12-24-2020

Hepatic Vein Flow Index During Orthotopic Liver Transplantation as a Predictive Factor for Postoperative Early Allograft Dysfunction

Yoshihisa Morita

Taro Kariya

Shunji Nagai
Henry Ford Health, snagai1@hfhs.org

Ahmed Itani
Henry Ford Health, AITANI1@hfhs.org

Michael Isley
Henry Ford Health, MISLEY1@hfhs.org

See next page for additional authors

Recommended Citation

Morita Y, Kariya T, Nagai S, Itani A, Isley M, and Tanaka K. Hepatic Vein Flow Index During Orthotopic Liver Transplantation as a Predictive Factor for Postoperative Early Allograft Dysfunction. J Cardiothorac Vasc Anesth 2020.

Authors
Yoshihisa Morita, Taro Kariya, Shunji Nagai, Ahmed Itani, Michael Isley, and Kenichi Tanaka

Journal of Cardiothoracic and Vascular Anesthesia 000 (2021) 1–8

Contents lists available at ScienceDirect

Journal of Cardiothoracic and Vascular Anesthesia

journal homepage: www.jcvaonline.com

Original Article

Hepatic Vein Flow Index During Orthotopic Liver Transplantation as a Predictive Factor for Postoperative Early Allograft Dysfunction

Yoshihisa Morita, MD[*,1], Taro Kariya, MD, PhD[†], Shunji Nagai, MD, PhD[‡], Ahmad Itani, MD[§], Michael Isley, MD[§], Kenichi Tanaka, MD, MSc[*]

[*]*Department of Anesthesiology, University of Maryland, Baltimore, MD*
[†]*Department of Anesthesiology, University of Tokyo, Tokyo, Japan*
[‡]*Transplant and Hepatobiliary Surgery, Henry Ford Hospital, Detroit, MI*
[§]*Department of Anesthesiology, Henry Ford Hospital, Detroit, MI*

Objectives: The authors devised a hepatic vein flow index (HVFi), using intraoperative transesophageal echocardiography and graft weight, and investigated its predictive value for postoperative graft function in orthotopic liver transplant.
Design: Prospective clinical trial.
Setting,: Single-center tertiary academic hospital.
Participants: Ninety-seven patients who had orthotopic liver transplant with the piggy-back technique between February 2018 and December 2019.
Measurements and Main Results: HVFi was defined with HV flow/graft weight. Patients who developed early graft dysfunction (EAD) had low HVFi in systole (HVFi sys, 1.23 *v* 2.19 L/min/kg, $p < 0.01$), low HVFi in diastole (HVFi dia, 0.87 *v* 1.54 L/min/kg, $p < 0.01$), low hepatic vein flow (HVF) in systole (HVF sys, 2.04 *v* 3.95 L/min, $p < 0.01$), and low HVF in diastole (HVF dia, 1.44 *v* 2.63 L/min, $p < 0.01$). More cardiac death, more vasopressors at the time of measurement, more acute rejection, longer time to normalize total bilirubin (TIME t-bil), longer surgery time, longer neohepatic time, and more packed red blood cell transfusion were observed in the EAD patients. All HVF parameters were negatively correlated with TIME t-bil (HVFi sys $R = -0.406$, $p < 0.01$; HFVi dia $R = -0.442$, $p < 0.01$; HVF sys $R = -0.44$, $p < 0.01$; HVF dia $R = -0.467$, $p < 0.01$). The receiver operating characteristic curve analysis determined the best cut-off levels of HVFi to predict occurrence of EAD (HVFi sys <1.608, HVFi dia <0.784 L/min/kg), acute rejection (HVFi sys <1.388, HVFi dia <1.077 L/min/kg), and prolonged high total bilirubin (HVFi sys <1.471, HVFi dia <1.087 L/min/kg).
Conclusions: The authors' devised HVFi has the potential to predict the postoperative graft function.

Key Words: early allograft dysfunction; piggy-back technique; orthotopic liver transplant; hepatic vein flow; transesophageal echocardiography

LIVER TRANSPLANTATION (LT) continues to be the gold standard for treating end-stage liver disease (ESLD), and the piggy-back technique has been widely used for orthotopic LT (OLT) since its introduction in 1989, mostly because of more stable intraoperative hemodynamics.[1,2] Outflow obstruction of the liver graft is a well-reported complication of the piggy-back technique, and may lead to allograft dysfunction, graft loss, and death.[2,3]

Intraoperative anesthetic management in LT can be challenging due to preoperative medical comorbidities, significant

This study was conducted at Henry Ford Hospital, then Y.M. was relocated to University of Maryland.

Y. Morita contributed the study for designing the study and manuscript writing. T. Kariya contributed for statistical analysis and helped with manuscript writing. A. Itani, M. Isley, and S. Nagai contributed for data gathering, and helped with manuscript writing. K. Tanaka contributed for manuscript writing.

[1]*Address correspondence to* Yoshihisa Morita, MD, Department of Anesthesiology, University of Maryland, 22 South Greene Street, Baltimore MD 21201.

E-mail address: ymorita@som.umaryland.edu (Y. Morita).

https://doi.org/10.1053/j.jvca.2020.12.034
1053-0770/

intraoperative hemodynamic changes, and periodic unexpected findings, such as intracardiac thrombi or pulmonary emboli;[4,5] and the usefulness of intraoperative transesophageal echocardiography (TEE) has been discussed in previous publications.[1,6,7] Although TEE use during LT can aid in the diagnosis and management of hemodynamic instability and is recommended in the practice guidelines from the American Society of Echocardiography (ASE)/Society of Cardiovascular Anesthesiologists (SCA) and the American Association for the Study of Liver,[8-10] its routine intraoperative use has limited scientific support.[6,7] Actually, TEE is relatively contraindicated in grade 3 or recently bleeding esophageal varices, which are common in ESLD, and the possibility for complications should not be ignored.[11-13] However, the biggest argument is that TEE findings can provide only a clinical impression, which is subjective to interobserver variability, although there is no doubt TEE provides important hemodynamic information.[1,7,14] An increasing number of reports show the usefulness of TEE to detect procedure-related complications, such as graft hepatic vein (HV) or inferior vena cava (IVC) stenosis.[6,10,15,16] However, no published study has performed the quantitative assessment of graft flow using intraoperative TEE. Because HV can be assessed with TEE, TEE-derived HV flow parameters have a potential to detect early allograft dysfunction (EAD) sooner and guide therapy to optimize the graft function. HV is the outflow of graft flow and can be an index of graft perfusion. Also, HV flow can be calculated using intraoperative TEE measurements. The authors' group recently demonstrated that hepatic vein flow index (HVFi), which was defined as TEE-measured HV flow/graft weight, potentially had good predictive value for postoperative EAD in piggy-back OLT patients.[17] The current study used the same methodology for calculating HVFi as the authors' previous retrospective study. The differences were (1) the current study was a prospective design, whereby HVFi was calculated before outcome data collection, and (2) the current study sought to demonstrate reproducibility of the HVFi score by means of intra-rater and inter-rater variances.

Methods

Study Design

This study was approved by the Henry Ford Health System Institutional Review Board (IRB #12156), and written consent was obtained before enrolling the patients. Also, this study was registered in ClinicalTrials.gov (NCT03814031).

This was a prospective, observational study of a cohort of adult patients who underwent OLT using the piggy-back technique between February 2018 and December 2019 at the Henry Ford Hospital in Detroit, Michigan. TEE data were collected from intraoperative TEE images as part of a prospective echocardiographic protocol measuring two-dimensional TEE-calculated hepatic vein flow (HVF) using transgastric modified HV view (Fig 1). In order to obtain the transgastric modified HV view, insert the probe into the stomach, find the transgastric basal view, rotate the probe right, identify the IVC as a

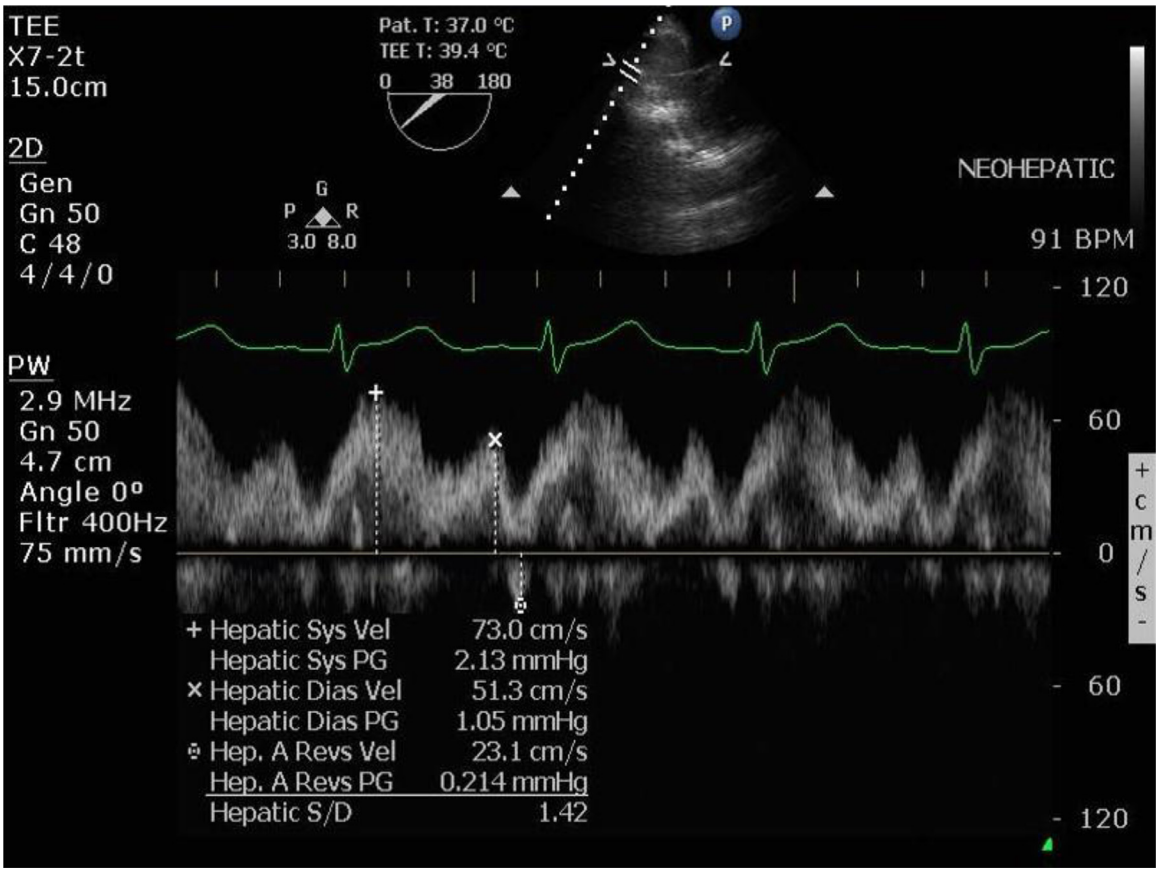

Fig. 1. Transgastric inferior vena cava view with hepatic vein velocity measurement.

large vascular structure in the liver, withdraw the probe to image drainage of the IVC into the right atrium, and adjust the omniplane angle (0˚-40˚) to image the HV as it drains into the IVC.

The patients' demographics, perioperative clinical information, and postoperative outcomes were collected from the authors' computerized patient database.

Patient Cohort

Inclusion criteria were adult patients undergoing the OLT piggy-back technique with TEE-measured HV flow between February 2018 and December 2019. Exclusion criteria were patient refusal to participate in the study, absolute TEE contraindication, inability to acquire appropriate images for HV flow measurement, or unavailability of a cardiac trained anesthesiologist.

All patients received general anesthesia with endotracheal intubation, standard American Society of Anesthesiologists monitoring, arterial blood pressure monitoring, central venous pressure monitoring, pulmonary artery pressure monitoring, and comprehensive TEE examination with designated protocol. Intraoperative anesthetics, mechanical ventilation, vasopressor, inotropic, and fluid/transfusion management were performed based on department protocol such as to maintain mean arterial pressure >65 mmHg, tidal volume 6-8 mL/ideal body weight (kg), positive end-expiratory pressure at 5-to-7 cmH_2O.

Data Collection

TEE images were collected intraoperatively by National Board of Echocardiography-certified advanced perioperative echocardiographers using an iE33 echocardiographic machine with an X7 TEE probe (Philips Medical Systems, Andover, MA), and were stored in Syngo Workflow (Siemens Medical Solution, Malvern, PA). Timing for acquiring TEE modified transgastric HV view was in the neohepatic phase before fascia closure. To obtain HV flow, the pulsed-wave Doppler (PWD) sample volume was set in the graft HV just distal to IVC-graft anastomosis where an acceptable flow envelope was obtained.

Echocardiography Parameters

Three investigators (A, B, and C), who were also National Board of Echocardiography-certified advanced perioperative echocardiographers, measured HVF in systole and diastole independently using TEE images, which were acquired by a single cardiac anesthesiologist (advanced TEE boarded). The authors calculated HVF as follows: HVF (L/min) = HV area (cm^2) x HV max velocity (cm/s) in systole and diastole x 60/1000, where HV area (cm^2) = square of HV radius (cm) x 3.14, and HV max velocity (cm/s) was measured by TEE PWD with sample volume selected in the HV (Fig 1), where diameter of HV was measured as well. Efforts were made to align PWD and HV. The authors defined HVFi as HVF/donor liver weight (kg). The authors adjusted HVF with graft weight because recently it is more common to assess graft flow with graft size.[18] To minimize selection bias, all the investigators were blinded to the hypothesis of the study.

Outcomes

The primary outcome was EAD, which was defined by the presence of one or more of the following: total bilirubin (t-bil) ≥10 mg/dL (171 μmol/L), or INR ≥1.6 on day 7, and ALT/AST >2,000 IU/L within the first seven days.[19,20] The secondary outcome was acute rejection within six-to-eight weeks after transplant, prolonged (>seven days) time to normalize total bilirubin (TIME t-bil), prolonged (>seven days) time to normalize INR (TIME inr), and prolonged (>seven days) time to normalize platelet count (TIME plt).

Statistical Analysis

For continuous variables, the normality test was performed using the Kolmogorov-Smirnov test. Continuous variables with normal distribution were displayed as mean ± standard deviation, and those with non-normal distribution were displayed as median and interquartile range. Categorical variables were presented as proportions and absolute numbers. The differences between the two groups were investigated using unpaired and paired Student t tests or the Mann-Whitney U test. The Chi-square or Fisher exact test was used for categorical variables. A correlation analysis was performed for HVFi and the times including TIME t-bil, TIME inr, and TIME plt (Spearman as non-normal distribution). Also, Youden's index was used for receiver operating characteristic (ROC) curve analysis to evaluate the appropriate cut-off value of HVFi for predicting EAD, acute rejection, and prolonged TIME t-bil (>seven days). The authors also performed subgroup risk adjustment analysis in the cardiac death group with bivariate analysis. Intrarater and inter-rater reliability analyses of HVFi were performed using intraclass correlation coefficient (ICC).[21-23] The authors randomly picked 30 images and obtained consistency ICC for interobserver variability using all 3three investigators (A, B, and C) and absolute-agreement ICC for intraobserver variability using investigator C, who measured all images twice with an interval of six-to-eight weeks.[23] For interobserver variability, three investigators post hoc determined HV diameter, peak systolic flow, and peak diastolic flow based on the PWD signal. All statistical analyses were performed using R (The R Foundation for Statistical Computing, Vienna, Austria. ver 4.0.2). All p values of less than 0.05 were considered statistically significant.

Sample Size Calculation

Assuming incidence of EAD was 23.2% (range of incidence was 2%-23%),[19,20] 70 patients in control and 21 patients in EAD were needed at the power of 80% and alpha 0.05 with achieving at least 0.7 for area under curve in ROC analysis. To be conservative and account for potential problems with imaging analysis, 97 patients were enrolled.

Results

Of the 120 eligible patients, 97 participated in the study (patient refusal to participate in the study: two patients, absolute TEE contraindication: five patients, damping of the HVs images: six patients, and technically challenging to obtain appropriate views for HVF measurement: ten patients). No turbulent flow was observed in HV in the authors' cohort. The characteristics of these 97 patients are shown in Tables 1 and 2. No significant gastrointestinal bleeding was reported in the authors' study. The median HVFi in the EAD group was significantly lower than the median HVFi in the non-EAD group. In addition, the best cut-off levels to predict EAD for HVFi sys was 1.608 and HVFi dia 0.784. Patients who developed EAD had low HVFi in systole (HVFi sys, 1.23 *v* 2.19 L/min/kg, $p < 0.01$), low HVFi in diastole (HVFi dia, 0.87 *v* 1.54 L/min/kg, $p < 0.01$), low HVF in systole (HVF sys, 2.04 *v* 3.95 L/min, $p < 0.01$), and low HVF in diastole (HVF dia, 1.44 *v* 2.63 L/min, $p < 0.01$). More cardiac death, more vasopressors at the time of measurement, more acute rejection, longer TIME t-bil, longer surgery time, and more packed red blood cell transfusion were observed in the EAD patients (Table 1). Correlation coefficients between HVFs and graft function index, such as TIME t-bil, TIME inr, and TIME plt, are shown in Table 3. All HVF parameters were correlated negatively with TIME t-bil (HVFi sys $R = -0.406$, $p < 0.01$; HFVi dia $R = -0.442$, $p < 0.01$; HVF sys $R = -0.44$, $p < 0.01$; HVF dia $R = -0.467$, $p < 0.01$). The scatter plot is shown in the EAD and non-EAD groups in Figure 2. The ROC curve analysis and Youden criterion determined the best cut-off levels of HVFis to predict occurrence of EAD (HVFi sys <1.608, HVFi dia <0.784 L/min/kg; Fig 3, A), acute rejection (HVFi sys <1.388, HVFi dia <1.077 L/min/kg; Fig 3, B), and prolonged high t-bil (HVFi sys <1.471, HVFi dia <1.087 L/min/kg; Fig 3, C). HVFi was superior to HVF in terms of predicting these outcomes. Subgroup risk adjustment by bivariate analysis in the cardiac death group is shown in Table 4. The authors chose donor age, model for end-stage liver disease (MELD), cold ischemic time (CIT), and warm ischemic time (WIT) as references based on previously reported risk factors for EAD.[19] The ICCs for the inter- and intraobserver analyses of HVFi were high both in HVFi sys (inter-rater 0.997, intrarater 0.998) and HVFi dia (inter-rater 0.993, intrarater 0.998; Table 5).

Table 1
Patient Demographics in EAD and Non-EAD Group

	EAD (n = 26)	No EAD (n = 71)	p Value
Donor Variables			
Age (y)	49 [40, 54.5]	41 [29, 54]	0.84
Female	15 (57.7%)	33 (46.5%)	0.37
DCD	9 (34.6%)	4 (5.63%)	<0.001
Liver weight (kg)	1.73 [1.6, 2.1]	1.7 [1.55, 1.90]	0.32
Recipient and Surgical Variables			
Age (y)	58 [45, 64.5]	55 [50.8, 64]	0.81
Female	11 (42.3%)	28 (39.4%)	0.82
MELD	22.5 [18, 28.8]	26 [17, 29]	0.69
HTN	15 (57.7%)	28 (39.4%)	0.166
DM	10 (38.5%)	15 (21.1%)	0.115
NASH	7 (26.9%)	13 (18.3%)	0.40
Alcoholic	4 (15.4%)	16 (22.5%)	0.576
HCC	2 (7.7%)	5 (7.0%)	1.0
Hepatitis C	0 (0%)	3 (4.2%)	0.562
Acute rejection	8 (30.8%)	5 (7.0%)	<0.01
Time to normal t-bil (d)	16 [10, 32]	5.5 [1, 20]	<0.01
Time to normal INR (d)	7 [5 to 9]	5 [4 to 7]	0.1
Time to normal platelet (d)	10 [8 to 13]	10 [8 to 12]	0.86
CIT (min)	306.5 [281.5, 345.8]	281.0 [246, 328]	0.08
WIT (min)	36.5 [29.3, 41]	33 [27, 44.5]	0.50
Op time (min)	415.0 [346.5, 472.8]	347 [300.5, 389.5]	0.001
Hepatectomy time (min)	95 [65, 101]	84 [55, 104]	0.27
Anhepatic time (min)	78 [60.0, 95]	70 [62, 83]	0.27
PRBC (unit)	4 [2, 9]	3 [0, 5]	0.02
FFP (unit)	7 [2.25, 12]	4 [2, 7.5]	0.06
Platelet (unit)	0.5 [0, 2]	0 [0, 1]	0.19
Cryoprecipitate (unit)	1 [0, 2]	0 [0, 2]	0.31
Cell savor (mL)	675 [450, 1325]	450 [225, 675]	0.06
Crystalloid (mL)	4000 [2625, 6175]	3200 [2000, 4400]	0.09
Colloids (mL)	700 [500, 1000]	750 [500, 1200]	0.67
UOP (mL)	525 [415, 966]	477 [321, 882.5]	0.44
EBL (mL)	1100 [1000, 2000]	1500 [1000 to 2200]	0.67

Abbreviations: CIT, cold ischemic time; DCD, donor of cardiac death; DM, diabetes mellitus; EAD, early allograft dysfunction; EBL, estimated blood loss; FFP, fresh frozen plasma; HCC, hepatocellular carcinoma; HTN, hypertension; MELD, model for end-stage liver disease; NASH, nonalcoholic steatohepatitis, PRBC, packed red blood cells; UOP, urine output; WIT, warm ischemic time.

Discussion

The authors' presented prospective observational study showed that HVFi and HVF obtained from intraoperative TEE were related to the postoperative graft function of OLT. HVF and HVFi were lower in patients with EAD and negatively correlated with the time to bilirubin normalization after the procedure. Lower HVFis were risk factors for EAD after adjustments with donor age, MELD, CIT, or WIT. ROC analyses revealed the cut-off values of HVFis to predict EAD, acute rejection, and prolonged high t-bil with fair sensitivity and specificity. HVFi was superior to HVF regarding these predictions because graft weight adjustment might have led to assess blood flow in each segment.[18]

In addition to intraoperative TEE's widely recognized purpose as a hemodynamic monitor in OLT, the benefits of assessing graft anastomosis patency with TEE qualitatively also have been reported.[6,10,15,16] This study was novel in that the authors quantitatively assessed HV flow and its correlation with postoperative graft function in the piggy-back technique. TEE is not without associated complications in ESLD, which include

Table 2
Hepatic Vein Parameters in EAD and Non-EAD Group

	EAD (n = 26)	No EAD (n = 71)	p Value
HV flow systolic index (L/min/kg)	1.23 [0.85, 1.73]	2.19 [1.28, 3.70]	< 0.001
HV flow diastolic index (L/min/kg)	0.87 [0.62, 1.32]	1.54 [1.07, 2.34]	< 0.001
HV flow systolic (L/min)	2.04 [1.38, 3.03]	3.95 [2.02, 6.40]	0.0035
HV flow diastolic (L/min)	1.44 [1.02, 2.20]	2.63 [1.69, 4.13]	0.0015
Portal vein flow (L/min)	1.27 [1.1, 1.5]	1.5 [1.2, 1.78]	0.34
Hepatic artery flow (L/min)	0.32 [0.2, 0.44]	0.35 [0.21, 0.59]	0.51
MAP at the time of measurement (mmHg)	65 [56.25, 70.25]	67 [62.0, 76.5]	0.16
CI at the time of measurement (L/min/m2)	4.86 [3.8, 5.85]	4.6 [3.28, 5.52]	0.587
More than 1 vasopressor at the time of measurement	22 (84.6%)	38 (53.5%)	< 0.01

NOTE. Vasopressors include vasopressin (0.01-0.03 unit/min) or norepinephrine (0.02-0.08 μg/kg/min).
Abbreviations: CI, cardiac index; EAD, early allograft dysfunction; HV, hepatic vein; MAP, mean arterial pressure.

Table 3
Spearman's Correlation Coefficients Between HVF and Graft Function Index

	TIME t-bil (d)	TIME inr (d)	TIME plt (d)
HVFi sys	−0.406 (p < 0.01)	−0.143 (p = 0.177)	−0.192 (p = 0.068)
HVFi dia	−0.442 (p < 0.01)	−0.142 (p = 0.179)	−0.0037 (p = 0.972)
HVF sys	−0.44 (p < 0.01)	−0.15 (p = 0.157)	−0.194 (p = 0.066)
HVF dia	−0.467 (p < 0.01)	−0.139 (p = 0.189)	−0.11 (p = 0.3)

Abbreviations: HVF, hepatic vein flow; HVFi dia, hepatic vein flow index in diastole; HVFi sys, hepatic vein flow index in systole; TIME inr, time to normalize INR; TIME plt, time to normalize platelet; TIME t-bil, time to normalize total bilirubin.

esophageal varices and coagulopathy, and its benefits and risks should be weighed on a case-by-case basis.[6,7] The ASE/SCA now recommends that images of the IVC and HVs be obtained as part of a comprehensive perioperative assessment,[8] and its value has been corroborated in several case reports[6,10,16,24-26] The modified HV view described in this study is not part of the basic TEE certification endorsed by the ASE/SCA,[8,27] and its utility has not been investigated widely in OLT. The authors believe that this is partly because of transplant anesthesiologists' unfamiliarity with obtaining this view. At the authors' institute, three out of the six transplant anesthesiologists are cardiac trained and readily available for acquiring necessary images, which might have led to a greater percentage of success in obtaining this view.

In previous studies, assessment of HV mostly has been done with perioperative transabdominal Doppler ultrasound, but mostly on waveform assessment. Britton, et al. reported damping of the HV signal, with Doppler ultrasound, as the first indication of rejection after pediatric LT.[28] The authors observed damping of the HV images in six patients, three of whom had acute rejection. Recently, Vetrugno et al. reported the importance of paying attention to HV-flow Doppler waveform by referring to detailed explanations on HV Doppler waveform.[10,29] Although Doppler ultrasound has the advantage of being able to identify flows in each HV, TEE comprehensively is able to assess HV flow, volume status, and cardiac function.

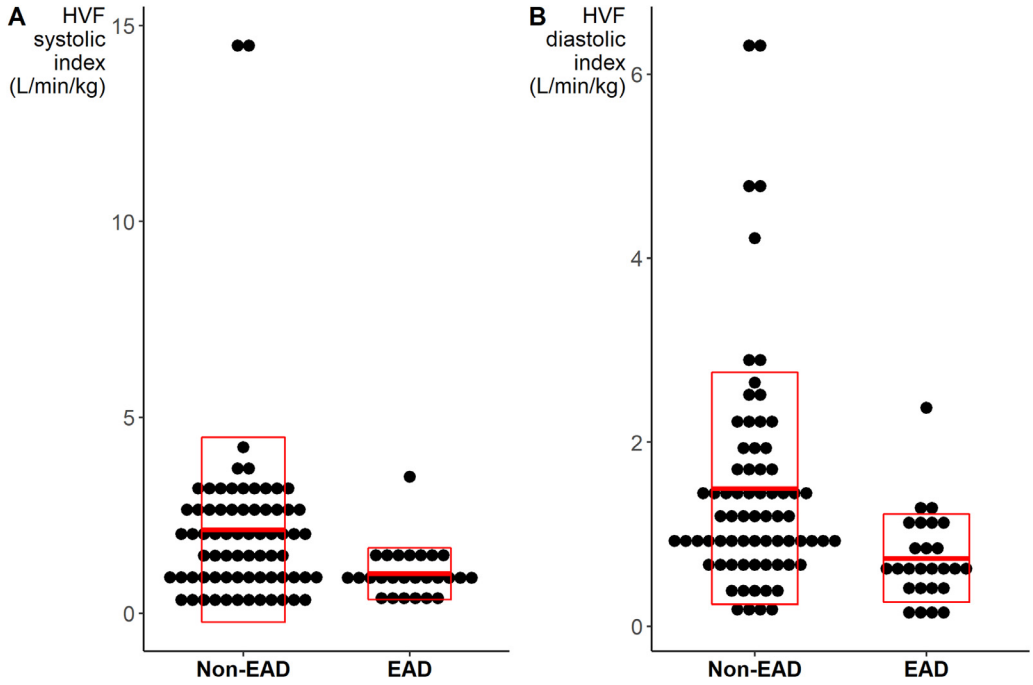

Fig. 2. Scatter plot distribution of HVF index in EAD and non-EAD group. (A) HVF systolic index grouped by EAD presence. (B) HVF diastolic index grouped by EAD presence. Note that each red box shows median 25 percentile and median 75 percentile in each group. Abbreviations: EAD, early allograft dysfunction; HVF, hepatic vein flow.

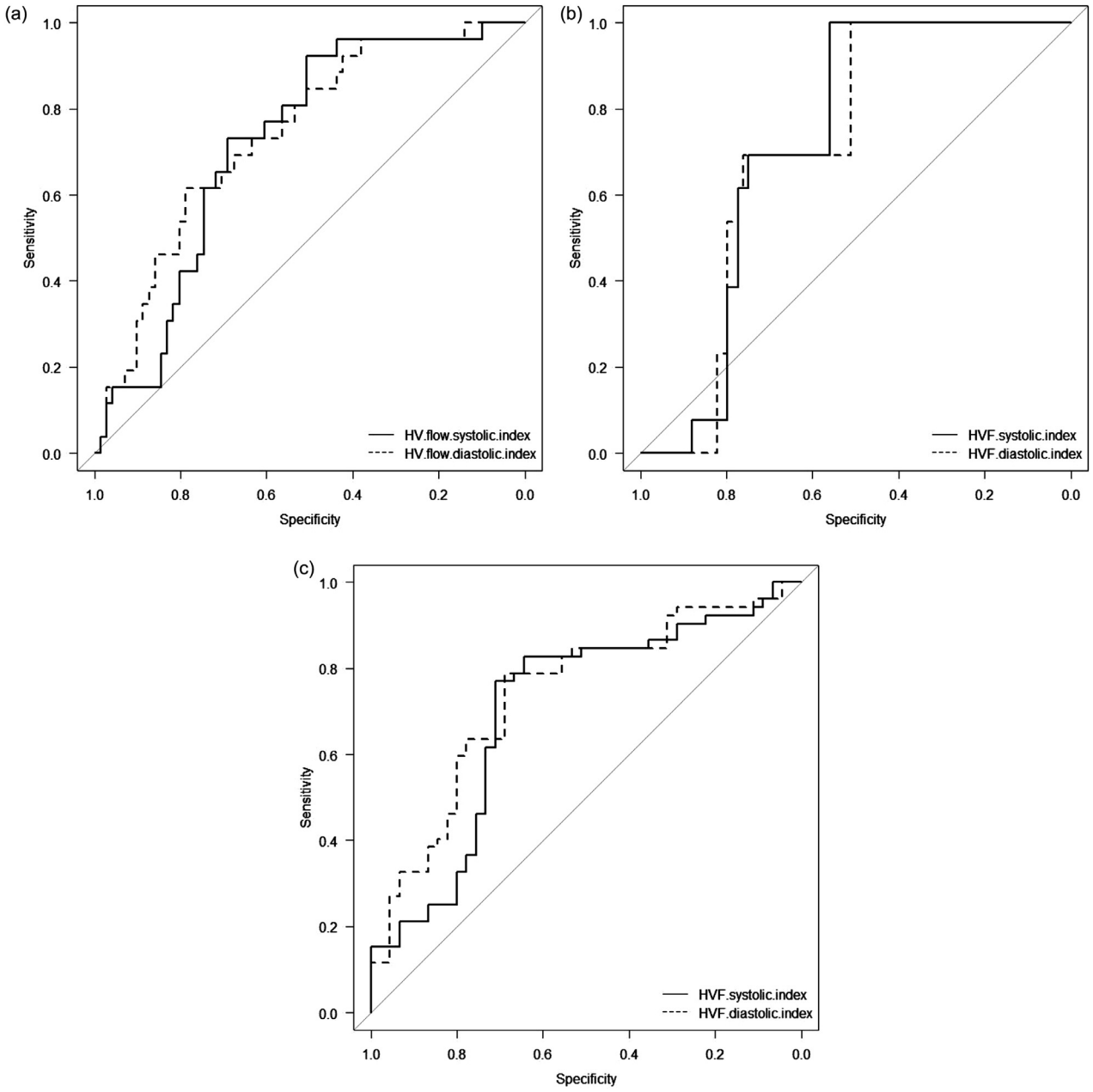

Fig. 3. (A). ROC curve analysis and Youden criterion to predict occurrence of EAD, HVFi sys <1.608 provides 53.5% specificity and 96.2% sensitivity in predicting EAD, while HVFi dia <0.784 provides 74.6% specificity and 65.4% sensitivity in predicting EAD (AUC 0.72 [95% CI 0.614-0.826] *v* 0.738 [95% CI 0.634-0.845], p = 0.425). AUC, area under the curve; CI, confidence interval; ROC, receiver operating characteristic.

(B). ROC curve analysis and Youden criteria to predict occurrence of acute rejection, HVFi sys <1.388 provides 56.0% specificity and 100% sensitivity in predicting acute rejection, while HVFi dia <1.077 provides 51.2% specificity and 100% sensitivity in predicting acute rejection (AUC 0.722 [95% CI 0.619-0.825] *v* 0.711[95% CI 0.6-0.821], p = 0.665) AUC, area under the curve; CI, confidence interval; HVFi dia, hepatic vein flow index in diastole; HVFi sys, hepatic vein flow index in systole; ROC, receiver operating characteristic.

(C). ROC curve analysis and Youden criteria to predict occurrence of prolonged TIME t-bil (TIME t-bil >7 days) HVFi sys <1.471 provides 71.1% specificity and 76.9% sensitivity in prolonged t-bil, while HVFi dia<1.087 provides 68.9 % specificity and 78.8 % sensitivity in prolonged t-bil (AUC 0.703 [95% CI 0.595-0.812] *v* 0.738 [95% CI 0.638-0.839], p = 0.128) AUC, area under the curve, EAD, early allograft dysfunction; HVFi dia, hepatic vein flow index in diastole; HVFi sys, hepatic vein flow index in systole; ROC: receiver operating characteristic, TIME t-bil: time to normalize total bilirubin.
EAD: early allograft dysfunction, HVFi: hepatic vein flow index

HV flow assessment would be important in predicting graft function given that inflow of the new graft includes the hepatic artery and portal vein, and outflow includes only the HVs. Suboptimal outflow may be due to suboptimal inflow or graft congestion, both of which are ominous signs for postoperative graft function. Previous correlation studies between intraoperative flow assessment of hepatic artery or portal vein and postoperative graft function were unable to show consistency in their correlation.[30-32] Takahashi et al. reported that this inconsistency between flow and graft function might be because of a

Table 4
Multivariable Logistic Regression for EAD

	OR (95% CI)	p Value
HVFi syst	0.313 (0.125-0.783)	0.013
Donor age	1.040 (0.988-1.090)	0.135
CIT	1.010 (0.998-1.010)	0.139
HVFi dia	0.136 (0.0285-0.646)	0.012
Donor age	1.050 (0.996-1.110)	0.071
CIT	1.010 (0.998-1.020)	0.118

Abbreviations: CI, confidence interval; CIT, cold ischemic time; EAD, early allograft dysfunction; HVFi dia, hepatic vein flow index in diastole; HVFi sys, hepatic vein flow index in systole; OR, odds ratio.

Table 5
ICC for HVFi sys and HVFi dia

	Group	ICC	95% CI
Inter-rater	HVFi sys	0.997	(0.995, 0.998)
	HVFi dia	0.993	(0.988, 0.996)
Intrarater	HVFi sys	0.998	(0.997, 0.999)
	HVFi dia	0.998	(0.996, 0.999)

Abbreviations: CI, confidence interval; HVFi dia, hepatic vein flow index in diastole; HVFi sys, hepatic vein flow index in systole; ICC, Intraclass Correlation Coefficient.

lack of consistency in the timing of measurements,[30] and the authors' data also showed that tendency. Another reason for this inconsistency could be explained by hepatic arterial buffer response. It is the ability of the hepatic artery to produce compensatory flow changes in response to changes in portal venous flow. This buffer system would adjust flows in hepatic artery and portal vein; however, it is not reported to affect HVF.[17]

This study was the first to assess HV flow (ie, outflow of the new graft) quantitatively using intraoperative TEE and its correlation with graft function. Reproducibility is the key for this new method of HVFi measurement, so choosing an easily measurable index is very important. The authors chose peak velocity over velocity time integral because of its simple measurement. The authors also devised HVFi, which is the ratio of HVF to graft weight. This HVFi worked better for predicting graft function. The authors assessed graft function in three ways: EAD, acute rejection, and TIME t-bil. EAD is a composite outcome that is reported to be correlated with graft loss and patient mortality.[19,20] Also, the authors chose trend of t-bil over trend of INR or platelet as an index of postoperative graft function because INR and platelet count can be affected by postoperative transfusion, as seen in differences of time to normalize t-bil, INR, and platelet in groups with EAD in Table 1. Not surprisingly, EAD, acute rejection, and TIME t-bil were significantly related. Obtaining the optimal modified TEE transgastric HV view is mandatory to measure HVF precisely in the neohepatic phase. Timing is vital; the retractor should be taken off for better alignment of the IVC and new graft, and perhaps before fascia closure, because the measurement might affect surgical decisions. Precise measurement of the HV radius is crucial because this number will be squared and affect more than HV velocity. Thus, obtaining images with clear margin HV is crucial.

At the authors' transplant institute, TEE is routine unless there is absolute contraindication; however, only cardiac trained anesthesiologists are able to pay attention to quantitative HV flow during OLT. This might be because cardiac anesthesiologists are familiar with assessing HV and IVC with TEE when they are confirming venous cannula position in cardiac surgeries. This emphasizes the importance of interaction between cardiac anesthesiologists and transplant anesthesiologists. The authors believe that TEE-modified transgastric HV view is encouraged because it is relatively easy to obtain with appropriate training, as 86.7% of the images were satisfactory for HVF assessment in this study; however, TEE probe manipulation should be minimized out of concern for esophageal varices and portal hypertensive gastropathy. For this reason, the measurement should be performed only for advanced TEE-boarded physicians. Alternative ultrasound imaging directly on the surface of the liver potentially could give similar measurements without TEE-related risks.

This study had some limitations. First, the limitations of a single center prospective study apply. Second, the authors assumed that the cross-section of HV was a circle, which might not always be true. Lastly, the authors' reproducibility assessment was done on the same images and might not be the best assessment for reproducibility of HVF in each hemodynamic situation. The rationale for choosing the same images for HVF assessment was that HVF theoretically is stable regardless of the sample volume location given the concept "continuity of flow" as long as hemodynamic situation is the same. The authors were able to say that reproducibility of HVF measurement for the same images is reasonable as long as Doppler image quality is optimal. Also, angulation of PWD and HV might have to be considered, even though efforts were made to align these two lines.

The authors' methodology of measuring HVF using TEE (both in systole and diastole) has the potential to predict the postoperative graft function before skin closure and postoperative management. The work that has been done in the current study was to propose a cut-off value for the novel HVFi score; however, the predictive value of this score is yet to be tested. In future study to determine the predictive value of the HVFi, this cut-off should be applied to a different sample in a prospective fashion. This would involve recruiting a sample of patients for planned OLT. First HVFi would be measured for all participants and a risk of EAD calculated. The risk of EAD in the study population based on HVFi then would be compared with actual EAD. Then, the predictive value of the HVFi also could be compared with a range of other predictive factors (eg, MELD, duration of surgery, and WIT to determine if addition of HVFi improves the risk estimate). The authors also might be able to discuss treatment options based on measured HVFi and other clinical information including low inflow and graft congestion.

The authors hope that this study will encourage transplant anesthesiologists to pay attention to graft flows with TEE in OLT.

References

1 Markin NW, Ringenberg KJ, Kassel CA, et al. 2018 clinical update in liver transplantation. J Cardiothorac Vasc Anesth 2019;33:3239–48.
2 Tzakis A, Todo S, Starzl TE. Orthotopic liver transplantation with preservation of the inferior vena cava. Ann Surg 1989;210:649–52.
3 Parrilla P, Sánchez-Bueno F, Figueras J, et al. Analysis of the complications of the piggy-back technique in 1,112 liver transplants. Transplantation 1999;67:1214–7.
4 Raval Z, Harinstein ME, Skaro AI, et al. Cardiovascular risk assessment of the liver transplant candidate. J Am Coll Cardiol 2011;58:223–31.
5 Peiris P, Pai SL, Aniskevich S 3rd, et al. Intracardiac thrombosis during liver transplant: A 17-year single-institution study. Liver Transpl 2015;21:1280–5.
6 Isaak RS, Kumar PA, Arora H. Pro: Transesophageal echocardiography should be routinely used for all liver transplant surgeries. J Cardiothorac Vasc Anesth 2017;31:2282–6.
7 Cywinski JB, Maheshwari K. Con: transesophageal echocardiography is not recommended as a routine monitor for patients undergoing liver transplantation. J Cardiothorac Vasc Anesth 2017;31:2287–9.
8 Hahn RT, Abraham T, Adams MS, et al. Guidelines for performing a comprehensive transesophageal echocardiographic examination: Recommendations from the American Society of Echocardiography and the Society of Cardiovascular Anesthesiologists. J Am Soc Echocardiogr 2013;26:921–64.
9 Murray KF, Carithers RL Jr. AASLD. AASLD practice guidelines: Evaluation of the patient for liver transplantation. Hepatology 2005;41:1407–32.
10 Vetrugno L, Barbariol F, Baccarani U, et al. Transesophageal echocardiography in orthotopic liver transplantation: A comprehensive intraoperative monitoring tool. Crit Ultrasound J 2017;9:15.
11 Soong W, Sherwani SS, Ault ML, et al. United States practice patterns in the use of transesophageal echocardiography during adult liver transplantation. J Cardiothorac Vasc Anesth 2014;28:635–9.
12 Markin NW, Sharma A, Grant W, et al. The safety of transesophageal echocardiography in patients undergoing orthotopic liver transplantation. J Cardiothorac Vasc Anesth 2015;29:588–93.
13 Spier BJ, Larue SJ, Teelin TC, et al. Review of complications in a series of patients with known gastro-esophageal varices undergoing transesophageal echocardiography. J Am Soc Echocardiogr 2009;22:396–400.
14 Dalia AA, Flores A, Chitilian H, et al. A comprehensive review of transesophageal echocardiography during orthotopic liver transplantation. J Cardiothorac Vasc Anesth 2018;32:1815–24.
15 Vetrugno L, Barnariol F, Bignami E, et al. Transesophageal ultrasonography during orthotopic liver transplantation: Show me more. Echocardiography 2018;35:1204–15.
16 Vanneman MW, Dalia AA, Crowley JC, et al. A focused transesophageal echocardiography protocol for intraoperative management during orthotopic liver transplantation. J Cardiothorac Vasc Anesth 2020;34:1824–32.
17 Morita Y, Navas-Blanco JR, Isley M, et al. Hepatic vein flow index during orthotopic liver transplantation as predictive factor for postoperative early allograft dysfunction. Echocardiography 2019;36:2282–3.
18 Eipel C, Abshagen K, Vollmar B. Regulation of hepatic blood flow: The hepatic arterial buffer response revisited. World J Gastroenterol 2010;16:6046–57.
19 Olthoff KM, Kulik L, Samstein B, et al. Validation of a current definition of early allograft dysfunction in liver transplant recipients and analysis of risk factors. Liver Transpl 2010;16:943–9.
20 Deschenes M. Early allograft dysfunction: Causes, recognition, and management. Liver Transpl 2013;19(Suppl 2):S6–8.
21 Koo TK, Li MY. A guideline of selecting and reporting intraclass correlation coefficients for reliability research. J Chiropr Med 2016;15:155–63.
22 Shrout PE, Fleiss JL. Intraclass correlations: Uses in assessing rater reliability. Psychol Bull 1979;86:420–8.
23 McGraw KO, Wong SP. Forming inferences about some intraclass correlation coefficients. Psychol Methods 1996;1:30–46.
24 Meierhenric R, Gauss A, Georgieff M, et al. Use of multi-plane transoesophageal echocardiography in visualization of the main hepatic veins and acquisition of Doppler sonography curves. Comparison with the transabdominal approach. Br J Anaesth 2001;87:711–7.
25 Aubuchon J, Maynard E, Lakshminarasimhachar A, et al. Intraoperative transesophageal echocardiography reveals thrombotic stenosis of inferior vena cava during orthotopic liver transplantation. Liver Transpl 2013;19:232–4.
26 Bjerke RJ, Mieles LA, Borsky BJ, et al. The use of transesophageal ultrasonography for the diagnosis of inferior vena caval outflow obstruction during liver transplantation. Transplantation 1992;54:939–41.
27 Reeves ST, Finley AC, Skubas NJ, Council on Perioperative Echocardiography of the American Society of Echocardiography; Society of Cardiovascular Anesthesiologists. Basic perioperative transesophageal echocardiography examination: A consensus statement of the American Society of Echocardiography and the Society of Cardiovascular Anesthesiologists. J Am Soc Echocardiogr 2013;26:443–56.
28 Britton PD, Lomas DJ, Coulden RA, et al. The role of hepatic vein Doppler in diagnosing acute rejection following paediatric liver transplantation. Clin Radiol 1992;45:228–32.
29 Scheinfeld MH, Bilali A, Koenigsberg M. Understanding the spectral Doppler waveform of the hepatic veins in health and disease. Radiographics 2009;29:2081–98.
30 Takahashi K, Nagai S, Putchakayala KG, et al. Prediction of biliary anastomotic stricture after deceased donor liver transplantation: The impact of platelet counts - a retrospective study. Transpl Int 2017;30:1032–40.
31 Pratschke S, Meimarakis G, Mayr S, et al. Arterial blood flow predicts graft survival in liver transplant patients. Liver Transpl 2011;17:436–45.
32 Spitzer AL, Dick AAS, Bakthavatsalam R, et al. Intraoperative portal vein blood flow predicts allograft and patient survival following liver transplantation. HPB (Oxford) 2010;12:166–73.