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

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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).

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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 cardiomyopathy 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.
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]. 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 $e'< 7 \text{ cm/s}$ or lateral $e'< 10 \text{ cm/s}$, average $E/e' > 14$, LA volume index $> 34 \text{ ml/m}^2$ and peak TR velocity $> 2.8 \text{ m/s}$. 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
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

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**Table 1. Patient characteristics based on left ventricular diastolic dysfunction**

| Variable                                    | Diastolic dysfunction \((n = 21)\) | No diastolic dysfunction \((n = 78)\) | \(P\)-value |
|----------------------------------------------|-----------------------------------|-------------------------------------|-------------|
| Age (years) \((\text{mean} \pm \text{SD})\) | 62.76 ±6.3                        | 55.99 ±12.3                        | 0.017*      |
| Gender, female \((n, \%)\)                 | 12 (57%)                          | 24 (31%)                           | 0.026*      |
| BMI \(\text{kg/m}^2\) \((\text{mean} \pm \text{SD})\) | 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 \((\text{mean} \pm \text{SD})\)  | 19.9 ±5.7                         | 22.4 ±8.6                          | 0.210*      |
| HgA\(_1c\) \((\text{mean} \pm \text{SD})\) | 5.0 ±1.3                          | 5.2 ±1.2                           | 0.601*      |
| QTC \((\text{mean} \pm \text{SD})\)      | 446.5 ±47.8                      | 448.5 ±49.7                        | 0.865*      |
| Length of intensive care (\(\text{days} \pm \text{SD}\)) | 4.5 ±5.7                         | 5.3 ±7.2                           | 0.624*      |
| Length of hospital stay (\(\text{days} \pm \text{SD}\)) | 13.3 ±9.55                       | 19.9 ±43.6                        | 0.514*      |
| Days on vasopressors \((\text{mean} \pm \text{SD})\) | 1.4 ±5.8                         | 0.196 ±0.75                       | 0.091*      |
| Days on mechanical ventilation \((\text{mean} \pm \text{SD})\) | 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
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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 parameters 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.
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