the United States. For our study year, 2014, the dataset contained more than 7 million hospital stays, a 20% stratified sample of 4411 nonfederal acute care hospitals in 45 states of the United States, representative of 95% of all national hospital discharges [10].

The principal diagnosis is defined as the primary diagnosis at the time of the patient's discharge. The NIS dataset includes the principal diagnosis and 24 secondary diagnoses, which correspond to the patient's comorbidities. The dataset also contains 15 procedural codes for procedures performed during the patient's hospital stay, and well as length of stay measured in days, total hospitalization charges, and other outcome measures used to calculate inpatient disease prevalence.

Study population

All patients within the database with an *International Classification of Diseases*, Ninth Revision, Clinical Modification (ICD-9 CM) principal diagnostic code for HH (275.01) were included in our study, and were compared to all other discharges that did not have an associated ICD-9 CM diagnostic code for HH. Of this population, patients with associated arthropathy who underwent replacement arthroplasty were identified using the ICD-9 CM procedural codes for hip (81.51), knee (81.54), shoulder (81.80), and ankle (81.56) replacement. In addition, data were obtained from patients who underwent revision surgeries to their previous joint replacement procedure by using the respective ICD-9 procedural codes (00.70–73, 81.53, 00.80–84, and 81.55). Patients with secondary causes of iron overload (eg, repeated transfusion therapy) were excluded from the study.

Variable definition

Extracted data were divided into patient and hospital characteristics. Patient characteristics included age, sex, ethnicity, median household income in zip code, Charlson Comorbidity Index, and weekend admission. Hospital characteristics included hospital region, teaching status, hospital bed size, and location. The HCUP divides the United States into 4 distinct geographic locations to create census regions (ie, Northeast, Midwest, South, West).

Each patient's vital status at discharge, length of hospital stay, and total hospitalization charges were also obtained from the NIS. To enable adjustment for patient comorbidities, the Deyo adaptation of the Charlson Comorbidity Index was used, which has been validated for large database analysis [11]. The cohorts were divided into 3 distinct age groups according to their respective age range, consisting of (1) young adults (20–39 years), (2) middle-aged adults (40–59 years), and (3) elderly patients (>60 years of age). No category of patients younger than 20 years of age was included, as it contained no patients in it.

Outcomes

The primary outcome of our study was to determine the use of joint replacement therapy in the HH population when compared to the general population. All outcomes were stratified by sex and age categories. Furthermore, the odds of undergoing joint replacement were substratified by the specific joint involved (ie, hip, knee, ankle, shoulder). The secondary outcome was resource utilization, measured by hospital length of stay, total hospitalization charges, and hospital costs. Total hospital charges represent the amount of money that each hospital billed to insurance companies for each case, while hospital costs represent the amount of money invested by each institution in providing patient care. Hospital costs were calculated by multiplying the cost-to-charge ratios for the respective institutions with the total hospitalization charges. Cost-to-charge ratios are provided by the HCUP on each discharge in the database to enable this calculation.

Statistical analysis

Discharge-level weights within the NIS were used to estimate the total number of patients who had HH and underwent joint replacement surgery [10]. The Fisher exact test was used to compare proportions and the Student *t*-test was used to compare means. A hybrid multivariate logistic regression model was constructed by determining which factors had an impact on the outcome on univariate analysis, so that only relevant variables would be included in the multivariate model. If these variables impacted the outcome in any direction with a *P* value less than 0.10, they were included in the multivariate logistic regression model. On multivariate logistic regression, odds ratios (ORs) and means were adjusted for age, sex, ethnicity, Charlson Comorbidity Index, median household income in the patient's zip code, hospital region, urban location, number of hospital beds, and teaching status. All statistical analyses were conducted using STATA, version 13 (StataCorp LP).

Results

A total of 18,250 patients with HH were included in the study, of whom, 7483 (41.0%) were women and 1155 (6.3%) underwent replacement arthroplasty during the study period. In patients with HH who underwent replacement arthroplasty, mean (SD) age was 66 (18) years, with a range from 21 to 86 years.

Patient characteristics

Patients with HH who underwent joint replacement surgery did not differ in age from patients without HH who underwent joint replacement. The vast majority of patients 1074 (93.0%) with HH who underwent joint replacement were white. Although the majority of patients without HH undergoing joint replacement were also white, this ethnicity represented 83.6% of the non-HH cohort, differing at a statistically significant level. The HH cohort was primarily composed of high-income patients as compared to the more evenly-distributed income brackets in the non-HH group. The 2 cohorts were almost exclusively admitted on weekdays, but did not differ in terms of day of admission, likely because these procedures are often done on an elective basis. In regards to comorbid conditions, although patients with HH displayed lower mean Charlson Comorbidity Indices compared to patients without HH (0.58 vs 0.66, respectively), these differences were not statistically significant (Table 1).

Hospital characteristics

Patients with HH undergoing joint replacement were more evenly distributed among the 4 geographic census regions, as compared to a

Table 1
Patient and hospital characteristics for patients with and without HH.

Characteristics	HH *N* = 18,250	No HH *N* = 1208,647	*P* Value
Age, y, mean (SD)	65.5 (18)	66.7 (17)	.52
Sex, female,%	41.0	60.3	<0.01
Ethnicity,%			<0.01
White	93.1	83.6	
African American	1.1	7.1	
Hispanic	2.6	5.1	
Other	2.6	4.1	
Weekend admission,%	0.6	3.1	.04
Income in zip code,%			
≤$37,999	14.1	21.3	<0.01
$38,000–47,999	31.2	28.3	
$48,000–63,999	21.2	25.8.1	
≥$64,000	34.5	24.6	
Charlson Comorbidity Index score,%			
0	60.6	57.7	.53
1–2	35.3	36.1	
≥3	4.1	7.2	
Region,%			
Northeast	25.3	18.1	<0.01
Midwest	21.92	25.7	
South	27.6	35.8	
West	25.2	20.4	
Urban location,%	89.9	90.2	.68
Hospital bed size,%			.87
Small	27.4	27.1	
Medium	27.8	28.7	
Large	44.8	44.2	
Hospital teaching status,%			.78
Teaching	60.8	60.1	
Non-teaching	39.2	39.9	

Abbreviation: HH, hereditary hemochromatosis.

predominance of the southern region in patients without HH. The vast majority of patients in both cohorts were seen at urban centers, which also shared the characteristics of being teaching institutions composed mostly of large bed size centers (Table 1).

Outcomes

Primary outcome

During the study period, 1155 (6.3%) patients with HH underwent replacement arthroplasty, compared to 3.4% of the non-HH population ($P<.01$). When stratifying by anatomical site of joint replacement, male patients with HH had significantly higher unadjusted rates of hip, knee, and ankle replacements than those without HH, but there was no difference in rate of shoulder replacement (Table 2 and Fig. 1).

Table 2
Joint replacement surgery in patients with and without HH, with special attention to hip, knee, shoulder, and ankle replacement (unadjusted).

Joint Replacement Type	HH	No HH	*P* Value
All, (%)	1155 (6.3)	1202,200 (3.4)	
Male	56.1%	41.3%	<0.01
Female	43.9%	58.7%	
Hip, (%)	511 (2.8)	388,947 (1.1)	
Male	58.1%	42.2%	<0.01
Female	41.9%	57.8%	
Knee, (%)	529 (2.9)	671,818 (1.9)	
Male	58.3%	41.9%	<0.01
Female	41.6%	58.1%	
Ankle, (%)	18 (0.1)	4415 (<0.01)	
Male	59.9%	42.7%	<0.01
Female	40.1%	57.3%	
Shoulder, (%)	37 (0.2)	35,359 (0.1)	
Male	59.8%	42.6%	.12
Female	40.2%	57.4%	

Abbreviation: HH, hereditary hemochromatosis.

After adjusting for confounders on multivariate regression analysis and stratifying by sex and age group, young adult female and elderly male and female patients with HH displayed increased adjusted OR (aOR) of undergoing joint replacement surgery compared to the non-HH population of corresponding sex and age. When stratifying for anatomic location of joint replacement arthroplasty, young adult females, middle-aged adults, and both male and female elderly patients had increased odds of hip replacement. Young adult females had increased aORs for knee replacement, while middle-aged adult male and female patients had increased odds of ankle replacement compared to patients with no HH of the corresponding sex and age (Table 3). There were no noted differences in terms of revision arthroplasty between the cohorts, stratifying by sex and age group (Table 4).

Resource utilization

Resource utilization was measured in terms of hospital length of stay, hospital costs, and total hospitalization charges. Comparatively, the 2 cohorts did not differ in unadjusted resource utilization measures (Table 5).

After adjusting for confounders on multivariate regression analysis and stratifying by sex and age group, both male and female young adults with HH displayed increased hospital length of stay, while young adult female patients had increased total hospital costs and total hospitalization charges compared to patients without HH of their corresponding age and sex who underwent joint replacement surgery (Table 6).

Discussion

Young adult female patients (20–39 years) and both male and female elderly patients with HH were found to be more likely to undergo joint replacement surgery when compared to patients without HH of their respective sex and age group. Despite the greater association with joint replacement surgery in young adult females and male and female elderly patients, only young adult females displayed increased resource utilization compared to non-HH patients of their corresponding sex and age group who underwent joint replacement surgery.

The positive association we found between HH and joint replacement surgery is consistent with previous studies. The Swedish National Patient Register, a large retrospective study, found that 5.7% of patients with HH underwent joint replacement or fusion of the hip, knee, or ankle over the course of 16,270 person-years [9]. Another cross-sectional prospective study found that 16.1% of 199 patients with HH underwent total replacement arthroplasty for severe osteoarthritis, with an OR of 9.0 [5]. The difference in magnitude of the aORs observed may be a product of a much smaller population of HH patients studied. Our findings were not unexpected, as arthropathy, which is often the presenting feature of the disease, is among the most common occurrences in this patient population and usually precedes the formal diagnosis by several years [4,12]. It should be noted that arthritis or any other adverse effects related to iron overload are uncommon in heterozygote patients with HH [13–15].

Our study shows that the patient cohort undergoing joint replacement arthroplasty who had HH tended to be proportionally composed of white male patients from a higher median income at their respective zip code. Despite that, on average, patients with HH had lower mean Charlson Comorbidity Indices compared to patients without HH, these differences did not reach a statistical significance.

Patients with HH are more than twice as likely to undergo hip replacement arthroplasty when compared to the general population. This is consistent with a previous study that found the rate of primary hip replacement to be 3.8% within the HH population, with a hazard ratio of 2.84 when compared to a matched cohort of patients without

Table 3
Unadjusted and adjusted OR of joint replacement surgery in patients with HH versus patients without HH, adjusted for age, sex, ethnicity, Charlson comorbidity index, median household income in the patient's zip code, hospital region, urban location, number of hospital beds, and teaching status, stratified by gender and age group.

	20–39 years old		40–59 years old		60 years or older	
	uOR (95%CI), p-value	aOR (95%CI), p-value	uOR (95%CI), p-value	aOR (95%CI), p-value	uOR (95%CI), p-value	aOR (95%CI), p-value
All	5.07 (2.11–12.20), $p<.01$	3.57 (1.47–8.69), $p<.01$	1.21 (0.93–1.58), $p=.16$	1.25 (0.93–1.67), $p=.14$	1.61 (1.38–1.88),$p<.01$	1.50 (1.28–1.76), $p<.01$
Male	1.94 (0.48–7.72), $p=.35$	1.92 (0.48–7.71), $p=.36$	1.37 (0.96–1.95), $p=.08$	1.32 (0.89–1.95), $p=.16$	1.78 (1.49–2.15), $p<.01$	1.55 (1.26–1.90), $p<.01$
Female	9.05 (2.89–28.39), $p<.01$	7.41 (2.38–23.03), $p<.01$	1.06 (0.69–1.62), $p=.79$	1.12 (0.71–1.76), $p=.61$	1.63 (1.28–2.07), $p<.01$	1.44 (1.11–1.86), $p<.01$
Hip	4.75 (1.54–14.67), $p<.01$	3.18 (1.01–9.99), $p=.05$	1.87 (1.33–2.62), $p<.01$	1.83 (1.28–2.61), $p<.01$	2.24 (1.77–2.83), $p<.01$	1.95 (1.52–2.49), $p<.01$
Male	1.36 (0.20–9.50), $p=.76$	1.33 (0.19–9.39), $p=.78$	2.10 (1.41–3.11), $p<.01$	2.05 (1.34–3.13), $p<.01$	2.49 (1.86–3.32), $p<.01$	2.11 (1.56–2.86), $p<.01$
Female	10.78 (2.65–43.74), $p<.01$	9.19 (2.28–36.97), $p<.01$	1.26 (0.63–2.54), $p=.52$	1.39 (0.68–2.82), $p=.36$	2.13 (1.46–3.10), $p<.01$	1.72 (1.15–2.61), $p<.01$
Knee	7.78 (1.92–31.45), $p<.01$	6.25 (1.55–25.25), $p=.01$	0.77 (0.50–1.16), $p=.21$	0.79 (0.50–1.25), $p=.31$	1.31 (1.06–1.61), $p=.01$	1.18 (0.94–1.47), $p=.15$
Male	5.52 (0.77–39.72), $p=.09$	5.69 (0.79–41.25), $p=.09$	0.75 (0.40–1.41), $p=.38$	0.67 (0.32–1.36), $p=.27$	1.40 (1.06–1.85), $p=.02$	1.14 (0.85–1.53), $p=.39$
Female	8.46 (1.18–60.66), p-.03	6.76 (0.96–47.99), $p=.06$	0.88 (0.50–1.57), $p=.68$	0.90 (0.48–1.67), $p=.75$	1.37 (0.99–1.88), $p=.06$	1.25 (0.89–1.75), $p=.20$
Ankle	Insufficient data*	Insufficient data*	13.61 (4.51–41.06), $p<.01$	15.85 (5.31–47.32), $p<.01$	2.36 (0.33–16.83), $p=.39$	1.89 (0.27–13.48), $p=.53$
Male	Insufficient data*	Insufficient data*	7.39 (1.13–48.32), $p=.04$	8.39 (1.30–53.98), $p=.03$	2.98 (0.41–21.37), $p=.28$	2.62 (0.36–18.78), $p=.34$
Female	Insufficient data*	Insufficient data*	23.97 (5.88–97.67), $p<.01$	28.8 (7.04–118.18), $p<.01$	Insufficient data*	Insufficient data*
Shoulder	Insufficient data*	Insufficient data*	0.59 (0.08–4.22), $p=.60$	0.61 (0.09–4.30), $p=.62$	2.08 (1.13–3.85), $p=.02$	1.55 (0.78–3.08), $p=.21$
Male	Insufficient data*	Insufficient data*	0.80 (0.11–5.71), $p=.83$	0.85 (0.12–6.09), p.88	1.71 (0.71–4.12), $p=.23$	1.52 (0.63–3.67), $p=.35$
Female	Insufficient data*	Insufficient data*	Insufficient data*	Insufficient data*	2.74 (1.14–6.58), $p=.02$	1.56 (0.50–4.83), $p=.44$

Abbreviations: uOR, unadjusted OR; aOR, adjusted odds ratio; HH, hereditary hemochromatosis.
* Insufficient data implies that the numbers were insufficient for a multivariate logistic regression model to run.

Table 4
Revision arthroplasty.

	20–39 years old		40–59 years old		60 years or older	
	uOR (95%CI), p-value	aOR (95%CI), p-value	uOR (95%CI), p-value	aOR (95%CI), p-value	uOR (95%CI), p-value	aOR (95%CI), p-value
All						
Male	Insufficient data*	Insufficient data*	0.64 (0.16–2.87), $p=.53$	0.70 (0.18–2.85), $p=.63$	0.80 (0.33–1.91), $p=.61$	0.59 (0.22–1.58), $p=.30$
Female	Insufficient data*	Insufficient data*	2.35 (0.97–5.72), $p=.06$	2.06 (0.76–5.57), $p=.16$	0.89 (0.34–2.38), $p=.83$	0.85 (0.32–2.26), $p=.74$
Hip						
Male	Insufficient data*	Insufficient data*	0.68 (0.10–4.83), $p=.70$	0.74 (0.10–5.31), $p=.77$	1.07 (0.35–3.34), $p=.90$	0.68 (0.17–2.72), $p=.59$
Female	Insufficient data*	Insufficient data*	2.52 (0.63–10.14), $p=.19$	1.35 (0.19–9.75), $p=.77$	1.19 (0.48–4.60), $p=.49$	1.41 (0.45–4.36), $p=.55$
Knee						
Male	Insufficient data*	Insufficient data*	0.61 (0.09–4.33), $p=.62$	0.68 (0.09–4.83), $p=.69$	0.57 (0.14–2.28), $p=.43$	0.53 (0.13–2.11), $p=.37$
Female	Insufficient data*	Insufficient data*	2.24 (0.72–7.00), $p=.16$	2.47 (0.79–7.74), $p=.12$	0.41 (0.06–2.89), $p=.37$	0.38 (0.05–2.74), $p=.34$

Adjusted odds ratio for revision arthroplasty in male and female patients with HH compared to patients without HH. Adjustment for age, sex, ethnicity, Charlson Comorbidity Index, median household income in the patient's zip code, hospital region, urban location, number of hospital beds, and teaching status was performed, as well as stratification for gender and age group.

Table 5
Unadjusted mean resource utilization for patients with and without HH who underwent joint replacement surgery.

Resource	HH	No HH	p-value
Length of stay, d	2.8	3.1	
Male	2.7	2.9	0.12
Female	3.0	3.2	
Hospital costs, USD	17,304	16,792	
Male	17,266	16,965	0.23
Female	17,360	16,677	
Total hospitalization charges, USD	60,316	60,093	
Male	58,469	60,536	0.08
Female	62,991	59,799	

Abbreviations: HH, hereditary hemochromatosis; USD, United States dollars.

HH within the Swedish general population [9]. Additionally, a recent study using the UK Biobank, a large volunteer cohort database from the United Kingdom, showed similar findings to our study. In that study, 1.59% of all hip replacements at baseline were homozygous for C282Y, with aORs of 2.62 and 1.90 for undergoing hip replacement in men and women with HH, respectively [16]. Similarly, a recent prospective cohort study of healthy middle-aged patients born in Australia, New Zealand, and Northern Europe demonstrated that patients homozygous for C282Y were at significantly higher risk for unilateral (5.4%; hazard ratio, 1.94) and bilateral (1.1%; OR, 5.86) primary hip replacement after adjustment for confounders [17].

Patients with HH were substantially more likely to undergo knee replacement surgery when compared to patients without HH, which was confirmed after adjusting for confounders and comparing to patients without HH. Furthermore, there were no appreciated age differences between the HH and non-HH cohorts, suggesting that HH does not necessarily speed up the joint degeneration process, but does show that joint degeneration is more likely to occur in HH. Previous studies have yielded conflicting findings when studying the association between HH and knee replacement [9,17]. Although the aforementioned prospective cohort study found an association between patients homozygous for C282Y and hip replacement, it did not find an association with total knee replacement [17]. Conversely, a large study of patients with HH showed that these patients were significantly more likely to undergo knee replacement surgery when compared to a matched cohort of patients without HH, with a hazard ratio of 2.14 [9]. Comparatively, and despite that the association between HH and knee replacement was not as strong as in other studies, our investigations did show an aOR of 1.41 of patients with HH undergoing joint replacement surgery compared to patients without HH.

Patients with HH were also substantially more likely to undergo ankle replacement when compared to the general population. Literature regarding the occurrence of ankle arthropathy in patients with HH is sparse, and it appears to be a relatively rare manifestation of joint disease in HH. For this very reason, data on ankle replacement surgery in patients with HH is also minimal. Several case reports and series have demonstrated that ankle arthropathy

Table 6
Additional resource utilization for patients with HH undergoing joint replacement surgery versus patients without HH undergoing joint replacement surgery, adjusted for age, sex, ethnicity, Charlson Comorbidity Index, median household income in the patient's zip code, hospital region, urban location, number of hospital beds, and teaching status, and stratified for gender and age group.

	20–39 years old		40–59 years old		60 years or older	
	uOR (95%CI), p-value	aOR (95%CI), p-value	uOR (95%CI), p-value	aOR (95%CI), p-value	uOR (95%CI), p-value	aOR (95%CI), p-value
Additional length of stay, d	3.34 (2.69–3.98), $p<.01$	2.67 (2.01–3.32), $p<.01$	0.47 (0.13–0.81), $p<.01$	0.29 (−0.06–0.65), $p=.10$	−0.07 (−0.31–0.17), $p=.56$	−0.04 (−0.29–0.20), $p=.72$
Male	1.95 (1.15–2.74), $p<.01$	1.81 (1.02–2.61), $p<.01$	0.23 (−0.51–0.66), $p=.30$	0.11 (−0.34–0.56), $p=.63$	−0.14 (−0.43–0.16), $p=.35$	−0.06 (−0.37–0.25), $p=.69$
Female	3.73 (2.77–4.70), $p<.01$	3.27 (2.83–4.25), $p<.01$	0.71 (0.22–1.20), $p<.01$	0.64 (0.32–1.15), $p<.01$	−0.04 (−0.42–0.35), $p=.84$	−0.01 (−0.39–0.38), $p=.97$
Additional hospital costs, USD	5497 (3511–7482), $p<.01$	3421 (1398–5445), $p<.01$	919 (−121–1960), $p=.08$	81 (−966–1130), $p=.88$	1480 (698–2262), $p<.01$	666 (−585–1917), $p=.30$
Male	983 (−765–2732), $p=.27$	575 (−1150–2302), $p=.51$	567 (−846–1980), $p=.43$	−317 (−1736–1101), $p=.66$	1105 (112–2099), $p=.03$	511 (−511–1534), $p=.33$
Female	7091 (3889–10,292), $p<.01$	5528 (2225–7223), $p<.01$	949 (−440–2339), $p=.18$	730 (−230–1852), p.22	1284 (76–2493), $p=.04$	666 (−583–1920), $p=.29$
Additional hospitalization charges, USD	21,122 (14,446–27,798), $p<.01$	12,753 (5839–19,666), $p<.01$	1021 (−1021–2262), $p=.65$	−2008 (−6463–2447), $p=.38$	4530 (971–8088), $p=.01$	1641 (−1990–5272), $p=.38$
Male	4608 (−2766–11,982), $p=.22$	3011 (−4535–10,556), $p=.43$	−1548 (−7572–4477), $p=.62$	−4748 (−10,794–1298), $p=.12$	1962 (−2480–6405), $p=.39$	473 (−4091–5035), $p=.84$
Female	26,409 (16,463–36,355), $p<.01$	13,803 (3258–15,894), $p<.01$	3085 (−2857–9027), $p=.30$	2495 (−954–4634), $p=.25$	5452 (73–10,831), $p=.05$	3609 (−1912–9130), $p=.20$

Abbreviations: HH, hereditary hemochromatosis; USD, United States dollars.

Fig. 1. Adjusted odds ratios by joint replacement subtype in patients with hereditary hemochromatosis compared to patients without hereditary hemochromatosis.

may be the presenting symptom for HH and is often painful and debilitating, but amenable to arthroplasty when identified [18–21]. A study investigated the outcomes of total knee arthroplasty in patients with HH, finding that the surgery was associated with low risk of adverse effects, produced appropriate pain relief, and restored functionality [22]. Nevertheless, the specific magnitude of the association between HH and knee replacement surgery had not been investigated, and was found in our study to be considerable. The rate of shoulder replacement was also higher in patients with HH, with a trend toward significance, a finding that has no current studies to compare to. Despite differences in joint replacement use between the cohorts, no considerable differences in economic burden or hospital length of stay were found.

Study strengths and weaknesses

The NIS is a large sample of inpatients representative of discharges within the United States, which is itself a large and heterogeneous population. Given the nature of the dataset, repeated admissions by individual patients cannot be tracked. Despite this limitation, procedural codes for joint replacements do correspond to the procedure being performed only during a single admission. Multivariate analysis allows for adjustment for confounders to yield more accurate and isolated associations between variables. However, as a retrospective, observational study, our analysis has intrinsic potential for selection bias. The administrative nature of the database, requiring identification of target populations by ICD-9-CM codes, depends on proper diagnosis and codification, which cannot be verified, as well as list maintenance. We are also unable to assess for laboratory test results or financial burden beyond the inpatient setting (ie, outpatient visits, post-discharge rehabilitation, prescription medication).

Conclusions

HH is frequently associated with considerable joint pathology, requiring joint replacement surgery at a higher rate than when HH is not present. Future research should focus on pathogenesis, early identification of patients at risk for developing arthritic changes secondary to HH, and the impact on resources that arthroplasty in HH imposes on the patient and health care institution. Prospective studies should investigate possible treatment options to slow the progression of joint disease due to HH.

Declaration of Competing Interest

None.

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