JACC: ASIA VOL. 3, NO. 3, 2023

EDITORIAL COMMENT

Diagnosing HFpEF and Predicting ESLD Liver Transplant Outcome Using HFA-PEFF Score*

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Cardiovascular events, including heart failure, are the third leading cause of mortality, after infection and multiorgan failure, in liver transplant (LT) recipients with end-stage liver disease (ESLD).[1] Cardiovascular events could not only happen in patients with pretransplant concurrent cardiovascular disease but also in patients without any previous cardiac disease, such as cirrhotic cardiomyopathy (CCM), because of the unique pathophysiological changes in patients with ESLD and the dramatic challenge the cardiovascular system faces after transplantation.[2] The main clinical characteristics of CCM include decreased systolic contractility conserves in response to physiologic or pharmacologic strain and diastolic dysfunction, etc. Furthermore, diastolic dysfunction with impaired ventricular relaxation and ventricular filling is a prominent feature of CCM.[3] It is well known that heart failure with preserved ejection fraction (HFpEF) is associated with diastolic dysfunction. Although patients with a confirmed pretransplant diagnosis of heart failure with reduced ejection fraction might be excluded from the transplantation list for being poor candidates, pretransplant HFpEF might be prevalent but underdiagnosed. The diagnosis of HFpEF is extremely challenging to make in the setting of CCM, given the overlapping symptomology between subclinical heart failure and ESLD, which could also manifest as breathlessness in the setting of ascites, decreased exercise capacity, and malnutrition. Accurate identification and staging of HFpEF due to cirrhotic cardiomyopathy need a more sophisticated investigation.

The 2019 Heart Failure Association (HFA)-PEFF diagnostic algorithm proposed by the European Society of Cardiology addressed the challenging part of the diagnosis of HFpEF.[4] It is a stepwise diagnostic process. Step 1 is pretest assessment (P = pretest assessment), including assessment of heart failure signs, symptoms, and other parameters. Step 2 is risk score calculation based on echocardiographic parameters and serum natriuretic peptides levels (E = echocardiography and natriuretic peptide score). A score of more than 5 points implies definite HFpEF, and a score of less or equal to 1 point makes HFpEF unlikely. Those with a score of 2 to 4 points would proceed to step 3: functional testing (F = functional testing), such as invasive hemodynamic exercise stress test, and last, step 4 (F2 = final etiology) to establish a possible specific cause of HFpEF.

In the issue of *JACC: Asia*, Shin et al[5] further addressed the challenging aspect of HFpEF diagnosis in patients with ESLD in a large single-center retrospective study conducted in the Republic of Korea. The study would like to answer the questions of how prevalent HFpEF is in patients with ESLD using only the step 2 HFA-PEFF diagnostic algorithm, and how the HFA-PEFF score is associated with the LT outcomes. A total of 3,244 patients with ESLD were enrolled in the Asan Liver Transplant Registry between 2008 and 2019 and were then followed up after LT until September 2020. These patients were divided into low- (score of 0 to 1), intermediate- (score of 2 to 4), and high- (score of 5 to 6) probability groups using the HFA-PEFF diagnostic score algorithm. It was found that 6.6% of patients with ESLD (215 of 3,244 patients) were classified as the high-probability group

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The author attests they are in compliance with human studies committees and animal welfare regulations of the author's institution and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

ISSN 2772-3747 https://doi.org/10.1016/j.jacasi.2023.04.005

of HFpEF and demonstrated a 46% (adjusted HR: 1.46; 95% CI: 1.08-1.98; $P = 0.013$) increased risk of median 5 all-cause mortality and 70% increased risk (adjusted HR: 1.7; 95% CI: 1.18-2.44; $P = 0.005$) of 1-year mortality compared with those in the low- and intermediate-probability groups. The odds of 30-day major adverse cardiovascular events in the high-probability group was also significantly higher as compared with the low-intermediate group (adjusted OR: 1.91; 95% CI: 1.37-2.68; $P < 0.001$). Moreover, in a subgroup of patients with a model for end-stage liver disease (MELD) score of more than 30, the post-LT cumulative survival rate at 12 years was significantly lower in the high-probability group as compared with those in the lower probability group (54.8% vs 88.9%, $P = 0.026$). This is the first report so far characterizing HFpEF in an ESLD population who underwent LT in a large study cohort using the HFA-PEFF score algorithm with transplantation outcome analysis. In line with the current study, Dimitroglou et al,[6] who performed a prospective cohort study enrolling patients with cirrhosis, reported that the 1- and 2-year cumulative mortality rate was higher with high HFA-PEFF scores as compared with those with intermediate/low scores. HFA-PEFF score is associated with survival after adjusting for cirrhosis severity using the MELD score. They concluded that the HFA-PEFF score is an independent predictor of 2-year mortality in patients with liver cirrhosis.

The MELD score has been the cornerstone of predicting LT outcomes and functioned as a marker for the urgency and priority of donor allocation before transplantation.[7] The current study also revealed that the HFA-PEFF score is associated with the MELD score. Patients with high-probability HFpEF scores showed higher MELD scores compared with those with low and intermediate HFpEF groups, indicating that worsening liver disease severity is associated with the occurrence of HFpEF. Again, the result is in concordance with Dimitroglou et al[6] who got similar results.

Besides the MELD score, multiple risk models have been proposed to predict post-LT outcomes including mortality.[8-10] Using the machine learning technique, Molinari et al[9] identified that recipient age, diabetes, MELD score, body mass index, and dialysis before LT as the strongest predictors for 90-day postoperative mortality through a study enrolling 30,458 adults who underwent LT in the United States between January 2002 and June 2013. Based on these preoperative characteristics, a weighted scoring system was developed. Similarly, yet differently, using the extreme gradient boosting algorithm of gradient-boosted modeling deep machine learning strategy, the current study characterized various risk factors and ranked their individual contribution to the high-probability group instead of building a model to predict postoperative mortality. It was found that the significant risk factors for high probability were female sex, anemia, age older than 65 years, hypertension, dyslipidemia, and low glomerular filtration rate. The clinical meaning of these findings is that it would be possible to identify these high-risk patients for HFpEF using the HFA-PEFF score algorithm even in the subclinical or asymptomatic stage. Meanwhile, it would be feasible to intervene early once the diagnosis is made and optimize those significant risk factors in the pretransplant stage, to improve LT outcomes. The authors should be congratulated for their solid work here.

Besides the preceding findings, the authors further explored briefly the pathophysiology behind them. Their previous work on patients with cirrhosis demonstrated that patients with ESLD who have altered ventricular-arterial (VA) coupling have poor post-LT survival.[11] It was shown that HFpEF arises from VA coupling associated with aging, female sex, and hypertensive cardiac remodeling.[12] It was also reported that women are more susceptible to HFpEF than men because they exhibit more concentric left ventricular remodeling and less ventricular dilatation in response to arterial hypertension.[13] Given the finding that female sex is the top influential factor for the high-probability group after adjusting for other risk factors, the authors concluded that women might be more subject to VA coupling-associated HFpEF, thus should gain more attention in clinical practice. The authors should be congratulated again for their endeavors and the preceding findings.

With the endemic of obesity, diabetes mellitus, and nonalcoholic fatty liver disease (NAFLD), it was projected that NAFLD-related cirrhosis would be the second cause or even the first cause of LT in the United States in the future.[14] NAFLD has been shown to increase the risk of cardiovascular disease, including HFpEF.[15] With the prevalence of NAFLD and its risk factors, it is expected that HFpEF would be also more and more prevalent in the LT society. Unfortunately, the current study did not enroll any patients with NAFLD-cirrhosis ESLD. It would be very interesting and informative if a further study could be undertaken by enrolling this specific patient population, further validating the findings generated in the current study. Furthermore, the study did not include

the posttransplant clinical heart failure events in the major adverse cardiovascular events categories while evaluating the short-term outcomes, which could have been a solid internal validation strategy for the rationale of using the HFA-PEFF risk score. Given that a large percentage of patients fell within the category of intermediate-risk group (73.1%, 2,371 of 3,244 patients) by HFA-PEFF score, which indicated that step 3 and step 4 further functional studies would be needed, it would be amazing if more work could be focused on this subgroup population in the future. Last, while building the multivariate regression model, the current study failed to take the potential confounder-pulmonary disease history/status into consideration, which might have biased the study results we observed here.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

The author has reported that she has no relationships relevant to the contents of this paper to disclose.

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KEY WORDS cirrhotic cardiomyopathy, diastolic dysfunction, ejection fraction, heart, liver transplantation