Editorial

Developing a new nomogram to predict early allograft dysfunction after liver transplantation: a nudge in the right direction

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Liver transplantation (LTx) is an established option for the treatment of end-stage liver disease, acute liver failure, and hepatic malignancies (1-3). Despite significant advances in clinical practice and scientific research on LTx, liver allograft dysfunction remains a significant clinical problem. Early allograft dysfunction (EAD) is a milder form of primary graft dysfunction that correlates with postoperative complications, higher mortality rates, and decreased graft survival (4). The frequency of EAD ranges from 15% to 30% after LTx from donors after brain death (DBD), reaching 68.4% after LTx from donors after cardiac death (DCD) (5). For living donor liver transplantation (LDLT), the prevalence of EAD is comparatively low, accounting for 18.1% of the recipients in our transplant center (4).

The concept of EAD was first described by Deschênes *et al.* in 1998 as a term used to identify poor graft function after LTx based on clinical and biological variables, including total serum bilirubin, prothrombin time, and the presence of hepatic encephalopathy (6). In the Model for End-Stage Liver Disease (MELD) era of organ sharing, the most widely used definition of EAD was proposed by Olthoff *et al.* (7) and is characterized by the following postoperative laboratory analyses: serum bilirubin ≥10 mg/mL on postoperative day (POD) 7, international normalized ratio (INR) ≥1.6 on POD7, or serum aminotransferase ≥2,000 IU/mL within the first post-transplant week. EAD is multifactorial and depends on the donor, recipient, and operative variables, among which graft quality strongly determines its occurrence. Some major efforts have been made to assess allograft function before LTx by evaluating different aspects of organ performance, such as bile secretion, hepatic protein synthesis, and organ morphology. Several studies have suggested that the mechanisms responsible for the occurrence of EAD are complex and mainly based on ischemia-reperfusion injury (IRI) (*Figure 1*). Recent studies have demonstrated that IRI severity and graft macrosteatosis are related to the incidence of EAD and graft survival (8,9). Specifically, a long cold ischemia time (CIT) and large-droplet macrovesicular steatosis (≥20%) of liver allografts have been identified as independent risk factors for EAD (8). Notably, surgeons still must rely on histopathological examination and morphological aspects of the organ for their decision on whether to use the graft. In recent years, concerns about risk factors and prediction of EAD have become widespread (*Table 1*). Indeed, studies focusing on objective methods of evaluating graft quality and predict its later function generate great interest.

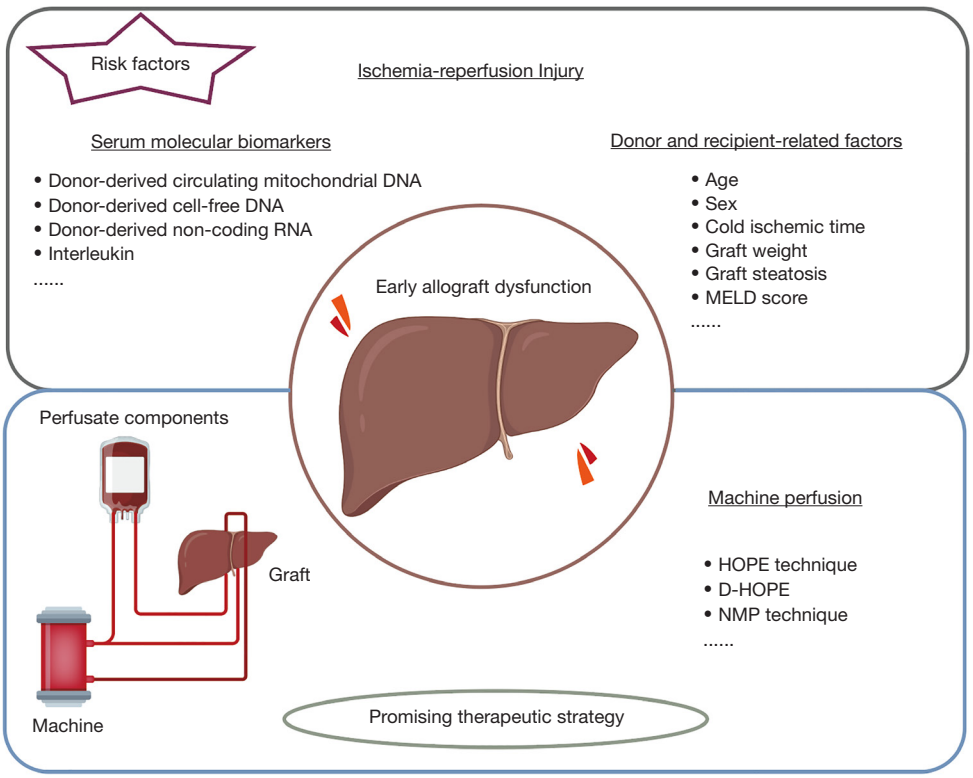

Figure 1 Risk factors and therapeutic strategies for EAD. MELD, Model for End-Stage Liver Disease. EAD, early allograft dysfunction; HOPE, hypothermic oxygenated perfusion; D-HOPE, dual hypothermic oxygenated machine perfusion; NMP, normothermic machine perfusion.

Recently, Wang *et al.* (10) performed a multicenter cohort study and established a nomogram to predict the incidence of EAD and EAD type B in DCD LTx patients based on a single-center training cohort (TC) (n=321) and validated it in a multicenter validation cohort (VC) (n=501). In their study, EAD recipients presenting only elevated aspartate aminotransferase (ALT) or aspartate aminotransferase (AST) levels were classified as having EAD type A, and the remaining patients were classified as having EAD type B. Their nomogram could effectively predict the incidence of EAD type B, which is a more severe subtype of EAD and associated with a relatively poor prognosis (10). Overall, the results indicated that graft weight (P=0.000), CIT (P=0.018), and MELD score (P=0.021) were independent risk factors for the incidence of EAD type B. Taken together, these are important insights for transplant physicians into the objective assessment of the risk of EAD and EAD type B.

EAD is a poorly defined clinical entity in which the allograft presents some degree of hepatic injury, but the liver functions sufficiently to support life. Although most clinicians and researchers agree that allograft function recovers, EAD correlates with graft loss and higher morbidity and mortality (7,10,11). Over the past decades, most classifications based on some clinical variable cut-offs have categorized recipients as showing a dysfunction; however, they have not graded the recipients' graft dysfunction. It is reassuring to note that the nomogram established by Wang *et al.* (10) showed good discrimination and calibration in the prediction of EAD type B, which has lower graft and patient survival rates. Beyond its utility as a valuable prediction tool for translational studies, nomograms could also be used to identify LTx recipients at the highest risk of EAD, allowing for possible mitigation of this risk with more proactive monitoring. One potentially promising preoperative therapeutic strategy is machine perfusion technology (*Figure 1*), which has been shown to attenuate hepatic IRI and potentially reduce EAD rates (12). Recipients with EAD are at greater risk of postoperative allograft failure, which may require retransplantation. Unfortunately, the binary nature of this type of EAD lacks granularity and fails to capture the continuum along which allograft failure occurs (10). Therefore, further evaluation

Table 1 Overview of published studies of EAD after LTx

Year	Authors	Region	N	Study period	Method	Results
2015	Ali *et al.*	Cambridge, UK	476	2000–2010	TCNB obtained after revascularization of the allograft (≈45–60 min)	Severe time-zero biopsy IRI was associated with EAD, 1-year graft failure, and poorer graft survival
2021	Ito *et al.*	California, USA	506	2012–2018	IPRBs obtained intraoperatively from the left lobe 2 or 3 h after portal reperfusion	Moderate to severe IRI, longer CIT, and large-droplet macrovesicular steatosis (≥20%) identified as independent risk factors for EAD
2010	Olthoff *et al.*	Philadelphia, USA	300	2004–2005	Graft and patient survival were tested to assess the predictive validity of the EAD definition Risk factors for EAD assessed by multivariable logistic regression	Donor age and donor MELD score were predictors of EAD, and establishment of contemporary definition of EAD
2013	Hoyer *et al.*	Essen, Germany	678	2003–2011	Univariable/multivariable logistic regression and Cox proportional hazards to identify prognostic donor factors	Donor BMI, gGT, macrosteatosis, and CIT were predictors of EAD
2021	Wang *et al.*	Hangzhou, China	VC, n=501 TC, n=321	2015–2017	Establish nomogram based on a single-center TC (n=321) and validated in a 3-center VC (n=501)	Graft weight, CIT, donor age, and MELD score were independent predictors of EAD
2020	Agopian *et al.*	California, USA	VC, n=3,201 TC, n=222	N/A	Compared the accuracies of L-GrAFT7, EAD, and MEAF through a VC and TC	L-GrAFT score was a highly accurate measure of EAD, and L-GrAFT7 could be used as an accurate clinical endpoint
2021	Avolio *et al.*	Rome, Italy	VC, n=1,609 TC, n=538	2016–2017	Developed a novel EASE score and then validated it internally as well as externally	EASE score reliably estimated EAF risk, and guided clinicians to allocate early liver retransplant, making it a valuable tool for quantifying early graft function
2021	Yoshino *et al.*	Melbourne, Australia	21	2019–2020	ddPCR measurement by QIAamp Circulating Nucleic Acid Kit (Qiagen, Germantown, MD, USA)	cmtDNA levels elevated in the EAD group in the early phase, who also had a second peak in cmtDNA at POD7
2022	Levitsky *et al.*	Illinois, USA	219	2010–2015 2019–2020	dd-cfDNA measurement by QIAamp Circulating Nucleic Acid Kit & Qubit 1X dsDNA HS Assay Kit (Invitrogen, Waltham, MA, USA)	Elevated dd-cfDNA represented a signal of early graft injury in LTR and was most prominent in AR than ADNR

Early phase, period between POD1 and POD4. EAD, early allograft dysfunction; LTx, liver transplantation; TCNB, Tru-Cut needle biopsies; IRI, ischemia-reperfusion injury; IPRBs, intraoperative postreperfusion biopsies; CIT, cold ischemia time; MELD, Model for End-Stage Liver Disease; BMI, body mass index; gGT, serum gamma-glutamyltransferase; VC, validation cohort; TC, training (trial) cohort; N/A, data not available; L-GrAFT7, Liver Graft Assessment Following Transplantation based on 7-day measures of post-liver transplantation; MEAF, the model for early allograft function; L-GrAFT, Liver Graft Assessment Following Transplantation; EASE, the early allograft failure simplified estimation; EAF, early allograft failure; ddPCR, droplet digital polymerase chain reaction; cmtDNA, circulating mitochondrial DNA; POD, postoperative day; dd-cfDNA, donor-derived cell free DNA; LTR, liver transplant recipient; AR, acute rejection; ADNR, acute dysfunction no rejection.

of the predictive ability to discriminate recipients with EAD who may experience early graft failure is warranted. We believe that a more comprehensive predictive model may warn clinicians that a recipient with EAD is at risk of primary nonfunction and can help them make decisions regarding potential retransplantation. In addition, we noted that the results of recent studies indicated that some molecular biomarker tests [e.g., donor-derived cell-free DNA and circulating mitochondrial DNA (cmtDNA)] show great potential in EAD prediction (13,14). We hypothesize that conventional clinical parameters combined with molecular biomarkers could lead to a more precise prediction.

In summary, designing a predictive model or nomogram is a practical and important approach to predicting EAD after LTx. With promising new preclinical data on the use of drugs, RNA interference, and extracellular vesicles to treat EAD, predictive models may also allow for allocation of what would undoubtedly be high-cost or high-resource interventions to recipients who stand to benefit the most. Nevertheless, listing a recipient with an EAD for retransplantation is still challenging for transplant surgeons. Although many predictive scores and models have been proposed, there is still a long path ahead for guiding the clinical diagnosis and treatment of EAD.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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