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Intraoperative Hyperspectral Imaging Predicts Early Allograft Dysfunction and Overall Survival in Liver Transplantation

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Objective: This study explored the novel application of hyperspectral imaging (HSI) for in vivo allograft perfusion assessment during liver transplantation (LT) and its potential value for predicting early allograft dysfunction (EAD), graft, and overall survival (OS).

Background: LT is a well-established therapy for acute and chronic liver diseases, with excellent outcomes. However, a significant proportion of recipients experience EAD, which affects graft and OS. EAD is associated with ischemia-reperfusion injury. HSI is a noninvasive imaging modality that provides information on tissue characteristics, such as tissue hemoglobin, water index, oxygenation, and perfusion.

Methods: We included all patients who underwent orthotopic LT with full-size allografts between 2019 and 2021. HSI was performed 15 minutes after reperfusion of the donor liver and subsequently analyzed. Furthermore, we collected data on postoperative graft function and clinical outcomes.

Results: A total of 73 LT recipients were included in this study. Around 56.9% had expanded criteria donors (N = 41). The mean model for end-stage liver disease score was 22 (±10). Eighteen patients (25%) had EAD. The statistical analysis demonstrated that recipients with EAD had significantly lower near-infrared (NIR) perfusion values after reperfusion. Recipients with low NIR had more pronounced reperfusion injury in postoperative laboratory studies. OS was significantly lower in recipients with low NIR than in those with high NIR (P = 0.049).

Conclusions: HSI is a promising, noninvasive tool, offering real-time, detailed graft perfusion assessment during LT. The fusion of spatial and spectral information is unique to HSI, making it an essential imaging technology for the further development of AI applications in surgery.

Keywords: early allograft dysfunction, hyperspectral imaging, ischemia-reperfusion injury, liver transplantation

INTRODUCTION

Liver transplantation (LT) has become an established therapeutic option for patients with acute and chronic liver diseases with excellent outcomes.[1,2] However, 20% to 40% of allografts develop impaired liver function after transplantation. Allograft dysfunction within the first 7 postoperative days is referred to as early allograft dysfunction (EAD). EAD is associated with significantly reduced organ and recipient survival.[3–5] A common definition of EAD is an increase of the alanine aminotransferase (ALT) or aspartate aminotransferase (AST) to >2000 U/l within the first week after LT, total serum bilirubin of >10 mg/dl, or an increase of the international normalized ratio (INR) to >1.6 on the 7th postoperative day.[4,5]

The etiology of EAD is not yet fully understood. Ito et al[6] showed that EAD correlates with the histological severity of the ischemia-reperfusion injury (IRI). IRI is the result of ischemic injury mainly of sinusoidal endothelial cells and the depletion of hepatocellular energy reserves during cold ischemia time.[7] This process is accelerated during warm ischemia, which leads to the formation of free radicals. Upon allograft reperfusion, the sinusoidal endothelium disintegrates, and the sinusoids constrict. An inflammatory reaction with secretion of inflammatory mediators by Kupffer cells leads to adherence and aggregation of leukocytes and thrombocytes and consecutive microthrombosis of the sinusoids, impairing microcirculation and causing interstitial edema.[7,8] The resulting organ damage is known as IRI. In its most severe form, the IRI can cause a "no flow" phenomenon with a total perfusion arrest within the allograft. A severe IRI has been shown to cause biliary complications and increase the incidence of acute allograft rejections.[9,10]

Therefore, intraoperative in vivo assessment of allograft reperfusion should reflect the extent of IRI and, consecutively, the risk of postoperative EAD. Reduced arterial and portal venous flow after reperfusion measured by Doppler ultrasound are important risk factors for primary nonfunction or EAD of the donor liver.[11,12] Another method for evaluating graft perfusion is indocyanine green (ICG) angiography. The ICG dye is injected intravenously and shows fluorescence under near-infrared (NIR) light. It can be detected with special camera systems and allows not only the evaluation of liver perfusion but also the perfusion of distinct anatomic structures such as

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the bile duct.[13] The quality of hepatic tissue perfusion measured using ICG angiography shows a significant correlation with the incidence of EAD.[14]

Hyperspectral imaging (HSI) is a radiation- and contact-free, noninvasive modality of tissue characterization and perfusion assessment approved for clinical use. HSI was developed in the 1970s by NASA for satellite-based characterization and cartography of geologic structures.[15] It relies on the simultaneous detection of a multitude of electromagnetic spectra. Therefore, in an HSI image, each pixel is composed of 2 spatial dimensions (x, y) and a spectral dimension (z), and is called a hypercube.[15] The obtained images are processed, and the distinct spectral characteristics of the tissue allow the extraction of parameters such as organ hemoglobin index (OHI), tissue water index (TWI), tissue oxygenation (StO_2), and tissue perfusion (NIR perfusion index) up to 6 mm in depth.[16]

The use of HSI in hepatopancreatobiliary surgery has been described previously for liver perfusion assessment after occlusion of the gastroduodenal artery in pylorus-preserving pancreaticoduodenectomy, demarcation of the resection plane in anatomic liver surgery, and assessment of liver perfusion quality after preoperative portal vein embolization.[17–19]

In transplant surgery, the use of HSI for the assessment of kidney allograft perfusion quality and its correlation with postoperative delayed graft function has been shown, as well as the evaluation of ureteral perfusion.[20] The feasibility of HSI has also been demonstrated in normothermic machine perfusion of donor livers, and a significant correlation of HSI measurements with pH and lactate levels has been demonstrated.[21] Furthermore, HSI has been used to noninvasively characterize the degree of hepatic steatosis.[22]

To the best of our knowledge, there are no published studies on the in vivo assessment of graft perfusion using HSI in LT and its impact on postoperative graft function.

This study aimed to evaluate the feasibility of HSI for allograft perfusion assessment in LT and its predictive value for the primary endpoint EAD. The secondary endpoints were overall organ and recipient survival, biliary complications, and graft rejection.

METHODS

Patients

All patients who underwent LT at our institution (University Hospital Leipzig, Germany) between February 2019 and November 2021 were included. The intraoperative use of the HSI system and prospective data collection were approved by the local ethics committee. All patients underwent orthotopic LT with full-size allografts of donors after brainstem death. Recipients who underwent split LT, machine perfusion of the donor organ, or retransplantation were excluded from the study. All recipients received immunosuppressive therapy with tacrolimus, mycophenolate mofetil, and steroids, according to our institution's protocol.

Clinical data were collected from organ donors and recipients. The following organ donor data were collected: donor age, donor body mass index (BMI), time of cross-clamp at organ procurement, and expanded criteria donor (ECD) status.

ECD status was defined according to Eurotransplant: donor age >65 years, intensive care unit stay with ventilation >7 days, BMI >30 kg/m^2, steatotic liver >40%, serum sodium >165 mmol/L, serum ALT >105 U/L, serum AST >90 U/L, serum Bilirubin >3 mg/dL or >51 µmol/L.[23]

All donor organs were stored in static cold storage using histidine-tryptophan-ketoglutarate solution.

The data collected from the recipients were age, sex, BMI, and model for end-stage liver disease score at the time of transplantation. Cold ischemic time (CIT) and warm ischemic time (WIT) were recorded. The CIT was defined as the time between the start of cold perfusion of the organ donor and the start of graft implantation in the recipient. The WIT was defined as the time from the start of graft implantation in the recipient to reperfusion of the graft with the recipient's blood. We performed simultaneous portal and arterial reperfusion for every transplantation in accordance with our institution's protocol. Furthermore, the operative time, number of packed red blood cell transfusions during transplantation, and inferior vena cava reconstruction technique (piggyback *vs* caval replacement) were recorded.

The following routine laboratory parameters were recorded daily for each recipient up to the 7th postoperative day: hemoglobin, AST, ALT, total bilirubin, albumin, and INR.

Our primary outcome was the occurrence of EAD according to the definition of Olthoff et al[4] and primary nonfunction. The secondary outcomes were graft survival, defined as the time from transplantation to either retransplantation or recipient death, and overall survival (OS), defined as the time from transplantation to recipient death. In addition, we recorded the incidence of biliary complications requiring interventions (either reoperation or interventional techniques), biopsy-proven cellular rejection, and antibody-mediated rejection proven by the detection of donor-specific antibodies.

Hyperspectral Imaging

HSI was performed using the TIVITA System (Diaspective Vision GmbH, Am Salzhaff-Pepelow, Germany). Image acquisition was performed 15 min after graft reperfusion. The HSI imaging system was placed above the graft with the aid of an inbuilt electro-optical positioning system, centering on liver segment four (IV). The distance from the graft was 30 cm. The light in the operating theater was dimmed during image acquisition to avoid reflection on the surface of the liver capsule.

Image processing took place using the software provided by the manufacturer (TIVITA Suite Tissue, Diaspective Vision GmbH, Am Salzhaff-Pepelow, Germany). The region of interest for the measurement of StO_2, NIR perfusion, the OHI, and the TWI was manually defined. Areas with light reflection artifacts were avoided. In this step, investigators were blinded for the patient outcome (Fig. 1).

Statistical Analysis

Quantitative variables are expressed as means with standard deviations. For comparison of groups, the t test and Mann–Whitney *U* test were performed. For all statistical tests, $P < 0.05$ was considered statistically significant. Statistical analysis was performed using IBM SPSS Statistics software (version 29; IBM, Armonk, NY).

RESULTS

Patient Characteristics

A total number of 73 patients were included in the study. The mean recipient age was 57 (±9) years, with 53 male (72.6%) and 20 female (27.4%) recipients. The mean age of the donors was 56 (±16) years. The mean recipient BMI was 27.04 (±4.43) and the mean donor BMI was 28.79 (±7.34). More than half of the donors were ECD (n = 41; 56.9%). The mean recipient model for end-stage liver disease score at the time of transplantation was 22 (±10).

However, 84.9% (n = 62) of all transplantations were performed using the piggyback technique, whereas 15.1% (n = 11) of the patients underwent transplantation with bicaval anastomosis. The mean operative time was 447 ± 101 minutes. The mean CIT was 673.67 minutes. The mean WIT was 50 ± 14 minutes. A mean of 4 units of red blood cell concentrate (250 mL each) was transfused. The mean intensive care unit stay was 10 days.

EAD was observed in 18 patients (25%). No patients in the cohort had primary nonfunction. Nine patients (12.7%) had histology-proven cellular rejection and 5 patients (7%) had antibody-mediated rejection. Postoperative biliary complications occurred in 12 (16.7%). There were no clinically apparent thromboses or relevant stenoses of hepatic artery, portal vein, or vena cava in the observation period.

Recipients With Early Allograft Dysfunction had Significantly Lower NIR Perfusion Values

The cohort was divided into recipients with and without EAD. Recipients with EAD had a significantly lower NIR perfusion index after reperfusion of the donor liver than those without EAD (0.13 *vs* 0.53; $P = 0.007$). No significant differences were observed for oxygenation (StO_2), TWI, and OHI (Fig. 2).

Furthermore, in recipients with EAD, we observed significantly higher donor BMI (31.46 ± 8.84 *vs* 27.33 ± 5.37; $P = 0.022$) and significantly longer cold ischemia time (743.28 ± 18.38 *vs* 648.02 ± 141.86 minutes; $P = 0.025$) than in recipients without EAD (Table 1).

We aimed to analyze the prognostic value of the NIR perfusion index for our primary endpoint EAD, and the OS. Therefore, we constructed a receiver operating characteristic curve with the primary endpoint EAD to determine the cutoff value for the NIR perfusion index. Receiver operating characteristic analysis yielded a significant area under the curve, indicating that the NIR perfusion index is of diagnostic value for EAD. The cutoff value determined by the Youden index was 0.0037 for the NIR perfusion index. This provided a sensitivity of 68% and a specificity of 73.3% (Fig. 3).

The entire recipient group was divided into a high- and a low-NIR perfusion index group. Comparison between these groups showed no significant difference in any donor and recipient variables, except for EAD ($P = 0.007$) and TWI ($P < 0.001$) (Table 2).

Recipients With Low-NIR Perfusion Index Had Signs of More Pronounced Reperfusion Injury

We compared the postoperative laboratory parameters of the patients with low and high NIR perfusion indices. Recipients

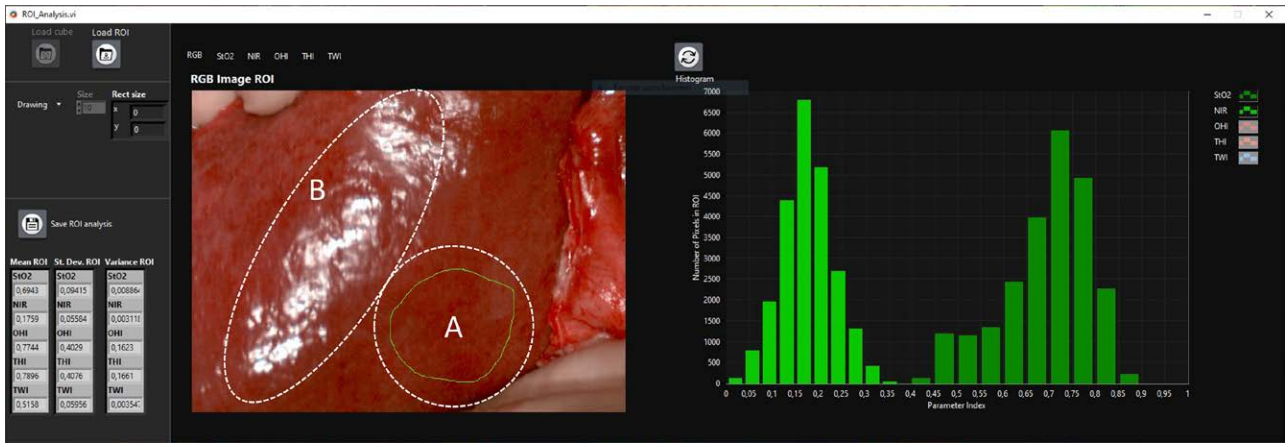

FIGURE 1. Exemplary picture of the image analysis using the TIVITA Suite Tissue software (Diaspective Vision GmbH, Am Salzhaff-Pepelow, Germany). The ROI for measurement of StO_2, near-infrared perfusion index, organ hemoglobin index, and tissue water index was manually defined (A). Areas with light reflection artifacts were avoided (B). ROI, region of interest.

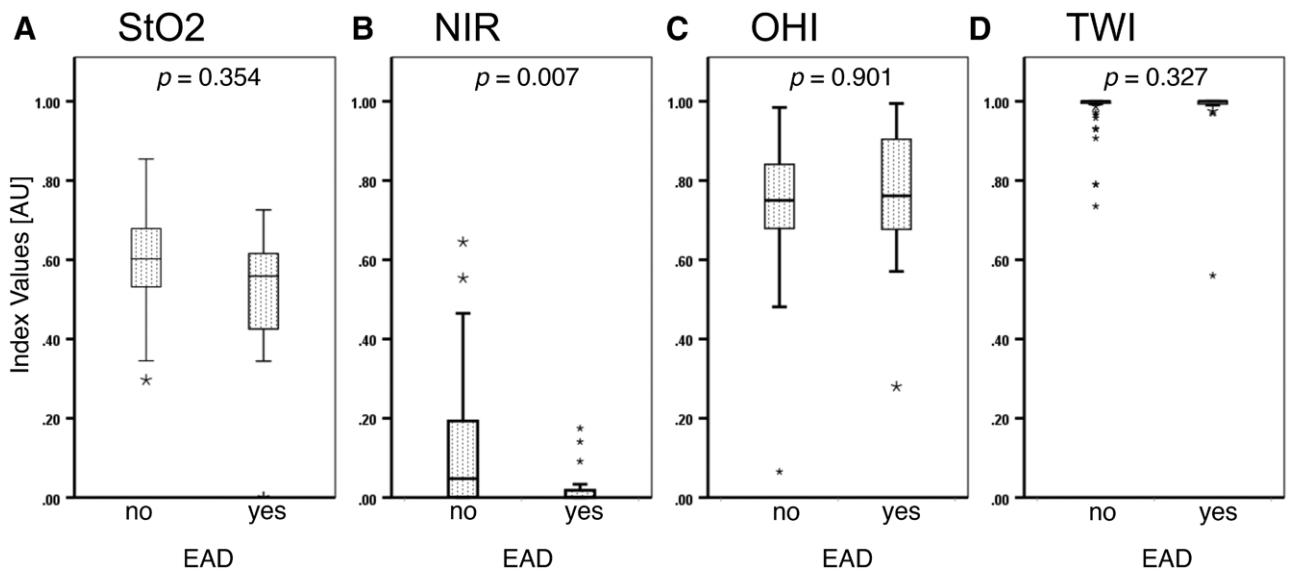

FIGURE 2. Comparison of StO_2 (A), NIR perfusion index (B), OHI (C), and TWI (D) between recipients with and without EAD as measured by hyperspectral imaging. *P* values were calculated by the Mann–Whitney *U* test.

TABLE 1.

Donor and Recipient Characteristics Grouped by the Occurrence of Early Allograft Dysfunction

		Early Allograft Dysfunction (EAD)								
		No				Yes				
		number	%	Mean	SD	number	%	Mean	SD	*P**
Donor age				55	17			58	11	0.554
Donor BMI				27.33	5.37			31.46	8.84	0.022
Expanded criteria donor	No	26	49.1			5	27.8			0.116
	yes	27	50.9			13	72.2			
Recipient gender	Male	38	70.4			14	77.8			0.543
	Female	16	29.6			4	22.2			
Recipient age				57	9			59	7	0.377
Recipient BMI				27.11	4.36			26.55	4.67	0.646
Recipient MELD				23	10			19	8	0.121
CIT (minutes)				648.02	141.86			743.28	180.38	0.025
WIT (minutes)				48.69	13.225			54.47	16.982	0.151
Operation time (minutes)				451	107			432	83	0.507
No. of red blood cell concentrates				4	4			3	3	0.106
Operation technique	Piggyback	44	81.5			17	94.4			0.186
	Bicaval anastomosis	10	18.5			1	5.6			
ICU stay (days)				11	20			8	5	0.497
Rejection	No	42	79.2			15	83.3			0.459
	Cellular	8	15.1			1	5.6			
	Humoral	3	5.7			2	11.1			
Postoperative biliary complications	No	43	79.6			17	94.4			0.144
	Yes	11	20.4			1	5.6			
HSI StO_2				0.59	0.13			0.5	0.18	0.064
HSI NIR				0.12	0.16			0.03	0.06	0.007
HSI OHI				0.75	0.16			0.76	0.19	0.901
HSI TWI				0.37	0.08			0.36	0.08	0.491

Values are presented as mean ± standard deviation for continuous variables and n (%) for categorical variables.

**P* for two-tailed *t* test (continuous variables) or chi-square test (categorical variables).

P values < 0.05 were considered statistically significant and are indicated as bold numbers.

MELD indicates model for end-stage liver disease.

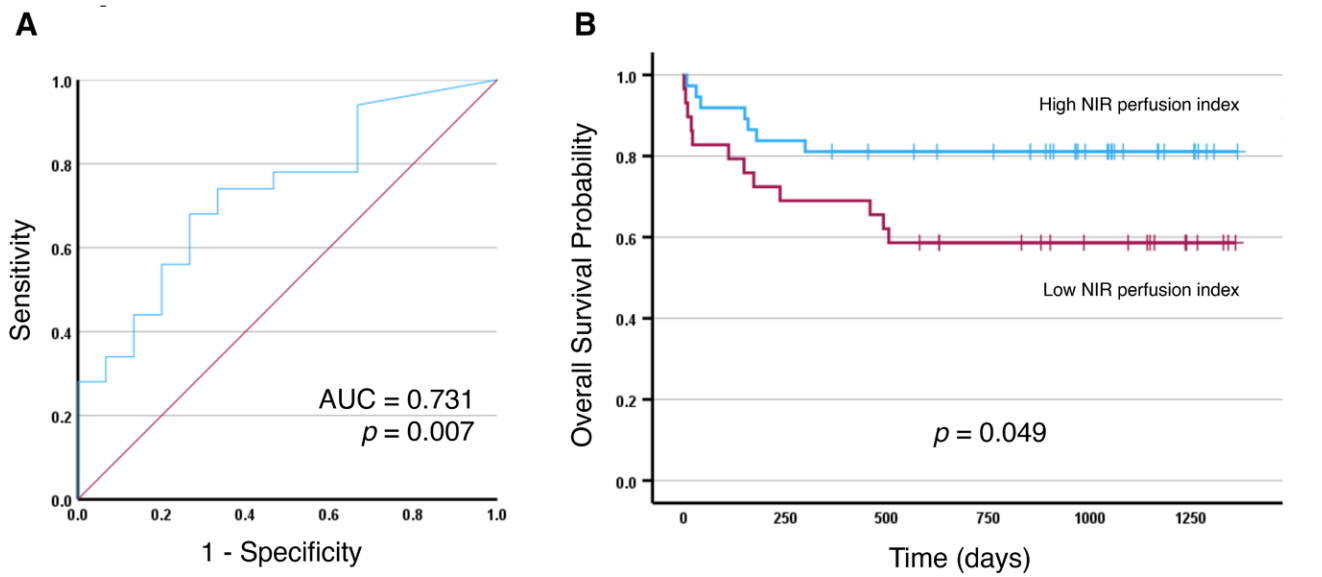

FIGURE 3. A, ROC curve for NIR perfusion index with EAD as binary outcome variable. B, Kaplan–Meier's analysis for overall survival based on NIR perfusion index with ROC-derived cutoff value. *P* values are calculated with the log-rank test. AUC, area under the curve; ROC, receiver operating characteristic.

with low NIR showed significantly higher ALT and AST values on postoperative days 1 and 2 after LT than those with a high NIR perfusion index (Fig. 4).

No significant difference was detected in the postoperative serum albumin, total bilirubin, and INR values between the low- and high-NIR perfusion index groups.

Recipients With Low-NIR Perfusion Index Have a Significantly Shorter Overall Survival

The mortality rate during the observation period was 27% (n = 20). None of the recipients in our cohort underwent retransplantation. However, 4 recipients died due to graft failure during follow-up. We performed Kaplan–Meier analysis

TABLE 2.

Donor and Recipient Characteristics Grouped by Receiver Operating Characteristic Derived Cutoff Value for the Near-infrared Perfusion Index

		NIR Perfusion Index								
		High				Low				
		Number	%	Mean	SD	Number	%	Mean	SD	*P**
Early allograft dysfunction	No	33	89.2			17	60.7			0.007
	Yes	4	10.8			11	39.3			
Donor age				55	16			58	15	0.517
Donor BMI				28.72	5.98			28.63	7.97	0.958
Expanded criteria donor	No	15	40.5			12	42.9			0.851
	Yes	22	59.5			16	57.1			
Recipient gender	Male	27	73			21	72.4			0.96
	Female	10	27			8	27.6			
Recipient age				56	11			58	6	0.419
Recipient BMI				27.42	4.47			25.98	4.3	0.195
Recipient MELD				24	9			22	10	0.438
CIT (minutes)				645.62	151.9			708.32	173.8	0.127
WIT (minutes)				50	12			49	17	0.892
Operation time (minutes)				450	105			438	106	0.668
Number of red blood cell concentrates				5	4			4	4	0.556
Operation technique	Piggyback	30	81.1			25	86.2			0.579
	Bicaval anastomosis	7	18.9			4	13.8			
ICU stay (days)				12	24			10	10	0.693
Rejection	No	27	75			24	85.7			0.55
	Cellular	6	16.7			3	10.7			
	Humoral	3	8.3			1	3.6			
Postoperative biliary complications	No	31	83.8			22	78.6			0.592
	Yes	6	16.2			6	21.4			
HSI StO_2				0.6	0.12			0.53	0.16	0.036
HSI NIR				0.18	0.16			0.0007	0.001	<0.001
HSI OHI				0.78	0.13			0.71	0.19	0.077
HSI TWI				0.4	0.07			0.34	0.07	<0.001

Values are presented as mean ± standard deviation for continuous variables and n (%) for categorical variables.

**P* for two-tailed *t* test (continuous variables) or chi-square test (categorical variables).

P values < 0.05 were considered statistically significant and are indicated as bold numbers.

ICU indicates intensive care unit; MELD, model for end-stage liver disease.

to assess the OS for recipients with versus without EAD and for recipients with low versus high NIR perfusion index. No difference in OS was detected between recipients with and without EAD on Kaplan–Meier analysis. However, the OS in recipients with a low NIR was significantly lower than that in recipients with a high NIR perfusion index (log-rank test: $P = 0.049$) (Fig. 3).

DISCUSSION

In light of the increasing demand and decreasing availability of optimal donor organs, maintaining excellent outcomes is a major challenge in contemporary transplant surgery. In our case series, as in other published studies, this development was reflected by a high proportion of ECD livers.[24] It has been shown that ECD grafts are more vulnerable to external factors such as CIT and have a higher rate of biliary complications, allograft dysfunctions, and graft failure.[25–27] As such, there is an increasing need for diagnostic tools for the early identification of recipients at risk of EAD.

Recently, machine perfusion of marginal donor organs aims at increasing their utilization and improving the safety of ECD graft transplantation. Traditional methods for graft perfusion evaluation, such as Doppler sonography with repeated sterile assessment, are cumbersome and bear the risk of graft contamination.[12] ICG angiography has been proven to be a feasible, contact-free method of perfusion assessment but has the disadvantage of requiring the intravenous application of iodine-containing contrast dye.[13] Being contact-free and noninvasive, HSI is an attractive imaging modality in intraoperative and in vitro settings. In our experience, the HSI image acquisition time is approximately 7 seconds, and the interference of HSI image acquisition with the operative procedure is minimal. HSI assessment of liver grafts has been demonstrated to be feasible for normothermic machine perfusion but was not yet correlated with postoperative recipient outcomes.[21]

In this study, we aimed to investigate the feasibility of HSI in LT and assess its diagnostic value in predicting graft function and patient outcomes.

Our data demonstrate that the NIR perfusion index measured immediately after reperfusion by HSI has a solid prognostic value regarding the postoperative development of EAD. Almost half of the patients with low-NIR perfusion values had EAD. This supports the pathophysiological findings that EAD might be the result of impairment at the level of postreperfusion microcirculation, as StO_2 (a measure of arterial inflow) and OHI (a measure of venous stasis) did not show any correlation with the development of EAD. Interestingly, TWI (a measure for tissue edema) was significantly higher in the low-NIR index group ($P < 0.001$), however, the difference was very small (0.40 ± 0.07 *vs* 0.38 ± 0.07, respectively).

In this cohort, recipients who developed EAD had a significantly higher donor BMI and CIT. These findings are in line with previously published data.[25,26] However, when divided into 2 groups according to their NIR perfusion index, there was no significant difference in donor BMI or cold ischemia time between recipients with high and low NIR. All remaining variables, except EAD, were equally distributed between the high- and low-NIR groups. This suggests that the quality of graft perfusion upon reperfusion, as represented by the NIR perfusion index, is an independent prognostic factor for EAD

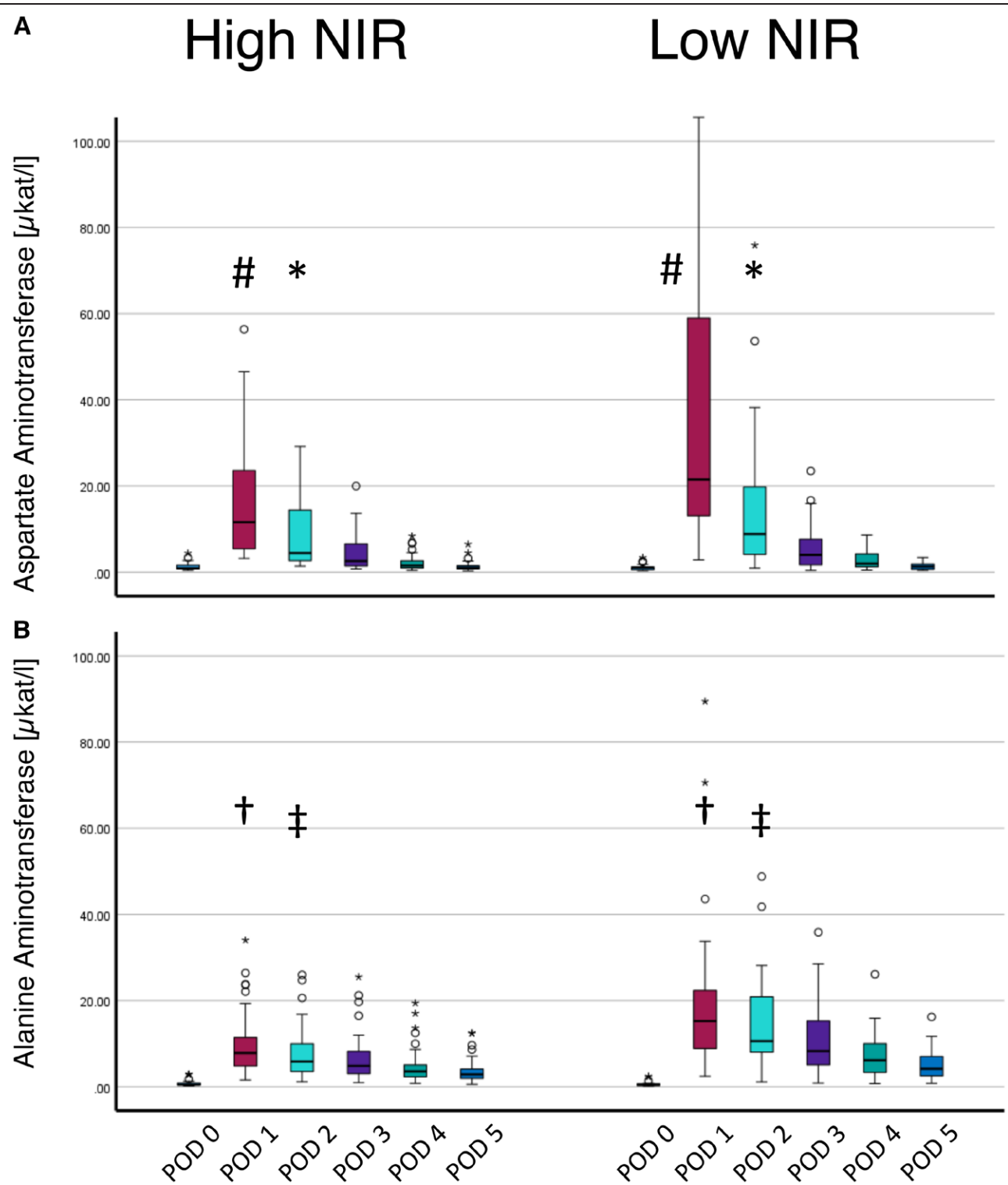

FIGURE 4. A, Aspartate aminotransferase and (B) alanine aminotransferase values for recipients with high- and low near-infrared (NIR) perfusion index based on receiver operating characteristic derived cutoff before liver transplantation (POD 0) and on POD 1 to 5. **#**19.3 ± 22 µkat/l *vs* 37.5 ± 33.3 µkat/l; $P = 0.016$. *****8.5 ± 8.7 µkat/l *vs* 15.4 ± 17.4 µkat/l; $P = 0.036$. **†**10.2 ± 7.7 µkat/l *vs* 20.4 ± 20 µkat/l; $P = 0.007$. **‡**8.1 ± 6.4 µkat/l *vs* 14.5 ± 11.5 µkat/l; $P = 0.007$. *P* values were calculated with a two-tailed *t* test. POD, postoperative day.

development. Furthermore, we found that the NIR perfusion index had a strong effect on overall patient survival even in this limited case series; when divided into high- and low-NIR perfusion index groups, Kaplan–Meier survival analysis showed a significant survival benefit for recipients in the high NIR index group. Larger prospective studies are needed to further investigate this phenomenon.

The limitations of HSI image processing are that the definition of the region of interest must be performed manually, which is time-consuming in everyday clinical practice. Although there is no automatic algorithm for tissue identification and assessment approved for clinical use, recent developments in machine learning and artificial intelligence will allow fully objective, automated image segmentation and analysis soon. There have

already been published case reports regarding tissue identification and the use of HSI in computer-assisted surgery.[28,29]

LIMITATIONS

In our center, we do not routinely procure graft biopsies. Graft biopsies solely for study purposes were not performed in this case series due to ethical reasons. Thus, this study represents a large, real-life case series, correlating HSI measurements with clinical outcomes of patients after liver transplants.

In the present study, the aim of HSI use was to objectively document the reperfusion quality in the recipient. This, of course, does not preclude the implantation of a poor graft. In the future, HSI might prove useful in the selection of good quality grafts, as a tool for surveillance of the graft during machine perfusion or even assessment of the graft before explantation.

Furthermore, continuous intraoperative HSI is not yet available, as capturing an HSI image requires turning off any external light source besides the HSI camera in the operating room, and thus interrupts the operation for a short time. Continuous HSI might become available, especially as it is integrated into laparoscopic and robotic camera systems.[30] A continuous HSI image acquisition during graft reperfusion may provide exciting insights into the physiology of the ischemia-reperfusion sequence in any solid organ transplantation procedure.

CONCLUSIONS

HSI is feasible and safe for assessing graft perfusion quality in LT. In our study, the NIR perfusion index acquired by HSI immediately after reperfusion showed diagnostic value for the development of EAD and correlated well with overall recipient and graft survival.

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