

2016 Liver Transplantation: Global view

Predictive factors of short term outcome after liver transplantation: A review

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Author contributions: De Pietri L designed the literature review strategy, critically planned the article structure and wrote the paper; Bolondi G contributed to the literature review and article writing; Mocchegiani F, Montalti R, Nicolini D and Vivarelli M critically reviewed the article and contributed to the literature review.

Conflict-of-interest statement: All authors have no conflict interests to declare.

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Manuscript source: Invited manuscript

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Received: March 23, 2016

Peer-review started: March 24, 2016

First decision: May 12, 2016

Revised: May 17, 2016

Accepted: June 2, 2016

Article in press: June 2, 2016

Published online: July 14, 2016

Abstract

Liver transplantation represents a fundamental therapeutic solution to end-stage liver disease. The need for liver allografts has extended the set of criteria for organ acceptability, increasing the risk of adverse outcomes. Little is known about the early postoperative parameters that can be used as valid predictive indices for early graft function, retransplantation or surgical reintervention, secondary complications, long intensive care unit stay or death. In this review, we present state-of-the-art knowledge regarding the early post-transplantation tests and scores that can be applied during the first postoperative week to predict liver allograft function and patient outcome, thereby guiding the therapeutic and surgical decisions of the medical staff. Post-transplant clinical and biochemical assessment of patients through laboratory tests (platelet count, transaminase and bilirubin levels, INR, factor V, lactates, and Insulin Growth Factor 1) and scores (model for end-stage liver disease, acute physiology and chronic health evaluation, sequential organ failure assessment and model of early allograft function) have been reported to have good performance, but they only allow late evaluation of patient status and graft function, requiring days to be quantified. The indocyanine green plasma disappearance rate has long been used as a liver function assessment technique and has produced interesting, although not univocal, results when performed between the 1st and the 5th day after transplantation. The liver maximal function capacity test is a promising method of metabolic liver activity

assessment, but its use is limited by economic cost and extrahepatic factors. To date, a consensual definition of early allograft dysfunction and the integration and validation of the above-mentioned techniques, through the development of numerically consistent multicentric prospective randomised trials, are necessary. The medical and surgical management of transplanted patients could be greatly improved by using clinically reliable tools to predict early graft function.

Key words: Liver transplant; Liver failure; Early allograft dysfunction; Primary non-function; Initial poor function; Outcome predictors; Post operative; Scoring system; Indocyanine green; Liver maximal functional capacity

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Core tip: The shortage of available livers and long waiting lists have led to increased transplantation of marginal organs. The model for end-stage liver disease allocation system distributes transplants to sicker patients, potentially impairing the final outcome. A serious pitfall is the lack of early postoperative tools to predict short-term outcome for grafts and patients after liver transplant. Here, we review the currently available functional tests and clinical scores that assess graft and patient status during the first week after liver transplantation to quickly guide the early postoperative surgical and intensive care management.

Bolondi G, Mocchegiani F, Montalti R, Nicolini D, Vivarelli M, De Pietri L. Predictive factors of short term outcome after liver transplantation: A review. *World J Gastroenterol* 2016; 22(26): 5936-5949 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v22/i26/5936.htm> DOI: <http://dx.doi.org/10.3748/wjg.v22.i26.5936>

INTRODUCTION

Liver transplant (LT) is a life-saving treatment for several end-stage liver diseases^[1,2]. Access to LT is now generally performed using the Model for End-Stage Liver Disease (MELD) score. Although created for different purposes, MELD is a simple and highly predictive system for 3-mo mortality for patients on the LT waiting list^[3].

Because of the reduced number of available organs, extended-criteria donors (ECD) are now routinely used for recipients with higher MELD scores, who cannot further delay intervention^[4,5], increasing postoperative mortality and complications in some reports^[6,7]. Due to the complexity of the surgical intervention and the critical status of transplanted patients, a large proportion of the overall complications occur within the first postoperative week after LT.

In this review, we will refer to early allograft dysfunction (EAD) as the sum of initial poor function

(IPF) and primary nonfunction (PNF). EAD, sepsis, secondary complications leading to revision surgery (*i.e.*, arterial or venous thrombosis) and the increased morbidity and mortality of transplanted patients prolong intensive care unit length of stay (ICU-LOS) and hospital length of stay (H-LOS), profoundly impacting the cost of patient management^[8-10]. The initial function of the allograft after LT is determined by donor, surgical and recipient factors, causing IPF incidence ranges between 8.7% to 24.7% and PNF incidence ranges between 0.9% to 7.2% in different LT casuistries^[11,12].

Early EAD diagnosis could allow health care professionals to promptly individuate and treat those patients facing the most worrying conditions. To date, we lack efficient techniques to detect the initial signs of EAD during the first few postoperative days (POD). In fact, despite several years of study on this topic, no concordant definition of EAD and PNF can be found in scientific literature, increasing confusion and contrasting results (see Table 1).

Here, we aim to review the state-of-the-art technologies and tests to assess general patient status, initial graft function and risk of PNF and death after LT, with a specific focus on the tools applicable during the first postoperative week.

PRE- AND INTRA-OPERATIVE PARAMETERS

Several scoring systems have been applied pre-operatively to predict LT outcome. Not being the main focus of this review, we briefly describe the most used ones.

MELD uses three objective laboratory parameters (INR, creatinine, and bilirubin). Low discriminatory power^[13,14] relegated it to be just one of the possible factors predicting patient survival rates, along with other sometimes better performing scores^[15]. MELD evolutions, such as MELD-Na^[16,17], D-MELD^[18] and others^[19], did not reach acceptable performances. The analysis of donor characteristics is also fundamental to optimise graft-recipient matching and to predict LT outcome. So, donor-risk index (DRI)^[20] and extended criteria donor score (ECDS)^[21] were proposed. ECDS, DRI and D-MELD, despite providing statistically significant results, had insufficient discriminatory power for short-term graft and patient survival^[22].

Survival outcome following liver transplantation (SOFT)^[23,24] and balance of risk (BAR)^[25] scores were designed to integrate donor, surgical and recipient risk factors (18 and 6 independent variables, respectively). BAR is a simpler score with extremely high specificity (98%) for identifying patients with high mortality risk. The Charlson Comorbidity Index (CCI)^[26] modified for specific LT needs (CCI-OLT) comprehensively assesses recipient clinical status before LT. All of them were affected by low discriminatory power, limiting their

Table 1 Recent definitions of initial poor function and primary non function

Ref.	IPF	PNF
Broering <i>et al</i> ^[107]	ALT or AST or GDH > 2000 IU/L FFP substituted for > 5 d postoperatively	Not-life sustaining graft leading to retransplantation or death within POD10
Nanashima <i>et al</i> ^[108]	Two consecutive measurements within POD3: ALT or AST > 1500 IU/L	IPF-induced retransplantation or death
Heise <i>et al</i> ^[109]	Scoring system based on ALT, AST, bile output, Prothrombin activity on POD1-3-7-14 (Berlin score ranging from 4 to 8) Berlin C (IPF): 7-8	
Tekin <i>et al</i> ^[110]	On POD7: AST > 1500 IU/L and PT > 20 s	Not-life sustaining graft leading to retransplantation or death within POD7
Ben-Ari <i>et al</i> ^[111]	AST or ALT > 2000 IU/L on POD2 INR > 1.6 on POD2-10 Bilirubin > 10 mg/dL on POD2-10	Not-life sustaining graft leading to retransplantation or death within POD10
Kremers <i>et al</i> ^[112]		ALT > 2500 IU/L Glucose < 60 mg/dL INR > 2.5 bile flow < 50 mL/d
Pokorny <i>et al</i> ^[113]	On POD5: AST > 2500 IU/L or clotting support > 2 d	Not-life sustaining graft leading to retransplantation or death within POD7
Monbaliu <i>et al</i> ^[114]		Persisting encephalopathy Irreversible metabolic acidosis Profound hypoglycaemia Severe coagulopathy Insufficient bile production Increased AST
Cieślak <i>et al</i> ^[115]	Within POD1-7 AST or ALT > 2500 IU/L or Prothrombin index < 50% [(AST+ALT)/2] on POD2: < 285 IU/L: good function 285-986 IU/L: average function > 986 IU/L: IPF	
Dhillon <i>et al</i> ^[116]		IPF-induced retransplantation or death within POD7
Nemes <i>et al</i> ^[117]	On POD5: [Serum bilirubin (µmol/L)]/[Prothrombin (%)] > 1	
Olthoff <i>et al</i> ^[81]	On POD1-7, one within: Bilirubin ≥ 10 mg/dL on POD7 INR ≥ 1.6 on POD7 ALT or AST > 2000 IU/L within POD7	
Stockmann <i>et al</i> ^[59] and Lock <i>et al</i> ^[60]	Two LiMax readouts during the first 24 h: LiMax = 60-120 µg/kg per hour	Two LiMax readouts during the first 24 h: LiMax < 60 µg/kg per hour
Máthé <i>et al</i> ^[118]	Two consecutive measurements within POD3: ALT or AST > 1500 IU/L	IPF-induced retransplantation or death

Table freely extracted from Olthoff *et al*^[81], Chen *et al*^[12] and Pareja *et al*^[106]. The mentioned studies are cited in chronological order. ALT: Alanine - aminotransferase; AST: Aspartate - aminotransferase; FFP: Fresh free plasma; GDH: Glutamate dehydrogenase; INR: International normalised ratio; LiMax: Liver maximal function Capacity; POD: Postoperative day; PT: Prothrombin time.

usefulness in individual cases, and scarce prediction of very short-term (1 mo) post-LT survival^[27,28].

Several of these studies focused only on patient outcome. For this reason, early retransplantation was a frequent criterion of exclusion in these publications, which consequently do not provide information about graft function and survival.

Intraoperative anaesthetic management and surgical techniques can strongly influence postoperative patient and graft function. Duration of the intervention, difficult arterial anastomosis, high blood loss and red blood cell transfusion^[29], intraoperative hemodynamic instability^[30], cold and warm organ ischemia time^[11,31], ischaemia/reperfusion (I/R) injury^[32] and the need for and number of necessary revision surgeries can have high impacts on graft functional restoration and patient outcome^[10,12].

To assess all of these variables, functional and analytic tests have been applied to LT.

A preoperative score implementing MELD + ICG

improved survival prediction power in patients with intermediate MELD (10-30), who are often more difficult to correctly prioritise for LT^[33]. Moreover, donor indocyanine green plasma disappearance rate (ICG-PDR) before liver removal was the only factor predicting 7-d graft survival (DRI and donor age were not correlated to graft survival)^[34]. Intraoperative ICG-PDR of 10.8%/min measured 60 min after organ reperfusion had the best specificity and sensitivity in predicting the development of severe EAD with an area under receiver operating characteristics (AUROC) = 0.944, performing better than any other clinical and laboratory parameter and with a negative predictive value (NPV) of 99.2%^[35].

Post-reperfusion lactate levels measured intraoperatively showed significant correlation with 3-mo patient mortality. Patients whose lactate values showed no reduction for 2 h after graft vascularisation experienced higher bilirubin levels from POD5 to POD23. These data came from a small study of 15

living donor liver transplant (LDLT) recipients^[36].

POSTOPERATIVE PARAMETERS

These parameters are the main focus of our review. Table 2 summarises the relevant studies mentioned below and their statistics. They are divided in functional tests (ICG-PDR, LiMAX, others), analytic tests [platelet counts, factor V, transaminases, bilirubin, INR, lactates and insulin growth factor 1 (IGF1)] and clinical scores [MELD, acute physiology and chronic health evaluation (APACHE), chronic liver failure - sequential organ failure assessment (CLIF-SOFA) and model for early allograft function scoring (MEAF)].

Functional tests directly quantify hepatic function. It means that they do not only account for patient and donor risk factors, but also estimate graft conservation, intra-operative organ insult and early postoperative graft function, offering a quantitative and comprehensive value of liver activity.

INDOCYANINE GREEN - PLASMA DISAPPEARANCE RATE

ICG has been used for 25 years to estimate liver function^[37]. ICG is a non-toxic dye that can be administered intravenously and detected by transcutaneous non-invasive densitometry^[38,39]. Normal Indocyanine green - plasma disappearance rate (ICG-PDR) values range from 18% to 25%-30%/min^[38,40]. Being water-soluble, its distribution volume equals plasma volume. ICG is extracted by the liver and excreted through the biliary system without undergoing metabolism or recirculation. For this reason, elimination rates are assumed to depend only on hepatic arterial blood flow and liver functionality. Very few allergic/anaphylactic reactions or thyrotoxicosis due to the iodine component of the solution have been reported. For this reason, ICG is considered a safe bedside tool for the dynamic assessment of implanted liver functionality^[41].

During LT intervention, ICG-PDR falls due to anaesthetic drugs causing haemodynamic hypotension and reduced/absent hepatic function (anhepatic phase). Immediately after graft reperfusion, supra-normal ICG-PDR is observed^[39]. Daily quantification of ICG-PDR from immediately after ICU admittance until POD7 has shown a rapid recuperation in values when appropriate graft function recovery was observed^[42,43]. Harmful conditions for the transplanted patient (EAD, hepatic artery thrombosis, acute rejection or sepsis) and mortality have been associated in those with smoother or absent amelioration of test values. The POD on which this difference becomes significant changes from POD1 to POD4 depending on the study. The critical PDR cut-offs found by Receiver Operating Characteristics analysis (ROC) were 9.6%-12.85%/min^[35,42-44].

A score was developed that considered the only

two independent variables correlating with 1-mo mortality or retransplantation within POD7 (the two primary end-points of the study), assigning 1 point for $\text{INR} \geq 2.2$ and 2 points for $\text{ICG-PDR} < 10\%$. When calculated on POD1, it had strong sensitivity (95%) and NPV (94%) for patients scoring 3. These results were confirmed in a validation cohort^[44]. Confirming the utility of integrating common clinical data with ICG-PDR to increase their specificity, a post hoc study showed that preoperative MELD > 25 and $\text{ICG-PDR} < 20\%$ within 6 h after ICU admission provided extremely rapid and sensitive results (up to 100%, $\text{AUROC} = 0.79$) for ICU- and H-LOS and H-mortality^[45].

A prospective study designed specifically for LDLT investigated 30 patients. EAD patients were characterised by a longer ICU-LOS and higher death rate (50%). Both EAD and non-EAD patients faced a decrease in PDR during the first 48 h after LDLT. Already from POD1 up to POD28, the non-EAD group had significantly higher PDR, while the EAD group showed a progressive deterioration of PDR (confirmed by histopathological analysis of the graft parenchyma). Independently by the absolute values, individual trends might be indicative of graft function and clinical complications. No other laboratory data correlated with the EAD diagnosis at any moment perioperatively^[46].

Finally, ICG-PDR was also proposed as a predictive tool for hepatic artery thrombosis and its management^[47].

A primary limitation to ICG-PDR reliability is given by hemodynamic instability (a frequent perioperative condition in LT) and altered hepatic blood flow^[48]. PDR is also altered by clinical conditions that burden the delicate function of an implanted liver, including cholestasis, hyperbilirubinaemia and capillary leakage^[49,50] because ICG and bilirubin use the same plasmatic transporter^[51]. The multiple confounders affecting PDR might explain the poor specificity and positive predictive value detected with this technique. Finally, ICG-PDR reference values vary among different studies (from 9.6% to 20%) and appear to be context-dependent, depending on the POD of evaluation and clinical complications affecting the patients. For example, sepsis is main cause of patient mortality after LT that consistently alters PDR values, increasing the confusion about reliable cut-off values for this technique^[42,52]. As criticised by Stockmann *et al*^[53], the scoring systems chosen to define IPF and PNF in some of these studies^[42-44] may have created biases or result overestimation. Because of the inability to uniformly diagnose these clinical conditions from the actual scores^[54], a better assessment would focus on patient outcome, as performed by Olmedilla *et al*^[44].

LIVER MAXIMAL FUNCTION CAPACITY

Liver Maximal Function Capacity (LiMax) is a real time breath test: ^{13}C methacetin is administered intravenously, selectively metabolised by cytochrome

Table 2 Overview of the studies applying the mentioned techniques specifically about liver transplant

Technique	Study	Type (P/R)	Primary end-point:	Sample	POD	Cut-off value	AUROC (95%CI)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
ICG-PDR	Olmedilla <i>et al</i> ^[83]	P	EAD prediction	172 LT: 31.9% HCC, 29.6% viral, 23.8% alcoholic	1	10%/min	0.967 (0.915-0.991)	100 (69-100)	90.4 (84.7-94.6)	40.00	100.00
	Levesque <i>et al</i> ^[82]	P	EAD prediction	72 LT (including LDLT)	0-5	12.85%/min		90.0	97.0		
	Schneider <i>et al</i> ^[83]	P	Graft loss or patient death on POD30	86 LT: 36% viral, 29% alcoholic	7	12.3%/min	0.729 (0.608-0.850)	69.0	67.0	57.00	77.00
Preoperative MELD + postoperative ICG-PDR	Klinzing <i>et al</i> ^[85]	P	ICU-LOS, mortality	50 LT	0 (< 6 h after ICU admission)	MELD > 25, ICG-PDR < 20%/min	0.79	100.0	59.0		
ICG-PDR + INR	Olmedilla <i>et al</i> ^[84]	P	1-mo mortality or need for retransplantation within POD7	332 LT (+77 validations)	1	ICG-PDR < 10%/min, INR > 2.2	0.76 (0.66-0.86)	48 (31-66)	95 (91-97)	50 (32-68)	94 (91-96)
LiMax	Lock <i>et al</i> ^[88]	P	EAD requiring reintervention before POD2 or causing death/retransplantation within POD14	99 LT: 32% alcoholic, 23% HCV	0	64 µg/kg per hour	0.960 (0.921-0.998)	100 (60-100)	92 (84-97)	53 (27-78)	100 (95-100)
Platelets count	Lesurtel <i>et al</i> ^[72]	R	Severe complications or 3-mo mortality	257 LT: 38% HCV	5	60 × 10 ⁹ /L	0.992 (0.975-1.000)	100 (31-100)	100 (94-100)	100 (31-100)	100 (94-100)
Factor V	Li <i>et al</i> ^[70]	R	EAD prediction	234 LDLT: 45% HCC	2	68 × 10 ⁹ /L	0.678	73.0	59.0		
	Zulian <i>et al</i> ^[76]	R	Graft failure within POD90	105 LT: 79.5% HCC, 76.2% HCV	2	41.50%	0.650	42.9	87.9	35.30	90.90
AST	Robertson <i>et al</i> ^[78]	P	Graft loss at POD90	1091 LT: 22% HCV	3	2 cut-offs: 106.5 IU and 2744.5 IU	0.739 (0.663-0.814)			34.62	99.45
Bilirubin	Wagener <i>et al</i> ^[80]	R	Graft loss or death within POD90	572 LT: 51.9% HCV	2	6.55 mg/dL	0.809 (0.742-0.877)	72.5	70.4		
Bilirubin, INR and transaminases	Olthoff <i>et al</i> ^[81]	R	EAD definition to predict mortality and graft loss	300 LT	7	Bilirubin > 10 mg/dL, INR > 1.6, ALT or AST > 2000 IU/mL	0.75-0.78				
Lactates	Wu <i>et al</i> ^[84]	P	EAD prediction	222 LT: 50% HBV, 41% HCC	1	24.80%	0.961 (0.948-0.974)	95.5	88.9		
IGF-1	Bassanello <i>et al</i> ^[88]	P	Explore GH/IGF-1 axis changes during the perioperative course of LT	15 LT: 52% viral, 20% alcoholic	7	n.a					
	Salso <i>et al</i> ^[90]	R	90-d patient survival	30 LT: 40% HCV, 20% HBV	15	90 mUI/mL	0.920	86.0	87.0		
	Nicolini <i>et al</i> ^[89]	P	3-yr actual survival	31 LT: 42.5% HCV	15	Normal values classified according to Immulite 2000® system reference-ranges					

MELD	Wagener <i>et al.</i> ^[80]	R	Graft loss or mortality within POD90	572 LT: 51.9% HCV	5	≥ 19	0.812 (0.739-0.886)	79.5	27.3	95.7
	Toshima <i>et al.</i> ^[91]	R	Graft loss or mortality within POD180	217 LDLT: 47.9% HCV	2	≥ 19	0.779	68.2	31.0	100.0
MELD lactate	Cardoso <i>et al.</i> ^[92]	P	Mortality within POD30	58 LT: 43% HCV, 26% alcoholic	1 h after surgery	26.3	0.933	100.0	74.9	100.0
APACHE IV	Hu <i>et al.</i> ^[199]	R	Mortality	195 LT	1	≥ 55.5	0.937 (0.892-0.981)	85.2	60.5	97.5
SOFA	Wong <i>et al.</i> ^[200]	R	3-mo mortality	149 LT: 53% HBV	7	≥ 8	0.953 (0.902-1.000)	95.0		
CLIF-SOFA	Pan <i>et al.</i> ^[104]	R	1-yr mortality	323 LT: 62% HBV, 27% hepatoma, 26% HCV	3	> 8	0.808 (0.729-0.888)	67.0		
MEAF	Pareja <i>et al.</i> ^[106]	R	EAD definition ti predict 3-mo mortality	874 LT (+200 validation)	3	> 8	0.877 (0.813-0.941)	64.0		

Sample: Only specified if a disease accounts for more than 20% of the overall sample. Where more than one study was present for a specific technique, chronological order has been adopted. Type P: Prospective; Type R: Retrospective; POD: Postoperative day in which best discriminating values were detected; PPV: Positive predictive value; NPV: Negative predictive value; LT: Liver transplant; LDLT: Living donor liver transplant; HCV: Hepatitis C virus; HBV: Hepatitis B virus; HCC: Hepatocellular carcinoma.

P450 1A2 (CYP1A2), an enzyme exclusively expressed by hepatocytes, and excreted by ventilation. Quantification of the ¹³CO₂/¹²CO₂ ratio after at least 6 h of fasting provides a specific estimation of enzyme kinetics. The systemic liberation of paracetamol is a reaction product. Healthy controls showed normal LiMax values > 315 µg/kg per hour^[55].

LiMax test was first tested in hepatic surgery. The extremely encouraging results^[55] allowed the development of single-patient decision algorithms^[56]. Non-critical but infra-normal LiMax test levels correlated with post-surgical complications, highlighting their relevance in patient monitoring during the postoperative ICU stay^[57]. From these initial studies, the field of investigation moved towards LT.

Ninety-nine LT patients were studied, and non-EAD patients showed significantly higher LiMax within 6 h after LT than EAD patients. The best discriminating cut-off point was 64 µg/kg per hour. False positive patients with late LiMax recovery on POD2-3 showed increased ICU-LOS and hemodialysis, justifying special attention from ICU doctors. No other variables were independently associated with EAD so early (not even ICG-PDR)^[58].

A quantitative and precise definition of EAD was determined using LiMax. Two cut-offs were arbitrarily decided at 60 and 120 µg/kg per hour. PNF was defined as LiMax < 60 µg/kg per hour, IPF was LiMax 60-120 µg/kg per hour, and immediate function was LiMax > 120 µg/kg per hour. Values were measured within 24 h after LT in the same previous 99 recipients, and post hoc analysis was performed. Using these cut-offs, IPF correlated with biochemical laboratory values (transaminases, bilirubin, INR, creatinine) and higher rates of post-transplant complications (hemodialysis and catecholamine support) but not with H-LOS and 2-year patient and graft survival. Slower restoration of LiMax values was detected in IPF patients up to POD28, while all immediate function patients recovered normal LiMax values by POD5. Three cases of PNF underwent immediate retransplantation. EAD patients were characterised by significantly higher DRI and donor age (no preoperative MELD differences were evaluated), showing postoperative LiMax correlating with both donor characteristics and recipient clinical progression^[59].

Immunosuppression is a principal treatment after LT. Tacrolimus, one of the most frequently used immunosuppressants, is metabolised by hepatocytes. Normal blood concentrations of tacrolimus might be toxic for patients developing EAD. In a following prospective observational study, graft function was quantified by LiMax during the first 5 d after LT. LiMax levels predicted the development of toxic levels of tacrolimus in patients with EAD and tacrolimus under-dosage in those with good graft function^[60]. Immunosuppression modulation of tacrolimus blood concentrations poorly correlates with ICG-PDR^[61].

A major concern about this technique is that it was developed and clinically applied by only a single study group. Although encouraging, few publications are available. The two major publications on LiMax and LT used the same group of 99 LT patients, limiting their significance. Wider, multicentre applications are required to verify reliability in different cohorts and clinical settings. Because of the extreme variability of cytochrome activity depending on external factors, some scepticism may arise, and extensive studies to confirm the inter-individual reliability and standardised cut-off values of this specific technique are needed.

OTHER FUNCTIONAL TESTS

Several other functional techniques were tested decades ago with promising results, such as the lidocaine-monoethylglycinexylidide (MEGX) injection test^[62,63] and the galactose elimination capacity^[64]. Unfortunately, hepatic blood flow, genetically-determined variation of enzymatic function, and different hepatic functionality consequences due to different pathologies, treatments and other external factors (such as drugs, dietary habits, nutritional status and coexisting pathologies) resulted in extremely high inter-individual variability and the impossibility in defining reliable cut-off values. Frequently, non-univocal experimental results and time-consuming techniques discouraged further clinical experimentation, and they never reached bedside utilisation.

Other breath tests based on stable isotopes or on specific mitochondrial functions were proposed to assess liver function capacity, but most of these techniques have never been used in specific correlation with the assessment of liver transplant patients and graft function^[65].

PLATELET COUNTS

Platelets are a blood component with a wide range of acute conditions, including inflammation, infections, tissue insults from I/R injury and tissue regeneration, acting an active role in LT^[66]. LT candidates frequently present low platelet counts due to congested splanchnic circulation, increased mechanical stress and reduced bone marrow activity. These causes are not immediately reverted by LT^[67].

Interestingly, red blood cells, plasma and platelet transfusions have been correlated with negative outcome after LT and might be associated with a lower nadir in postoperative platelet count^[68-70]. Thrombocytopenia after LT is associated with increased EAD, early development of bacterial and fungal infections (before POD14), and patient mortality^[68,71].

In a retrospective study, patients were divided into two groups based on their platelet count on POD5 after LT, and a cut-off value was set at 60×10^9 platelets/L based on the best AUROC. MELD > 25 and platelet count < 60×10^9 platelets/L were the best predictors of severe postoperative complications and mortality, increased ICU-LOS and H-LOS independently of preoperative levels and intraoperative transfusions. POD5 platelet count showed to be a reliable predictor of short-term outcome after LT (within POD90). Unfortunately, platelet counts decrease from immediately post-transplant until POD 3-6, returning to preoperative levels by week 1-2, thus severely limiting the utility and power of this parameter in early graft assessment^[72].

Another retrospective study investigated the role of postoperative platelet count in 234 LDLT patients^[70]. In this specific field of hepatic surgery, platelet

transfusions have been reported to improve graft regeneration^[73,74]. A cut-off of 68×10^9 platelets/L for the immediate postoperative platelet count was determined following ROC analysis. Values lower than this cut off were found to be a risk factor for IPF incidence and severe complications. No differences were found for the 90-d mortality rate, PNF and ICU-LOS.

Weak statistics in few retrospective studies limit our knowledge of the meaning of platelet count post-LT. Finally, it is not easy to understand if postoperative thrombocytopenia is a cause or a consequence of EAD.

FACTOR V

Coagulation factors I, II, VII, VIII, IX, X, and XI, protein C, protein S and anti-thrombin are produced by the liver. Thus, coagulation relies heavily on its conserved synthetic capacity. Factor V is a cofactor for the prothrombinase complex, that activates prothrombin to thrombin, interacts with several coagulation factors, and also modulates the anticoagulant pathway by down-regulating factor VIII activity. Factor V does not depend on vitamin K for its production and is characterised by a short half-life (< 24 h), strictly tracing liver function at the moment of its dosage. For this reason, it has been found to be a good prognostic marker of fulminant liver failure^[75].

When specifically tested for LT, factor V measurement on POD2 was retrospectively found to be an independent predictor for both 90-d graft function and overall survival^[76]. A cut-off was set at 41.5% after ROC analysis. No differences in preoperative data distinguished the groups with high vs low POD2 factor V. Plasma transfusions did not differ significantly between these two groups and therefore did not create misleading artefacts in data interpretation. Good specificity (87.9%) and NPV (90.9%) were detected for 3-mo graft survival. Also the 5-year patient survival rate correlated with Factor V levels on POD2.

TRANSAMINASES, BILIRUBIN AND INR

Aspartate and alanine transaminases (AST and ALT) are enzymes involved in amino acid metabolism. ALTs are more liver-specific, but ASTs occur at higher concentrations in the liver^[77]. IPF and PNF definitions in the early 1990s were based on extremely high levels of transaminases as an estimate of hepatic damage and hepatocellular lysis. Then, both bile production/bilirubin levels and prothrombin time (PT) were investigated, focusing attention on the synthetic activity and functional state of the liver.

Recently, a large prospective study found that AST on POD3 plus AST and ALT on POD7 are predictors of early (within POD90) graft failure from both general and liver-specific causes. The best AUROC with an extremely high NPV (99.34%) was detected for AST on POD3. Accordingly, patients were divided into 4

risk groups, which also correlated with 1-, 3- and 12-mo mortality rates, ICU-LOS, renal replacement therapy and incidence of septic complications. For the first time, non arbitrary cut-off levels and POD of measurement for transaminases were defined. Moreover, AST on POD3 mirrors hepatic damage due to long times in performing vascular reconstruction, long cold ischemia times and preoperative MELD values^[78].

After deceased cardiac donor LT, non-anastomotic biliary strictures are a major cause of ALT peak \geq 1300 IU/L and EAD, likely because of longer ischemia time and immunological causes^[79].

A monocentric retrospective analysis, postoperative AST (POD1-5), creatinine (POD3-7), INR (POD0-7), bilirubin (POD0-7) and MELD scores (POD0-7) strictly correlated with graft dysfunction within POD90. The best AUROCs, for MELD on POD5 and bilirubin on POD2, did not statistically differ in their predictiveness. Thus, total bilirubin > 6.55 mg/dL on POD1-2 should alert clinicians^[80].

Olthoff *et al.*^[81] excluded INR and bilirubin up to POD7, suggesting that those values might still reflect recipient pre-transplant status and not graft functionality. However, AST and ALT were evaluated daily on POD1-7, immediately reflecting eventual graft injury. Their EAD definition showed good prediction of 6-mo mortality, with a relative risk = 10.7 (95%CI: 3.5-31.9). Similar results were found for 6-mo graft loss.

The rapid kinetics of AST and ALT should be considered to assess graft viability and trial endpoints in LT. The majority of peak ASTs are detected at 6 h post-reperfusion, with a time window between 5 and 11 h. These could be missed if AST determination relies only on routinely taken samples, usually after ICU arrival. The precise timing of the first blood sample or a specific time window should be indicated to make the results more reproducible and avoid erroneous classification of serum transaminases^[82].

LACTATES

Lactates, the waste products of cellular metabolism, are mainly metabolised by the liver. Thus, liver function and its restoration after LT might be reflected by abnormally elevated lactate levels. A damaged liver can itself be a source of lactate.

ICU survival has been predicted by calculating the percentage of lactate reduction between the time of admission and 6 h after admission^[83]. An observational prospective study divided 222 consecutive LT patients into two groups, those who developed EAD and those who did not. Initial absolute lactate values did not differ between the two groups, but clearance during the first 6 hours of ICU stay was significantly higher in the non-EAD group. AUROC of 0.961, for a cut-off point of 24.8% of clearance, was much higher than other significant parameters; an odds ratio of 169 (95%CI:

52.49-544.13) was calculated for the prediction of EAD. The group with a lower clearance showed higher in-hospital mortality but no differences in 1-year mortality. So, early measurement of lactates allows immediate functional graft assessment rather than a medium- or long-term clinical outcome prediction. The ease of the technique makes it readily available at the bedside^[84].

IGF1

Hepatic dysfunction affects several biochemical processes taking place in this organ. One fundamental endocrine axis involving the liver, is the Growth Hormone (GH) - IGF1 axis. Liver damage measured through clinical scales such as MELD or Child-Pugh correlates with decreased levels of IGF1, which is synthesised by the hepatocytes, and consequently with increased GH levels^[85,86]. IGF-1 and GH levels correlate with common enzymes to assess liver function and to describe post-LDLT liver regeneration in both donors and recipients^[87]. In LT, peri-operative quantification of IGF-1 showed a dramatic decrease during the anhepatic phase, with levels already significantly rising 30 min after the completion of the surgery and completely normalising between POD7 and 28. From POD7, significantly lower levels were detected in patients who developed IPF^[88]. Consequently, the prospective 3-years follow up a small group of 31 transplanted patients showed that 18 of them already had normalised IGF-1 levels on POD15, and their actual 3-year survival rates were significantly improved. Decreased levels of IGF-1 during the whole 1st year after LT were found in patients transplanted with livers from donors older than 65. From POD90, low IGF-1 levels significantly correlated with increased ECD score^[89]. The IGF-1 serum test is a quick, inexpensive and reproducible immunometric assay, giving this parameter an advantage over other molecules in the prediction of initial graft function. Unlike ICG-PDR, IGF-1 determination is not influenced by patient hemodynamic instability or hyperbilirubinaemia.

Unfortunately, in the above mentioned studies, significant results were found only starting from POD7^[88] and POD15^[89] respectively. Similar results were found in another retrospective study with a small sample of 30 LT patients who only found predictive IGF-1 values for the 90-d survival rate on POD15^[90]. Thus, to date this technique cannot be applied during the first postoperative week in the ICU to guide treatments and strategies.

POSTOPERATIVE MELD SCORE, MELD LACTATE

The poor performance of preoperative MELD in predicting post-LT graft and patient survival has already been

discussed. Despite this consideration, postoperative MELD has been used repeatedly for this purpose because of its simplicity and easily measurable variables. It performs well as a predictor of 90-d graft failure (defined as patient death or re-transplantation). MELD > 18.9 on POD5 had the best performance and better predictive power of all commonly available data. No significant difference was found between MELD values recorded from POD0 to POD7, but the best AUROC (> 0.8) was on POD5^[80].

After LDLT, postoperative MELD < 19 on POD2 (up to POD14) performed better than preoperative MELD in predicting 6-mo graft survival, with a peak of AUROC (0.933) and specificity (100%) on POD7^[91]. The MELD lactate score 1 h after the end of the LT surgery was found to be a predictor of 30-d patient survival. At that time of early patient recovery, lactates are able to account for I/R liver damage, donor liver problems (not always predictable before LT), general recipient status, infections and surgical problems. Most non-survivors with high MELD-lactate scores died in ICU within a few days after LT^[92].

APACHE

This score, created in the 1980s^[93] and successively modified until APACHE IV^[94-96], aimed to predict mortality in critically ill patients. Not being specifically designed for transplanted patients, when used alone APACHE II displays overestimation problems regarding patient mortality and low AUROC values^[97,98]. Then, a specific correction factor for LT was created to correct APACHE (APACHE-LT). When APACHE II-LT was calculated on POD1, it performed better than any other scoring system, with statistically non-significant differences between predicted and observed mortality^[99].

Contrasting results about APACHE II came from different clinical studies, likely because of different sample groups in different geographical regions^[98,100,101]. This confirmed the weakness of clinical scores applied alone in predicting patient outcome.

CLIF-SOFA

SOFA is a scoring system allowing the quantification of the number and severity of apparatus dysfunction in a critically ill patient^[102]. An adjusted SOFA score accounting for end-stage liver disease was defined CLIF-SOFA^[103].

When tested to predict 3- and 12-mo mortality in a unicentric cohort of 149 LT patients retrospectively divided in 1-year survivors and non-survivors, SOFA had the best discriminatory power (higher than MELD). 323 patients from the same cohort were then analysed using CLIF-SOFA. An excellent AUROC was detected, with significantly best discriminatory power on POD1-7 with respect to MELD and SOFA. The best AUROC (0.877) for CLIF-SOFA occurred on POD7. Significantly

different cumulative survival rates for CLIF-SOFA ≤ 8 vs CLIF-SOFA > 8 were detected^[104].

These two studies come from a single group, and more than 50% of patients in both studies had Hepatitis B (and 27% hepatomas in the latter case) that required LT, reflecting the geographical area of the provenance of these studies. These facts might affect the results and reduce their reproducibility.

After LDLT, SOFA score on POD7 had the highest power to predict 3-mo mortality^[105].

MEAF

A biochemical-based scoring system was developed after retrospectively collecting data from a unicentric database (829 recipients) and then tested on a validation group (200 recipients) from a different centre^[106]. Primary end-points were patient mortality at 3, 6, and 12 mo after LT, PNF and EAD. The highest ALT, AST, INR and PT levels within the first 3 postoperative days and bilirubin on POD3 were found to reliably describe EAD. MEAF is calculated through a non-linear regression model and is completely calculable on POD3. Slight evidence of correlation of the MEAF score with 3-mo mortality was found (confidence interval 1.01-1.41). However, the 3-mo mortality rate rose to 40.6% for patients with MEAF > 8. A sharp increase in the development of PNF and EAD was registered for those with MEAF > 7. Significant correlation of MEAF with ICU and hospital stay was also found. All data were confirmed and strengthened in the validation cohort. The nature of MEAF makes it a more flexible tool than those using pre-established cut-offs, likely increasing its value with respect to older EAD definitions.

The simplicity of this model and its rapid applicability on POD3 make it a suitable candidate for predicting PNF, 3-mo graft loss and patient mortality.

CONCLUSION

Although there are a wide variety of laboratory and functional tests available to directly or indirectly quantify graft function after LT, it is still difficult to predict graft and patient survival after this major surgical intervention. Many efforts were made to individuate diagnostic EAD criteria or critical patient conditions early (within the first few PODs), which might be essential for a successful outcome of LT. Rapid and precise instruments to understand initial graft function and other comorbidities affecting the recipient could guide the medical staff to more effective, and aggressive when necessary, strategies to support both liver and general condition after LT. Encouraging results come from functional tests like LiMax test and ICG-PDR which could not only predict the outcome but even indicate the best therapeutic decisions. Although several limitations and contradictions have been illustrated, MEAF and other scoring systems, might

become reliable, simple and cheap predictors during the first PODs.

Unfortunately, few techniques have revealed consistent initial results probably for their retrospective, monocentric nature, for the small number of subjects studied and for the low predictive power. The lack of unique definitions of reference values and occasional high economical costs also limit their usage. By critically considering the statistics and the clinical samples reported in this review, it might be possible to integrate different scoring systems and functional tools, instead of using single indices, to better assess early graft function offering help in surgical and medical early postoperative patient management. The creation of such a complex analysis is beyond the aims of this review and the possibilities of the authors. Multicentric prospective trials should be performed to avoid wasting the resources and clinical knowledge currently available.

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P- Reviewer: Bramhall S, Makisalo H, Stauffer K **S- Editor:** Ma YJ

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ISSN 1007-9327



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