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The primary aim of *World Journal of Hepatology* (*WJH*, *World J Hepatol*) is to provide scholars and readers from various fields of hepatology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJH mainly publishes articles reporting research results and findings obtained in the field of hepatology and covering a wide range of topics including chronic cholestatic liver diseases, cirrhosis and its complications, clinical alcoholic liver disease, drug induced liver disease autoimmune, fatty liver disease, genetic and pediatric liver diseases, hepatocellular carcinoma, hepatic stellate cells and fibrosis, liver immunology, liver regeneration, hepatic surgery, liver transplantation, biliary tract pathophysiology, non-invasive markers of liver fibrosis, viral hepatitis.

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ORIGINAL ARTICLE

Retrospective Study

Diabetes mellitus is not associated with worse short term outcome in patients older than 65 years old post-liver transplantation

Saad Alghamdi, Shaden Alamro, Dhari Alobaid, Elwy Soliman, Ali Albenmousa, Khalid Ibrahim Bzeizi, Saleh Alabbad, Saleh A Alqahtani, Dieter Broering, Waleed Al-Hamoudi

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Abstract

BACKGROUND
Non-alcoholic fatty liver disease 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
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-LT based on the following variables: Survival at one year; acute cellular rejection (ACR) rates; intensive care unit (ICU) and hospital length of stay; 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 score at time of transplantation was 22 (6-39), 39% of patients had hepatocellular carcinoma and 77.7% underwent living donor LT. The one-year survival was similar between DM patients and others, 91%. 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-d 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

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

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INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is increasingly becoming a global healthcare challenge with an estimated worldwide prevalence of 24%[1,2]. The leading causes behind the increase are obesity, diabetes mellitus (DM) and dyslipidemia[3]. In recent years, the term metabolic dysfunction-associated fatty liver disease 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[3]. 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 (LT) worldwide[6] 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 LTs will be performed on older patients with DM or obesity.

More people above the age of 65 have become candidates for LT[10]. Studies demonstrate that age alone should not disqualify patients from LT 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 DM, that contribute to worse short- and long-term outcomes which vary across transplant centers[10]. Therefore, LT candidates undergo extensive cardiopulmonary evaluation prior to transplantation.

DM is associated with increased mortality among patients with liver cirrhosis[11]. Studies demonstrate that long-term outcomes after LT 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 (ACR) 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 DM as an independent predictor of short-term outcomes in LT recipients aged 65 and over.

MATERIALS AND METHODS

Using our electronic medical record system, we retrospectively collected data of patients who underwent LT from January 2001 until December 2019 at King Faisal Specialist Hospital & Research Center 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-LT 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. 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 LT 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, or portopulmonary hypertension. Patients with HCC were discussed in the tumor multidisciplinary board for locoregional therapy options while completing the workup or waiting for LT. The MELD score was assessed and updated regularly. All patients were seen in the outpatient clinics regularly and within three months prior to their LT.

The standard immunosuppression protocol in our institution includes calcineurin inhibitors and mycophenolate mofetil during the first 6-12 mo after transplantation and oral prednisone for the first 3 mo. The doses of immunosuppressive medications were adjusted according to their serum levels and were modified in patients with renal impairment. We aim to minimize immunosuppression post liver transplantation in patients with HCC.

Statistical analysis

We used SPSS software (version 21.0; SPSS, Inc., Chicago, IL, United States) 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 LT during the study period. Living donor LT 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 LT was HCV (52, 35.1%) followed by NASH (51, 34.5%).

There was a similar median follow-up of 33.5 mo for both diabetic and non-diabetic groups, with a one-year survival rate of 89% (Figure 1). ACR 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 LOS was comparable (DM = 23 d and non-DM = 22 d; 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-d 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%.

Table 1 Baseline characteristics of the studied sample

Variables		All, *n* = 148	DM, *n* = 98	No DM, *n* = 50	*P* value
Age (years)[1]		68.5 ± 3.3	68.4 ± 3.1	68.5 ± 3.9	0.578
Gender (Male)[2]		100 (67.6%)	69 (70.4%)	31 (62.0%)	0.301
Living Donor[2]		115 (77.7%)	79 (80.6%)	37 (74.0%)	0.355
Cause of liver disease[2]	HCV	52 (35.1%)	32 (32.7%)	20 (40%)	0.341
	HBV	24 (16.2%)	14 (14.3%)	10 (20%)	
	NASH	51 (34.5%)	35 (35.7%)	16 (32%)	
	Others	21 (14.2%)	17 (17.3%)	4 (8%)	
HCC[2]		58 (39.2%)	40 (40.8%)	18 (36.0%)	0.570
MELD[2]		22 (6-39)	22 (6-39)	21 (8-35)	0.833
BMI[1] (kg/m^2)		26.7 ± 5.1	26.2 ± 4.6	28.6 ± 6.1	0.048[a]
HTN[2]		52 (35.1%)	42 (42.9%)	10 (20.0%)	0.006[a]
Hyperlipidemia[2]		10 (6.8%)	9 (9.2%)	1 (2.0%)	0.100
CAD[2]		4 (2.7%)	3 (3.1%)	1 (2.0%)	0.692
CKD[2]		40 (26.4%)	28 (28.6%)	12 (24.0%)	0.554
On insulin[2]		60 (41.2%)	60 (60.2%)	0	
On OHA[2]		46 (31.1%)	46 (46.9%)	0	
HbA1c[1]		5.9 ± 1.7	6.5 ± 1.7	4.6 ± 0.8	0.000[a]
Length of stay (days)[3]		24 (2-275)	23 (2-275)	22 (4-149)	0.717

[a]$P < 0.05$.
[1]Results in mean ± SD.
[2]Results in counts (percentage).
[3]Results in median (range).
DM: Diabetes mellitus; BMI: Body mass index; CKD: Chronic kidney disease; HbA1c: Hemoglobin A1c; CAD: Coronary arterial disease; HBV: Hepatitis B; HCC: Hepatocellular carcinoma; HCV: Hepatitis C; HTN: Hypertension; MELD: Model for end-stage liver disease; NASH: Non-alcoholic steatohepatitis; OHA: Oral hypoglycemic agent.

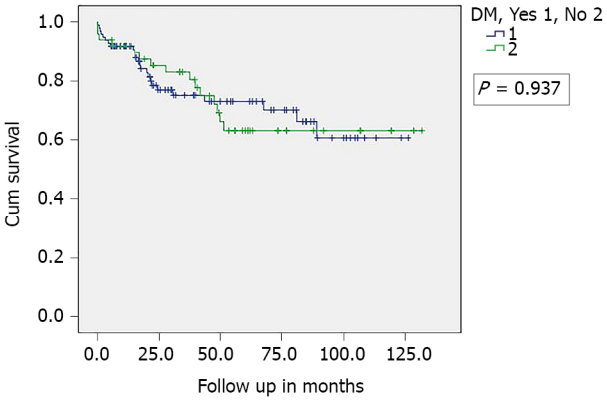

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Figure 1 One-year survival in our sample. DM: Diabetes mellitus.

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 living

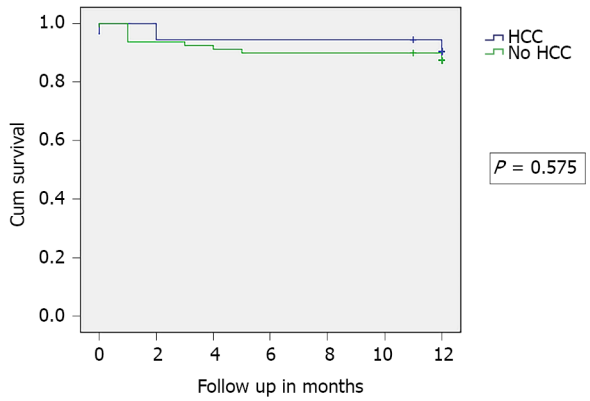

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Figure 2 Survival and hepatocellular carcinoma in our sample. HCC: Hepatocellular carcinoma.

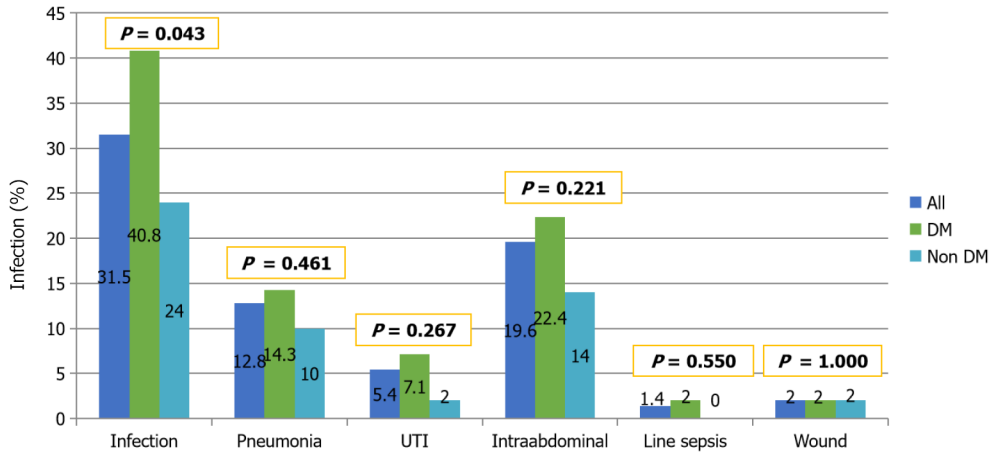

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Figure 3 Infection rates in our sample. DM: Diabetes mellitus; UTI: Urinary tract infection.

donor LT. 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*[12] 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*[18] 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 LOS[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 LOS 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 LT 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 LT is similar to patients without diabetes. The presence of DM in elderly liver transplant candidates should not discourage physicians when considering patients for LT.

ARTICLE HIGHLIGHTS

Research background

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

Research motivation

To address the impact of DM 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 LT.

Research objectives

To determine the short term impact of DM in older patients post LT.

Research methods

This is a retrospective study of previously collected data from a high volume single transplant center. We included all patients who are 65 years old or older at the time of transplantation and assessed important short term outcomes such as one year survival, intensive care unit length of stay and acute cellular rejection.

Research results

One-year survival was comparable between diabetic and nondiabetic elderly patients undergoing LT. Acute cellular rejection rates were comparable between diabetic and nondiabetic elderly patients undergoing LT. Intensive care unit, hospital length of stay, and readmissions were comparable between diabetic and nondiabetic elderly patients undergoing LT.

Research conclusions

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

Research perspectives

The presence of DM in elderly liver transplant candidates should not discourage physicians when considering patients for LT.

FOOTNOTES

Author contributions: Alghamdi S, Bzeizi KI, Alabbad S, Alqahtani SA, Broering D and Al-Hamoudi W contributed equally to this work; Alghamdi S, Alamro S, Alobaid D and Soliman E designed the research study; Alghamdi S, Alamro S, Alobaid D, Soliman E, Albenmousa A, Bzeizi KI and Al-Hamoudi W analyzed the data and wrote the manuscript; Alghamdi S, Albenmousa A, Bzeizi KI, Alqahtani SA and Al-Hamoudi W performed the research; Alghamdi S, Bzeizi KI, and Al-Hamoudi W contributed new reagents and analytic tools; All authors have read and approved the final manuscript.

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