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Name of Journal: *World Journal of Hepatology*

Manuscript NO: 79138

Manuscript Type: ORIGINAL ARTICLE

Retrospective Study

Diabetes Mellitus is Not Associated with Worse Short Term Outcome in Patients older than 65 Years old Post Liver Transplantation

Diabetes Mellitus and Liver Transplantation outcome

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Abstract

BACKGROUND

Non-alcoholic fatty liver disease (NAFLD) is a global health care challenge and a leading indication of liver transplantation (LT). Hence, more patients with diabetes mellitus (DM) are undergoing LT, especially, above the age of 65.

AIM

The aim of the study was to evaluate the impact of DM on short-term outcomes post LT in patients over the age of 65.

METHODS

We collected data of patients who underwent LT from January 2001 until December 2019 using our electronic medical record. We assessed the impact of DM on short-term outcomes, one-year, post- liver transplantation based on the following variables: survival at one year; acute cellular rejection (ACR) rates; intensive care unit (ICU) and hospital length of stay (LOS); and readmissions.

RESULTS

Total of 148 patients who are 65 year or older underwent LT during the study period. The mean age is 68.5 ± 3.3 years and 67.6% were male. The median Model for End-stage Liver Disease (MELD) score at time of transplantation was 22 (6-39), 39% of patients had hepatocellular carcinoma (HCC) and 77.7% underwent living donor LT. The one-year survival was similar between DM patients and others, 91%. Acute cellular rejection (ACR) occurred in 13.5% of patients ($P = 0.902$). The median ICU stay is 4.5-day $P = 0.023$. The rates of ICU and 90-days readmission were similar ($P = 0.821$) and ($P = 0.194$), respectively.

CONCLUSION

The short-term outcome of elderly diabetic patients undergoing LT is similar to others. The presence of DM in elderly LT candidates should not discourage physicians from transplant consideration in this cohort of patients.

Key Words: Acute cellular rejection, diabetes mellitus, elderly, graft survival, liver transplantation.

Alghamdi S, Alamro S, Alobaid D, Soliman E, Albenmoussa A, Bzeizi KI, Alabbad S, Alqahtani SA, Broering D, Al-Hamoudi W. Diabetes Mellitus is Not Associated with Worse Short Term Outcome in Patients older than 65 Years old Post Liver Transplantation. *World J Hepatol* 2022; In press

Core Tip: Diabetes mellitus is very common in elderly patients who are candidates for liver transplant. In a single center experience, diabetes mellitus did not affect the short term outcome in elderly patients who underwent liver transplantation. Hepatitis C virus and non-alcoholic steatohepatitis were the leading indications for liver transplantation. Majority of patients in this study had living liver donors.

² **INTRODUCTION**

Non-alcoholic fatty liver disease (NAFLD) is increasingly becoming a global healthcare challenge with an estimated worldwide prevalence of 24%.^{2,3} The leading causes behind the increase are obesity, diabetes mellitus (DM) and dyslipidemia.¹ In recent years, ³the term metabolic dysfunction-associated fatty liver disease (MAFLD) has been put forward as a more inclusive name for NAFLD, however this has not been universally accepted as of yet. Similarly, NAFLD, previously considered a disease of exclusion, is widely accepted as a disease of inclusion and can co-exist with additional chronic liver diseases.¹ It is linked to insulin resistance and fat metabolism dysregulation,⁴ and it can progress to non-alcoholic steatohepatitis (NASH) and advanced cirrhosis in 25% of patients.⁵ Therefore, after the advent of effective direct

antiviral therapy for hepatitis C (HCV), NAFLD is now becoming a leading indication for liver transplantation worldwide⁶ and expected to surpass other indications.⁵

Currently, the prevalence of NAFLD in Saudi Arabia is 25%, one of the highest rates in the world.⁷ Studies have shown a progressive rise in obesity and diabetes in Arab countries and Saudi Arabia.⁸ It is not surprising, therefore, that an estimated 30% of the Saudi population could have NAFLD by 2030.⁷ In addition, the median age of the population is also increasing.⁹ Hence, an increasing number of liver transplantations will be performed on older patients with diabetes mellitus or obesity.

More people above the age of 65 have become candidates for liver transplantation.¹⁰ Studies demonstrate that age alone should not disqualify patients from liver transplantation if they have no other major contraindications. Functional status and comorbidities are particularly important considerations regarding transplantation in this cohort of patients. Older people often have multiple comorbidities, such as coronary artery disease and diabetes mellitus, that contribute to worse short- and long-term outcomes which vary across transplant centers.¹⁰ Therefore, liver transplantation candidates undergo extensive cardiopulmonary evaluation prior to transplantation.

Diabetes mellitus is associated with increased mortality among patients with liver cirrhosis.¹¹ Studies demonstrate that long-term outcomes after liver transplantation on both patient and graft survivals, particularly in older populations, are poor; while studies of short-term outcomes are limited.¹² The impact of diabetes on short-term outcomes such as intensive care unit (ICU) stay, length of hospital stay, and acute cellular rejection is unknown with regard to Saudi Arabia. Knowledge of these outcomes can inform guidelines for recipient suitability, pre-operative assessment, and immediate post-operative management.

This study aims to evaluate the role of diabetes mellitus as an independent predictor of short-term outcomes in liver transplantation recipients aged 65 and over.

MATERIALS AND METHODS

Using our electronic medical record system, we retrospectively collected data of patients who underwent liver transplantation from January 2001 until December 2019 at King Faisal Specialist Hospital & Research Center (KFSH&RC) in Riyadh. We included all patients who were 65 years or older at the time of transplantation.

We collected basic demographic data (age, gender), Body Mass Index (BMI), indication for transplantation, presence of co-morbidities (DM, hypertension, dyslipidemia, coronary heart disease), and outcomes. We assessed the impact of DM on short-term outcomes, one year, post- liver transplantation based on the following variables: survival at one year; ACR rates; ICU and hospital length of stay (LOS); and readmissions. The diagnoses of DM, hypertension, dyslipidemia, and coronary artery disease were based on the International Classification of Diseases, 10th Revision (ICD-10). Acute cellular rejection (ACR) must have been biopsy proven with histological changes consistent with ACR.

The Institutional Research Board at King Faisal Specialist Hospital and Research Center approved the study. The consent was waived given the retrospective nature of the study.

Transplantation Evaluation and Follow Up

Generally, listing patients for liver transplantation and ranking them on the waitlist at our center is based on the Model for End Stage Liver Disease (MELD).¹³ Patients were assigned to one of the following rankings: 1) Status 1A for acute liver failure; 2) The calculated MELD score; and 3) MELD exception for patients with hepatocellular carcinoma (HCC), hepatopulmonary syndrome (HPS), or portopulmonary hypertension. Patients with HCC were discussed in the tumor multidisciplinary board for locoregional therapy options while completing the workup or waiting for liver transplantation. The MELD score was assessed and updated regularly. All patients were seen in the outpatient clinics regularly and within three months prior to their liver transplantation.

Statistical Analysis

We used SPSS software (version 21.0; SPSS, Inc., Chicago, IL, USA) for statistical analyses. Data are described in counts and percentages, medians and ranges, and means and standard deviations. Fisher exact or chi-square tests were used to compare categorical variables. Mann-Whitney and t tests were used for continuous nonparametric and parametric variables, respectively. Kaplan-Meier curves were used to estimate 1-year patient survival rates, and log-rank test was used to compare survival between the groups. A significance level of $\alpha = 0.05$ was set.

RESULTS

A total of 148 patients aged 65 years or older underwent liver transplantation during the study period. Living donor liver transplantation was performed on the majority of the patients (115, 77.7%). The baseline characteristics are summarized in table 1. Patients were predominantly male (100, 67.6%) with a mean age of 68.5 ± 3.3 years. The median MELD score was 22 (6–39) just prior to transplantation, and hepatocellular carcinoma was present in 58 (39.2%) of patients, with or without other liver diseases.

Risk factors - namely hyperlipidemia, essential hypertension, cardiac ischemia, and renal impairment - were similar for both diabetic and non-diabetic patients (table 1). Nondiabetic patients (non-DM) had a higher BMI (28.6 ± 6.1) than patients with diabetes (DM), $P = 0.048$. The main indication for liver transplantation was HCV (52, 35.1%) followed by NASH (51, 34.5%).

There was a similar median follow-up of 33.5 months for both diabetic and non-diabetic groups, with a one-year survival rate of 89% (figure 1). Acute cellular rejection arose in 20 (13.5%) of the total study population (DM = 13, 13.3% and non-DM = 7, 14%; $P = 0.902$). With regard to ICU readmission, the DM rate was 11 (11.2%) while non-DM was 5 (10%; $P = 0.821$). Although hospital length of stay was comparable (DM = 23 days and non-DM = 22 days; $P = 0.717$), the median ICU stay was shorter in days for DM patients, DM = 4 (1–70) compared to non-DM = 5 (2–185), $P = 0.023$. The 90-day readmission rate was likewise largely similar (DM = 38.8% and non-DM = 28%; $P =$

0.194). The presence of HCC did not affect survival outcomes within the first year after transplantation (figure 2).

In the first-year post-transplantation, 31.5% of patients experienced at least one infectious event. DM patients had a higher rate of infections (40.8% *vs* 24%, $P = 0.043$). However, there has been no statistically significant difference regarding the site of infection, (figure 3). Intrabdominal infections are the most commonly seen infectious source 22.4% followed by pneumonia 14.3%.

DISCUSSION

Data from recent literature suggests that diabetics who are candidates for, or are in the post-operative context of, LT might have severe negative impact on the long-term outcome of these patients. Therefore, adequately controlling diabetes is crucial to increasing candidacy for LT and improving long-term outcomes.¹⁴ The short-term outcome of diabetes among older patients undergoing LT is unknown. Furthermore, the data are extremely limited in this subgroup of patients who have undergone LDLT. Our results showed an excellent one-year survival rate of 89%, which is comparable with the survival rate among highly performing LT centers.^{15,16} We also found that the survival rate was similar between deceased-donor and living-donor LT patients in this cohort. The presence of DM before LT did not have a negative impact on short-term survival. *Aravinthan et al* showed that neither pretransplant nor posttransplant DM affect the survival post-LT.¹² However, an association was found between chronic renal failure, major cardio-vascular diseases and pretransplant DM. In contrast to our study, they included younger patients as well, with a median age of 54. Other larger studies have shown that DM has a statistically significant negative effect on patient and graft survival.¹⁷

Both patients with diabetes and those without experienced ACR at a similar rate. Several reports illustrated an increased risk of ACR and graft loss among patients with pretransplant DM. Most ACR occurs within the first year after transplantation. A study by *Lieber et al* demonstrated an increased risk of ACR among patients with

posttransplant DM,¹⁸ although a smaller study did not detect any effect of either pre-transplant DM or post-transplant DM on ACR.¹⁹ In general, however, patients with pre-transplant DM experience worse graft survival rates.^{17,20} As expected, more diabetic patients had infections in their first-year post transplantation. The infection specific site was similar between both groups. Despite increased infectious complications in the DM patients, the survival rate is similar as outlined above.

Both groups had similar ICU and hospital stays, and the rate of readmission was also similar. A large study of 3772 patients from the United Kingdom with a 20% prevalence of diabetes showed that DM did not have any effect on length of stay.²¹ However, a study of 12442 patients from the United States of America with a 24% prevalence of diabetes found that diabetic recipients perform worse with regard to length of stay and readmissions.¹⁶ The differences, though, are small and may not be clinically relevant. Rather, individual patient factors are more important. A study by *Washburn et al*²² showed that MELD score and increasing age are independent predictors of hospital LOS. The overall median LOS was higher than what has been reported in the literature by other centers. This is primarily because of the nature of the health-care system in Saudi Arabia, which has few available acute rehabilitation centers and primary care physician networks. Therefore, patients remain in the hospital until they are fully mobile and independent before discharge.

Overall, the principle limiting factors of this study are its' retrospectivity and the single-center experience. Nevertheless the data can be considered representative of our region since over half of LTs in Saudi Arabia are performed at our center.²³ Furthermore over the last decades, advances have been made in the medical management of liver transplantation patients resulting in improved early outcomes, though not significantly improved long-term survival.²⁴ Another potential limiting factor is the low number of deceased donors in our cohort. One last limitation for this study is that we did not use the random forest survival analysis, an analysis representing the rapid rise of artificial intelligence in medicine, which surpasses traditional statistical approaches in terms of accuracy and explainable utility.

CONCLUSION

The short-term outcome of elderly diabetic patients undergoing liver transplantation is similar to patients without diabetes. The presence of diabetes mellitus in elderly liver transplant candidates should not discourage physicians when considering patients for liver transplantation.

ARTICLE HIGHLIGHTS

Research background

More patients older than 65 undergo liver transplantation nowadays. Significant number of those patients have diabetes mellitus.

Research motivation

To address the impact of diabetes mellitus on short term outcome post liver transplant in patients older than 65. There is limited data in the literature particularly for patients undergoing living donor liver transplantation.

Research objectives

To determine the short term impact of diabetes mellitus in older patients post liver transplantation.

Research methods

Retrospective study of previously collected data from a single center.

Research results

One-year survival was comparable between diabetic and nondiabetic elderly patients undergoing liver transplantation.

Acute cellular rejection rates were comparable between diabetic and nondiabetic elderly patients undergoing liver transplantation.

Intensive care unit, hospital length of stay, and readmissions were comparable between diabetic and nondiabetic elderly patients undergoing liver transplantation.

Research conclusions

Diabetes was not found to affect the short-term outcomes in elderly patients undergoing liver transplantation.

Research perspectives

The presence of diabetes mellitus in elderly liver transplant candidates should not discourage physicians when considering patients for liver transplantation.

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