Original paper

Left ventricular diastolic dysfunction in liver transplantation: a stronger association with non-alcoholic steatohepatitis

Hemnishil K. Marella[1], Faisal Kamal[2], Rahul Peravali[3], Jake Jacob[4], Satheesh P. Nair[5]

[1]Department of Medicine, University of Tennessee Health Science Center, Memphis TN, USA
[2]Division of Gastroenterology and Hepatology, University of Tennessee Health Science Center, Memphis, TN, USA
[3]College of Medicine, University of Tennessee Health Science Center, Memphis, TN, USA
[4]Department of Medicine, Baylor College of Medicine, Houston, TX, USA
[5]Division of Transplant Surgery, Department of Surgery, Methodist University Hospital Transplant Institute, University of Tennessee Health
 Science Center, Memphis, TN, USA

Abstract

Aim of the study: Cardiovascular death is an important cause of mortality in end stage liver disease (ESLD) patients undergoing orthotopic liver transplant (OLT). Left ventricular diastolic dysfunction (LVDD) is often the early manifestation and only measurable manifestation of cirrhotic cardiomyopathy. Therefore, it is important to understand the risk factors for LVDD in ESLD patients undergoing OLT and its immediate impact post-operatively.

Material and methods: Electronic medical records (EMR) of 100 consecutive patients who underwent OLT were reviewed at the University of Tennessee/Methodist University Hospital in Memphis, Tennessee, USA. Transthoracic echocardiogram (TTE) reports were accessed to evaluate for LVDD based on the latest 2016 American Society of Echocardiography and European Association of Cardiovascular Imaging guidelines. The clinical and demographic variables were obtained and variable quality measures, incidence of cardiac arrhythmias, and 30-day all-cause mortality were compared.

Results: Patients with LVDD were older (62.7 ±6.3 years vs. 55.9 ±12.3 years, $p = 0.017$) and were more often female (57% vs. 31%, $p = 0.026$). In addition, patients with non-alcoholic steatohepatitis (NASH) were more likely to have LVDD (48% vs. 12%, $p = 0.001$). In contrast, patients with alcoholic liver disease were less likely to have LVDD (10% vs. 33%, $p = 0.032$). In a multivariate logistic regression analysis, NASH (OR = 4.4 [95% CI: 1.33-14.5], $p = 0.015$) and female gender (OR = 3.31 [95% CI: 1.09-9.99], $p = 0.033$) were independent predictors of LVDD.

Conclusions: In our cohort of patients, the presence of NASH was associated with a higher risk of LVDD. However, presence of LVDD did not influence immediate post-transplant outcome or 30-day all-cause mortality.

Key words: non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), left ventricular diastolic dysfunction (LVDD).

Address for correspondence:

Dr. Hemnishil K. Marella, Department of Medicine, University of Tennessee Health Science Center, 956 Court Ave., Suite H314 Memphis, TN 38163, phone: 502-330-8670, e-mail: hkmarella@gmail.com

Introduction

Cardiovascular death is an important cause of mortality in end stage liver disease (ESLD) patients undergoing orthotopic liver transplantation (OLT) [1, 2]. Cardiac dysfunction secondary to cirrhotic cardiomy-opathy is seen in up to 50% of cirrhotic patients [3]. Characteristics of cirrhotic cardiomyopathy include impaired contractility, electrophysiological abnormalities, and left ventricular diastolic dysfunction (LVDD) [4, 5]. LVDD is often the early manifestation and only measurable manifestation of cirrhotic cardiomyopathy

[6]. Therefore, it is important to examine the predictors and risk factors of LVDD among cirrhotic patients undergoing OLT and its immediate impact post-operatively.

Material and methods

Patient characteristics

The cohort consisted of 100 consecutive patients who underwent OLT, at the University of Tennessee/ Methodist University Hospital in Memphis, Tennessee, USA. Transthoracic echocardiogram (TTE) reports were reviewed to identify the patients with LVDD. Evaluation of LVDD will be described below. One patient was excluded due to insufficient TTE data ($n = 1$). There were no patients in this study with systolic dysfunction or pre-existing history of coronary artery disease. The following demographic and clinical variables were obtained from electronic medical records (EMR): age, gender, height, weight, body mass index (BMI), sodium, creatinine, albumin, total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, hemoglobin A1c, platelet count and INR. The medical history of patients such as hyperlipidemia, hypertension diabetes/glucose intolerance etc. was also recorded. The etiology of cirrhosis in the cohort was based on the clinical liver biopsy report prior to OLT or explant liver pathology report. The immediate perioperative outcome was measured by the duration of vasopressor therapy, days on mechanical ventilation, length of intensive care unit (ICU) stay, and overall length of hospital stay and 30-day all-cause mortality.

Echocardiography

Transthoracic echocardiography was performed by an experienced operator and the echocardiogram was read by a board-certified cardiologist. The TTE reports within 6 months of the OLT were accessed, and the latest 2016 American Society of Echocardiography (ASE)/European Association of Cardiovascular Imaging (EACVI) recommendations were used to define LVDD and to grade the LVDD [7]. Important variables for determining LVDD include septal e' and/or lateral e', average E/e' ratio, left atrial (LA) volume index, and peak tricuspid regurgitation (TR) velocity. Early diastolic mitral annulus velocity (e') is estimated by tissue doppler. The E/e' ratio is derived by using the trans-mitral early peak velocity (E) via pulsed wave doppler over e'. LA volume index is the value of LA volume divided by body surface area and is also used

to estimate diastolic dysfunction. Finally, peak TR velocity is assessed by doppler to further evaluate LVDD [7]. The presence or absence of LVDD in patients with a normal left ventricle ejection fraction (LVEF) in this study was based on the assessment of these four variables. The cutoff values for these variables include: septal $e' < 7$ cm/s or lateral $e' < 10$ cm/s, average $E/e' > 14$, LA volume index > 34 ml/m^2 and peak TR velocity > 2.8 m/s. LVDD is absent if more than half of the available variables are normal (< 50% positive), present if more than half of the available variables are abnormal (> 50% positive) and in cases in which half of the variables do not meet the cutoff value, the study is indeterminate (50% positive) [7].

Statistical analysis

Statistical analysis was performed using descriptive statistics; 2-tailed unpaired t-test, Fisher's exact test and the chi-squared test were applied as appropriate for continuous and categorical data. Patient characteristics were summarized as means and standard deviation. A p-value < 0.05 was considered statistically significant. Multivariate logistic regression analysis was performed to identify predictors of LVDD. Data were analyzed using STATA 15 (StataCorp, College Station, TX).

Results

The mean age of patients in the cohort was 57.3 ±11.6 years. The most common etiologies for ESLD were hepatitis C ($n = 34$), alcoholic cirrhosis ($n = 28$), and non-alcoholic steatohepatitis (NASH) ($n = 19$).

Characteristics of patients in this cohort based on LVDD are shown in Table 1. Patients with LVDD were older (62.7 ±6.3 years vs. 55.9 ±12.3 years, $p = 0.017$) and were more often female (57% vs. 31%, $p = 0.026$). In addition, patients with NASH were more likely to have LVDD (48% vs. 12%, $p = 0.001$). In contrast, patients with alcoholic liver disease were less likely to have LVDD (10% vs. 33%, $p = 0.032$).

A multivariate logistic regression analysis including age, gender and diagnosis of NASH was performed to predict LVDD. In this multivariate analysis, NASH (odds ratio [OR] = 4.4 [95% CI: 1.33-14.5], $p = 0.015$) and female gender (OR = 3.31 [95% CI: 1.09-9.99], $p = 0.033$) were independent predictors of developing LVDD. However, the presence of LVDD did not adversely impact immediate transplant outcomes such as length of intensive care ($p = 0.624$), length of hospital stay ($p = 0.514$), number of days on mechanical ventilation ($p = 0.511$), duration of vasopressor therapy ($p = 0.091$), and incidence of cardiac arrhythmias in

Table 1. Patient characteristics based on left ventricular diastolic dysfunction

Variable	Diastolic dysfunction (*n* = 21)	No diastolic dysfunction (*n* = 78)	*P*-value
Age (years) (mean ± SD)	62.76 ±6.3	55.99 ±12.3	0.017#
Gender, female (*n*, %)	12 (57%)	24 (31%)	0.026*
BMI kg/m^2 (mean ± SD)	27.7 ±5.73	28.1 ±12.3	0.783#
NASH, *n* (%)	10 (48%)	9 (12%)	0.001^
Hepatitis C, *n* (%)	7 (33%)	27 (35%)	0.913^
Alcohol, *n* (%)	2 (10%)	26 (33%)	0.032^
Other, *n* (%)	2 (10%)	16 (21%)	0.246^
History of hyperlipidemia, *n* (%)	4 (19%)	8 (10%)	0.273^
History of hypertension, *n* (%)	8 (38%)	25 (32%)	0.602^
History of diabetes, *n* (%)	9 (43%)	19 (24%)	0.095^
History of smoking, *n* (%)	5 (24%)	31 (40%)	0.178^
MELD-Na (mean ± SD)	19.9 ±5.7	22.4 ±8.6	0.210#
HgA$_{1c}$ (mean ± SD)	5.0 ±1.3	5.2 ±1.2	0.601#
QTC (mean ± SD)	446.5 ±47.8	448.5 ±49.7	0.865#
Length of intensive care (days) (mean ± SD)	4.5 ±5.7	5.3 ±7.2	0.624#
Length of hospital stay (days) (mean ± SD)	13.3 ±9.55	19.9 ±43.6	0.514#
Days on vasopressors (mean ± SD)	1.4 ±5.8	0.196 ±0.75	0.091#
Days on mechanical ventilation (mean ± SD)	2.4 ±5.3	1.6 ±4.6	0.511#
Incidence of cardiac arrhythmias (*n*)	1	6	0.642^
30-day mortality (*n*)	1	7	0.530^

*Chi-squared test; #2 tailed t-test; ^Fisher's exact test; HgA$_{1c}$ was available in 63 patients

the post-operative period (*p* = 0.642). More importantly, 30-day all-cause mortality was not affected the presence of LVDD (*p* = 0.530).

The demographic and clinical characteristics of patients with NASH cirrhosis vs. other etiologies of cirrhosis, denoted as non-NASH, are compared in Table 2. Patients with NASH were older (64.7 ±3.66 years vs. 55.7 ±12.23 years, *p* = 0.002) and had a higher mean BMI (30.5 kg/m^2 vs. 27.4 kg/m^2, *p* = 0.030). As expected, NASH patients had a statistically significantly higher prevalence of diabetes (68% vs. 19%, *p* < 0.001), but no significance was noted in the prevalence of hypertension (47% vs. 30%, *p* = 0.149) or hyperlipidemia (16% vs. 11%, *p* = 0.586). Interestingly, NASH patients were more likely to have LVDD (53% vs. 14%, *p* < 0.001).

Discussion

LVDD is often the early manifestation and only measurable manifestation of cirrhotic cardiomyopathy [6]. Therefore, it is important to examine the predictors and risk factors of LVDD among cirrhotic patients undergoing OLT and its immediate impact post-operatively. In this study, a multivariate analysis indicated

that patients with LVDD were more likely to be female, and more likely to have NASH. In fact, almost half (48%) of patients with LVDD had NASH. Our results establish a strong association of NASH and LVDD in decompensated cirrhotic patients undergoing OLT.

NASH is the liver manifestation of a metabolic disorder and is the most severe form of non-alcoholic fatty liver disease (NAFLD). Cardiac remodeling and impaired cardiac function in NAFLD patients are thought to be driven by insulin resistance and pro-inflammatory cytokines such as interleukin-1, interleukin-6, and tumor necrosis factor (TNF) [8-12]. These inflammatory cytokines are hypothesized to lead to subclinical myocardial changes that could lead to LVDD [9, 11, 13]. Moreover, impaired glucose uptake in the myocardium in patients with NAFLD has been shown to cause oxidative stress leading to ventricular stiffening, further contributing to LVDD [9, 10].

Few studies have used histologically proven NAFLD to demonstrate subclinical cardiac remodeling and LVDD [14-16]. However, these studies provide conflicting reports on the relationship between NAFLD and LVDD. For example, Simon *et al.* [16] showed that NAFLD was associated with significant

Table 2. Demographic and clinical features of patients with non-alcoholic steatohepatitis (NASH)

Variable	NASH (*n* = 19)	No NASH (*n* = 80)	*P*-value
Age (years) (mean ± SD)	64.7 ±3.66	55.7 ±12.23	0.002#
Gender, female (*n*, %)	9 (57%)	27 (31%)	0.267^
BMI kg/m² (mean ± SD)	30.5 ±6.41	27.4 ±5.23	0.030#
LV diastolic dysfunction *n* (%)	10 (53%)	11 (14%)	0.000*
Hyperlipidemia, *n* (%)	3 (16%)	9 (11%)	0.586^
Hypertension, *n* (%)	9 (47%)	24 (30%)	0.149^
Diabetes, *n* (%)	13 (68%)	15 (19%)	0.000*
Smoking, *n* (%)	5 (26%)	31 (39%)	0.311^
MELD-Na (mean ± SD)	21.0 ±5.23	22.1 ±8.74	0.596#
HgA$_{1c}$ (mean ± SD)	5.64 ±1.35	5.0 ±1.09	0.070#
AST (mean ± SD)	1136.6 ±1892	799.5 ±1286	0.354#
ALT (mean ± SD)	573.26 ±911	447.2 ±737	0.524#
Albumin (mean ± SD)	3.34 ±1.19	3.04 ±0.57	0.108#
Bilirubin (mean ± SD)	2.81 ±2.53	5.70 ±7.59	0.106#
Alkaline phosphatase (mean ± SD)	120.16 ±44.4	158.55 ±160.9	0.307#
QTC (mean ± SD)	459.9 ±33.9	445.3 ±51.9	0.244#
Length of intensive care (mean ± SD)	6.05 ±9.94	4.9 ±6.0	0.526#
Length of hospital stay days (mean ± SD)	13.6 ±11.5	13.7 ±13.9	0.971#
Days on vasopressors (mean ± SD)	0.37 ±1.21	0.48 ±3.12	0.878#
Days on mechanical ventilation (mean ± SD)	3.28 ±8.98	1.43 ±2.91	0.127#
Incidence of cardiac arrhythmias (*n*)	0	7	0.181^
30-day mortality (*n*)	0	8	0.151^

Chi-squared test; #2 tailed t-test; ^Fisher's exact test; HgA$_{1c}$ was available in 63 patients

echocardiographic abnormalities consistent with progressive LVDD; however, the study was limited by a small sample size and did not account for confounders of NASH and heart failure. Karabay *et al.* [14] compared an NAFLD cohort to healthy controls. The NAFLD cohort was noted to have subclinical myocardial dysfunction, though with no relationship to the severity of the NAFLD. In addition, the study was a comparison of the means between NAFLD patients and controls and did not take into consideration covariates. Petta *et al.* [15] in a multivariate model found no significant differences in left ventricular mass or early annular diastolic tissue velocity in NAFLD patients. Our results are consistent with Simon *et al.* [16], but given the conflicting evidence in the literature future studies are needed to further validate our results.

In order to further assess the impact of LVDD on liver transplant outcome, we monitored parameters such as length of intensive care unit stay, length of hospital stay, days on vasopressors, and days on mechanical ventilation. In our cohort, none of these pa-rameters significantly differed between patients with LVDD and patients without LVDD. Moreover, it is important to note that 30-day all-cause mortality was not influenced by LVDD in our cohort. Future studies should investigate the 1- or 2-year mortality to further characterize the long-term impact of LVDD on transplant outcome.

In conclusion, the presence of NASH was associated with a higher risk of LVDD in our cohort of patients. However, presence of LVDD did not influence immediate post-transplant outcome or 30-day all-cause mortality. Limitations of this study include its sample size, short post-transplant outcomes follow-up, and retrospective design. In the future, long-term prospective studies with a large sample size need to be performed in order to develop predictive models that may better identify those at risk and explore potential interventions to mitigate that risk.

Disclosure

The authors report no conflict of interest.

References

1. Liu H, Lee SS. Predicting cardiovascular complications after liver transplantation: 007 to the rescue? Liver Transpl 2011; 17: 7-9.

2. Watt KD, Pedersen RA, Kremers WK, et al. Evolution of causes and risk factors for mortality post-liver transplant: results of the NIDDK long-term follow-up study. Am J Transplant 2010; 10: 1420-1427.

3. Rahman S, Mallett SV. Cirrhotic cardiomyopathy: Implications for the perioperative management of liver transplant patients. World J Hepatol 2015; 7: 507-520.

4. Izzy M, VanWagner LB, Lin G, et al. Redefining Cirrhotic Cardiomyopathy for the Modern Era. Hepatology 2020; 71: 334-345.

5. Liu H, Jayakumar S, Traboulsi M, et al. Cirrhotic cardiomyopathy: Implications for liver transplantation. Liver Transpl 2017; 23: 826-835.

6. Wiese S, Hove JD, Bendtsen F, et al. Cirrhotic cardiomyopathy: pathogenesis and clinical relevance. Nat Rev Gastroenterol Hepatol 2014; 11: 177-186.

7. Nagueh SF, Smiseth OA, Appleton CP, et al. Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging 2016; 17: 1321-1360.

8. Adams LA, Anstee QM, Tilg H, et al. Non-alcoholic fatty liver disease and its relationship with cardiovascular disease and other extrahepatic diseases. Gut 2017; 66: 1138-1153.

9. Anstee QM, Mantovani A, Tilg H, et al. Risk of cardiomyopathy and cardiac arrhythmias in patients with nonalcoholic fatty liver disease. Nat Rev Gastroenterol Hepatol 2018; 15: 425-439.

10. Lautamaki R, Borra R, Iozzo P, et al. Liver steatosis coexists with myocardial insulin resistance and coronary dysfunction in patients with type 2 diabetes. Am J Physiol Endocrinol Metab 2006; 291: E282-290.

11. Targher G, Bertolini L, Rodella S, et al. NASH predicts plasma inflammatory biomarkers independently of visceral fat in men. Obesity (Silver Spring) 2008; 16: 1394-1399.

12. VanWagner LB, Wilcox JE, Colangelo LA, et al. Association of nonalcoholic fatty liver disease with subclinical myocardial remodeling and dysfunction: A population-based study. Hepatology 2015; 62: 773-783.

13. Targher G, Day CP, Bonora E. Risk of cardiovascular disease in patients with nonalcoholic fatty liver disease. N Engl J Med 2010; 363: 1341-1350.

14. Karabay CY, Kocabay G, Kalayci A, et al. Impaired left ventricular mechanics in nonalcoholic fatty liver disease: a speckle-tracking echocardiography study. Eur J Gastroenterol Hepatol 2014; 26: 325-331.

15. Petta S, Craxi A. Epicardial fat in patients with non-alcoholic fatty liver disease. J Hepatol 2015; 62: 1215.

16. Simon TG, Bamira DG, Chung RT, et al. Nonalcoholic Steatohepatitis is Associated with Cardiac Remodeling and Dysfunction. Obesity (Silver Spring) 2017; 25: 1313-1316.