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## Retrospective Study

# Safety and outcomes of hip and knee replacement surgery in liver transplant recipients

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## Abstract

### BACKGROUND

Liver transplant (LT) is becoming increasingly common with improved life expectancy. Joint replacement is usually a safe procedure; however, its safety in LT recipients remains understudied.

### AIM

To evaluate the mortality, outcome, and 90-d readmission rate in LT patients undergoing hip and knee replacement surgery.

### METHODS

Patients with history of LT who underwent hip and knee replacement surgery between 2016 and 2019 were identified using the National Readmission Database.

### RESULTS

A total of 5046119 hip and knee replacement surgeries were identified. 3219 patients had prior LT. Mean age of patients with no history of LT was 67.51 [95% confidence interval (CI): 67.44-67.58], while it was 64.05 (95%CI: 63.55-64.54) in patients with LT. Patients with history of LT were more likely to have prolonged

length of hospital stay (17.1% *vs* 8.4%,  $P < 0.001$ ). The mortality rate for patients with no history of LT was 0.22%, while it was 0.24% for patients with LT ( $P = 0.792$ ). Patients with history of LT were more likely to have re-admissions within 90 d of initial hospitalization: 11.4% as compared to 6.2% in patients without history of LT ( $P < 0.001$ ). The mortality rate between both groups during readmission was not statistically different (1.9% *vs* 2%,  $P = 0.871$ ) respectively.

## CONCLUSION

Hip and knee replacements in patients with history of LT are not associated with increased mortality; increased re-admissions were more frequent in this cohort of patients. Chronic kidney disease and congestive heart failure appear to predict higher risk of readmission.

**Key Words:** Liver transplant; Hip replacement surgery; Knee replacement surgery

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**Core Tip:** Patients receiving liver transplants (LTs) are having longer life expectancy. This resulted in an increasing number of patients with LTs requiring hip and knee surgery, with data about their outcomes being limited. The aim of this analysis is to evaluate the safety of these procedures in LT patients and provide more guidance on expected outcomes. This study concluded that LT patients are not at risk of higher mortality albeit increased morbidity.

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## INTRODUCTION

Joint replacement surgery is one of the most performed elective surgical procedures. Both total hip arthroplasty (THA) and total knee arthroplasty (TKA) have proven to be highly beneficial orthopedic procedures[1]. Liver cirrhosis is an established risk factor for complications after THA and TKA. Patients with cirrhosis had longer lengths of stay, more frequent discharges to nursing facilities, increased 90-d readmission rate, and higher medical complications including urinary tract infections, acute kidney injury (AKI), need for blood transfusions, gastrointestinal hemorrhage, dislocations, infections, and revisions within 90 d[1]. One-year and longer-term mortality rates were higher in patients with cirrhosis. A model for end-stage liver disease score of 10 or higher predicted a three-fold increased likelihood of complications[1]. A recent meta-analysis examining 527 patients with history of liver pathology undergoing total joint arthroplasty (TJA) showed higher risk of infection and mortality[2].

Liver transplant (LT) is the only curative treatment for patients with liver cirrhosis and end stage liver disease[3]. The prevalence of liver transplantation, which ranks second only to kidney transplantation among solid organ transplantations in the United States, has increased[4]. The increasing 5-year graft survival rate of more than 70% has led to better outcomes with LT[3-5]. With increased life expectancy in the LT cohort, reduced bone mineral density, and higher risk of hip osteonecrosis from immunosuppressive drugs, this cohort becomes at higher risk of needed TKA[6-10].

Arthroplasty is generally safe in healthy, immunocompetent individuals, but its safety in LT patients remains controversial[11]. Previously, a meta-analysis examined the complication rates in 3024 LT patients undergoing THA or TKA [12]. This demonstrated that LT patients benefit functionally from both THA and TKA, but at the cost of increased infection-related complications, reoperation/revision, arthrotomy, and specific medical complications, including AKI and blood transfusion[12]. Other previous studies from small cohorts have addressed the issue of safety but had demonstrated conflicting results[13-17].

Current data describing the mortality rates and readmission rates of these patients after total joint replacement are insufficient to adequately assess complications due to the small cohort size. This makes it difficult to draw conclusions when considering the decision for joint replacement. As more LT patients seek evaluation for degenerative hip disease, a better understanding of the mortality rate and 90-d readmission rates in this high-risk cohort is needed. The aim of this study is to evaluate the mortality outcome and 90-d readmission rates in LT patients undergoing THA and TKA using the National Readmission Database (NRD). Compared to a control cohort, we hypothesize that LT patients undergoing THA or TKA will show a measurable increase in mortality and 90-d readmission rates.

## MATERIALS AND METHODS

Patients with history of LT who underwent hip and knee replacement surgery between 2016 and 2019 were included in

the study. Patients were selected from the Healthcare Cost and Utilization Project databases (HCUP). The HCUP databases are sponsored by the Agency for Healthcare Research and Quality. The NRD database is the largest HCUP database and contains unweighted data from over 7 million hospital admissions each year. The data represent a 20% random sample of participating hospital discharges from 46 states. The NRD database is de-identified and available to the public. Thus, it is not considered human subject research and is exempted from review by the institutional review board. To assure a meaningful study cohort the investigators agreed upon a minimum study cohort of 250000 admissions. The International Classification of Diseases Code, 10<sup>th</sup> Revision Clinical Modification (ICD-10) was used to identify the patients. 90-d readmission rates and diagnoses were identified ([Supplementary material](#)). Multiple logistic regression model was used to identify the factors associated with readmission.

### Statistical analysis

Continuous variables were described using mean  $\pm$  SD, while categorical variables were described using proportion (percentage). Categorical variables were compared using the Rao-Scott  $\chi^2$  test, and continuous variables were compared using a survey-weighted Student's *t*-test. Multivariate analysis was performed using logistic regression models to decrease bias and adjust for possible confounding factors. Statistical analysis was performed by a biomedical statistician. All analyses were performed using STATA BE 17.

### Inclusion criteria

The inclusion criteria including: (1) Patients > 18 years old; (2) Patient with history of LT; and (3) Patient needing hip and/or knee replacement surgery from 2016-2019.

### Exclusion criteria

The exclusion criteria including: (1) Patient < 18 years old; (2) Patient needing any other kind of transplant; (3) Patients admitted for other type of orthopedic surgeries; and (4) Patients admitted after more than 90 d of initial admission.

## RESULTS

### General characteristics

A total of 5046119 hip and knee replacement surgeries were identified between the year 2016 and 2019. 3219 patients had prior LT. Mean age of patients with no history of LT was 67.51 [95% confidence interval (CI): 67.44-67.58], while it was 64.05 (95%CI: 63.55-64.54) in patients with LT. Patients without history of LT had mean length of hospital stay (LOS) 2.87 d (95%CI: 2.84-2.91) as compared to 3.86 d (95%CI: 3.62-4.11),  $P < 0.001$ . Medicare was the most common primary expected payer. Urban teaching hospitals were the most common ([Table 1](#)).

### Outcomes

Patients with history of LT were more likely to have prolonged LOS (17.1% *vs* 8.4%,  $P < 0.001$ ), develop AKI (11.1% *vs* 3.2%,  $P < 0.001$ ), and have sepsis (1.2% *vs* 0.3%,  $P < 0.001$ ). The mortality rate for patients with no history of LT was 0.22%, while it was 0.24% for patients with LT. No significant difference was found ( $P = 0.792$ ). Patients with history of LT were more likely to have readmissions within 90 d of initial hospitalization: 11.4% compared to 6.2% in patients without history of LT ( $P < 0.001$ ). The mortality rate between both groups during readmission was not statistically different (1.9% *vs* 2%,  $P = 0.871$ ) respectively. Mortality was mainly caused by sepsis, pulmonary embolism and AKI. There was no significant statistical difference between the 2 groups in rate of prosthetic infections during readmission (10.1% *vs* 12.1%,  $P = 0.34$ ) and gastrointestinal (GI) bleed (4.7% *vs* 5.9%,  $P = 0.47$ ).

### Multivariate analysis

Multiple logistic regression analysis showed that the odds ratio (OR) for 90-d readmission in LT patients was 1.54 (95%CI: 1.29-1.84). These readmissions were statistically associated with the presence of chronic kidney disease (CKD) (OR = 1.416, 95%CI: 1.39-1.44) and underlying congestive heart failure (OR = 1.72, 95%CI: 1.69-1.76) ([Table 2](#)).

## DISCUSSION

Liver transplantation is a lifesaving treatment for patients with end-stage liver disease. With increasing advances in surgical technique, patient/graft selection, and immunosuppression, long-term survival after LT continues to improve. More LT patients are likely to become candidates for THA and TKA due to the increased risk of avascular necrosis and longer patient longevity. Postoperative complications and higher readmission rates are significant concerns in this cohort. While only a few small-cohort studies have reported postoperative complications in LT patients undergoing THA or TKA, no available data suggest readmission rates and predictors of readmissions. This study found 3219 LT patients identified among 5046119 patients who underwent hip and knee replacement surgeries between 2016 and 2019. The mean age of the LT cohort was 64.05 compared to 67.51 in the non-LT cohort. Overall, the LT cohort had a higher readmission rate at 90 d, longer hospital stays, and a higher risk of AKI and sepsis. CKD and congestive heart failure appear to predict a higher risk of readmission at 90 d. No significant difference in mortality rate, prosthesis infection, and gastrointestinal



**Table 1 Compares demographics and main outcomes between the two groups during index admission**

General characteristics	Patients with history of LT, <i>n</i> = 3218	Patients without LT, <i>n</i> = 5042901	<i>P</i> value
Mean age at admission	64.05 ± 0.49	67.51 ± 0.46	< 0.001
LOS	2.87 ± 0.03	3.86 ± 0.25	< 0.001
Mortality	8 (0.24%)	11154 (0.22%)	0.792
Primary expected payer			
1: Medicare	2104	3056650	< 0.001
2: Medicaid	189	212763	
3: Private	837	1592682	
4: Self-pay	13	26225	
5: No charge	4	3057	
6: Other	71	149442	
Location/teaching status of hospital			
1: Rural	191	498918	< 0.001
2: Urban nonteaching	509	1278335	
3: Urban teaching	2517	3268866	
CHF	263	260627	< 0.001
Renal failure	1461	434965	< 0.001
Coronary artery disease	454	661069	0.276

LT: Liver transplant; CHF: Chronic heart failure; LOS: Length of hospital stay.

**Table 2 Predictors of readmissions at 90-d (multivariate analysis)**

	Odds ratio, 95%CI	<i>P</i> value
Liver transplant	1.54 (1.29-1.83)	< 0.0001
Age	1.01 (1.009-1.01)	< 0.0001
Female	0.86 (0.85-0.87)	< 0.0001
DM	1.19 (1.16-1.22)	< 0.0001
CHF	1.72 (1.69-1.76)	< 0.0001
LOS	1.05 (1.04-1.06)	< 0.0001
Renal failure	1.42 (1.39-1.44)	< 0.0001
Rheumatoid arthritis	1.26 (1.23-1.29)	< 0.0001
Chronic pulmonary disease	1.34 (1.32-1.36)	< 0.0001
Obesity	0.98 (0.97-1.01)	0.78

Multivariate logistic regression model for predictors of readmissions at 90-d for patients with history of liver transplant. CI: Confidence interval; DM: Diabetes mellitus; CHF: Chronic heart failure; LOS: Length of hospital stay.

bleeding was observed.

Recent studies examining the outcomes of THA or TKA after LT are small and limited. There is little data on readmission rates and mortality in this population. It appears that LT patients were more likely to be readmitted within 90 d than control patients (11.4% *vs* 6.2%, *P* < 0.001). Multiple logistic regression analysis showed that the OR for 90-d readmission in LT patients was 1.54 (95%CI: 1.29-1.84). Predictors of increased 90-d readmission rates were also analyzed, including patient's age, LOS, chronic heart failure (CHF), CKD, lung disease, and diabetes mellitus with complications. Among these factors, CHF (OR = 1.72, 95%CI: 1.69-1.76, *P* < 0.001) and CKD (OR = 1.42, 95%CI: 1.39-1.44, *P* < 0.001) predicted a higher risk of readmission.

Mortality during this short follow-up period was also analyzed to better capture the mortality rate associated with TKA/THA compared to other causes. Few studies have reported short-term mortality risk. Inacio *et al*[18] reported a 1-year mortality rate of 0.5% in the 45-54 age group. Another meta-analysis reported that 1-year mortality year for the LT cohort undergoing THA or TKA was 4.35%. The observed one-year mortality rate in LT patients is more like cirrhotic patients undergoing THA and TKA, which was measured at 5% in 115 patients by Tiberi *et al*[1]. This study did not find an increased mortality rate among the LT group (0.24% in LT compared to 0.22% in controls,  $P = 0.792$ ). In addition, there was no significant difference in mortality rates between the two groups during readmission (1.9% *vs* 2%,  $P = 0.871$ ).

Suppression of humoral immunity by lifelong immunosuppressants increases postoperative complications[17,19,20]. The incidence of systemic infections, particularly sepsis and AKI was significantly increased in the LT cohort after 90 d compared to the control group. The LT cohort in our study had a higher risk of AKI than controls (11.1% *vs* 3.2%,  $P < 0.001$ ). A meta-analysis of 3024 LT patients reported a higher risk of complications in the LT group, with AKI being the highest OR among all complications[12]. The trend towards higher AKI rates has also been reported in patients with cirrhosis after arthroplasty. Tiberi *et al*[1] found a higher risk of AKI in patients with cirrhosis compared to controls after 90 d (10% *vs* 1%). In addition, significantly higher AKI rates were found in other types of transplantation. Choi *et al*[21] reported higher odds (OR = 22.25,  $P < 0.001$ ) of developing AKI in the kidney and LT after THA compared to controls. Cavanaugh *et al*[22] reported a higher incidence in the kidney (OR = 3.48) and in cardiac, lung, and pancreas transplant patients (OR = 4.42) receiving TKA and THA, while Klement *et al*[19] reported significantly higher AKI rates in the kidney (OR = 6.03), lung (13.180), heart (19.660) and pancreas (7.780) transplanted patients who received TKA at 90 d. Post operative AKI can be linked to poor patient outcomes, including increased length of stay, cost and increased probability of discharging to extended-care facilities. Additionally, postoperative AKI is responsible for 25%-90% of in-hospital deaths[23].

Increased susceptibility to systemic and local infections is a major concern in LT patients undergoing THA or TKA. A meta-analysis by Han *et al*[12] reported higher rates of local and systemic infections both at 90 d and at all time points in the LT cohort compared to the control group. Additionally, this study found that LT patients undergoing TKA, compared to those undergoing THA, had a higher rate of joint infection at all time points. Onochie *et al*[24] had similar findings, a meta-analysis of chronic liver disease patients undergoing THA *vs* controls, demonstrated infection rates of 0.5% at a mean follow-up of 13.5 mo. The finding of higher rates of infection in patients with cirrhosis after arthroplasty is a general trend. While Jiang *et al*[25] found that a diagnosis of cirrhosis is the highest independent risk factor for periprosthetic infection, Deleuran *et al*[26] reported higher rates of infection in cirrhotic patients undergoing THA or TKA at one year with an incidence of 3.1% *vs* 1.4% in controls. Higher infection rates after arthroplasty are also observed in other types of organ transplant patients[19,22]. Our study found an increased risk of sepsis in the LT group (1.2% *vs* 0.3%,  $P < 0.001$ ), but no significant difference between prosthetic infections was observed (10.1% *vs* 12.1%,  $P = 0.34$ ). Delayed infection, however, remains a known risk.

The risk of bleeding tendency remains a paramount consideration with THA and TKA after LT. Hepatic reserve is a major concern, as a decrease in liver functions can lead to a decrease in platelets and clotting factors, and an increased risk of bleeding. Oya *et al*[16] study reported an increased incidence of intraoperative blood loss in a small cohort of 7 patients (303.6 mL *vs* 163.4 mL,  $P < 0.01$ ). A few studies have also reported increased blood transfusion rates in the LT group[13, 19,20,22]. This study reported no significant difference in GI bleeding between the two groups (4.7% *vs* 5.9%,  $P = 0.47$ ). Nevertheless, careful assessment and evaluation of the bleeding profile should be performed in this population before considering THA or TKA.

In summary, LT patients appear to have longer hospital stays compared to nontransplant recipient patients (17.1% *vs* 8.4%,  $P < 0.001$ ). This is consistent with the study of Aminata *et al*[13], which found a significant difference between the LOS in 33 LT who underwent THA compared to non-transplant patients (16 d *vs* 10 d).

Strengths of this study include an adequate sample size to report readmission rates, predictors of readmission, short-term mortality risk, and complication rates statistically and accurately in the LT cohort. To the authors' knowledge, this is the first study to examine the 90-d readmission rates in LT *vs* a control cohort for patients after THA or TKA. The coding and size of the database allowed comparison between the LT cohort and a large control cohort. This also enabled multiple logistic regression analysis to analyze predictors of readmissions.

This study is not free from limitations. Surgical variables unique to transplantation were not available, such as the regimen, dose and duration of immunosuppression, and the type of transplant (related donor). Also, the indication of joint replacement is not available. Another limitation is unavailability of the temporal relationship between the timing of LT and joint replacement in addition to degree of immunosuppression and performance status of patients and laboratory results.

Like any database query using ICD-10 codes, the quality of the data depends on the accurate coding at the time of the patient encounter. Although this data was collected by the United States NRD, this could encourage other countries with national registries to perform a similar analysis to see if these results can be generalized outside the United States. Finally, patient satisfaction, hip and knee outcome scores, and functional measurements were not included in this database.

## CONCLUSION

In conclusion, THA or TKA after LT is not associated with measurably increased mortality but has an increased risk of 90-d readmission. The most prominent risk factors for readmissions are CHF and CKD. While the LT cohort showed an increased risk of AKI and sepsis, there was no increased risk of gastrointestinal bleeding and prosthesis infection. Careful patient selection and medical optimization can reduce readmission rates, risk of mortality, and postoperative complica-



ations in LT patients undergoing THA or TKA. Hopefully the results of this study will provide orthopedic surgeons with accurate readmission profiles to appropriately counsel their patients about the inherent readmission risks after THA and TKA, in LT patients.

## ARTICLE HIGHLIGHTS

### Research background

Solid organ transplants are rising with recipients having longer life span. This puts them at risk of needing joint replacement surgery during their life time. The outcomes of these surgeries are understudied which raises the need for studies to evaluate benefits and risks in this cohort.

### Research motivation

The question is whether patients with liver transplant (LT) are at increased risk of developing complication or have a higher mortality when needing hip or knee replacement surgery.

### Research objectives

The main objective is to prove the LT patients are not at increased risk of complications when needing hip or knee replacement surgery which will allow these patients to get this surgery when needed. Also, this study aims to identify factors associated with increased morbidity which can help modify these factors.

### Research methods

Patients were selected from the Healthcare Cost and Utilization Project databases (HCUP). The HCUP databases are sponsored by the Agency for Healthcare Research and Quality. The International Classification of Diseases Code, 10<sup>th</sup> Revision Clinical Modification was used to identify the patients.

### Research results

Patients with a history of LT undergoing knee or hip replacement have longer hospital stay, increase morbidity but no increase mortality as compared to patient with no history of LT.

### Research conclusions

The results show that hip and knee replacement are safe procedures in patients with LT.

### Research perspectives

More research is needed in identifying risk scores to stratify LT patients as either high or low risk for joint replacement surgery.

## FOOTNOTES

**Author contributions:** Ahmed M contributed to the conception and literature review of the manuscript; Ahmed M, Abumoawad A, and Elsafy H designed this study; Ahmed M and Jaber F drafted the manuscript; Abumoawad A collected the data; Jaber F, Al Momani L, Likhitsup A, and Helzberg JH involved in the critical reviewing of the manuscript; Elsafy H contributed to the analytic plan; Helzberg JH supervised and edited the manuscript.

**Institutional review board statement:** This study is performed based on the Healthcare Cost and Utilization Project databases. The HIPAA Privacy Rule sets national standards for patient rights with respect to health information. This rule protects individually identifiable health information by establishing conditions for its use and disclosure by covered entities.

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