

2016 Liver Transplantation: Global view

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

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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.

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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]	On POD5: [Serum bilirubin (μmol/L)]/[Prothrombin (%)] > 1	IPF-induced retransplantation or death within POD7
Nemes <i>et al</i> ^[117]	On POD1-7, one within: Bilirubin ≥ 10 mg/dL on POD7 INR ≥ 1.6 on POD7 ALT or AST > 2000 IU/L within POD7	
Olthoff <i>et al</i> ^[81]		
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*^[112] 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%, 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> ^[33]	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> ^[42]	P	EAD prediction	72 LT (including LDLT)	0-5	12.85%/min		90.0	97.0		
	Schneider <i>et al</i> ^[43]	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> ^[45]	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> ^[44]	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)
	Lock <i>et al</i> ^[38]	P	EAD requiring reintervention before POD2 or causing death/retransplantation within POD14	99 LT: 32% alcoholic, 23% HCV	0 1	64 µg/kg per hour 43 µg/kg per hour	0.960 (0.921-0.998) 0.992 (0.975-1.000)	100 (60-100) 100 (31-100)	92 (84-97) 100 (94-100)	53 (27-78) 100 (31-100)	100 (95-100) 100 (94-100)
Platelets count	Lesurtel <i>et al</i> ^[72]	R	Severe complications or 3-mo mortality	257 LT: 38% HCV	5	60 × 10 ⁹ /L		58.0	61.0		
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 Immunolite 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)					
	Toshima <i>et al</i> ^[94]	R	Graft loss or mortality within POD180	217 LDLT: 47.9% HCV	2	≥ 19	0.779	68.2	79.5	27.3	95.7	
MELD lactate	Cardoso <i>et al</i> ^[92]	P	Mortality within POD30	58 LT: 43% HCV, 26% alcoholic	7	26.3	0.933	100.0	74.9	31.0	100.0	
APACHE IV	Hu <i>et al</i> ^[199]	R	Mortality	195 LT	1 h after surgery	≥ 55.5	0.937 (0.892-0.981)	85.2	91.1	60.5	97.5	
SOFA	Wong <i>et al</i> ^[120]	R	3-mo mortality	149 LT: 53% HBV	7	≥ 8	0.953 (0.902-1.000)	95.0	91.0			
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	87.0			
MEAF	Pareja <i>et al</i> ^[106]	R	EAD definition ti predict 3-mo mortality	874 LT (+200 validation)	7	> 8	0.877 (0.813-0.941)	64.0	95.0			

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 an 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.

REFERENCES

- 1 **Martin P**, DiMartini A, Feng S, Brown R, Fallon M. Evaluation for liver transplantation in adults: 2013 practice guideline by the American Association for the Study of Liver Diseases and the American Society of Transplantation. *Hepatology* 2014; **59**: 1144-1165 [PMID: 24716201]
- 2 **European Association for the Study of the Liver. Electronic address: easloffice@easloffice.eu**. EASL Clinical Practice Guidelines: Liver transplantation. *J Hepatol* 2016; **64**: 433-485 [PMID: 26597456 DOI: 10.1016/j.jhep.2015.10.006]
- 3 **Wiesner R**, Edwards E, Freeman R, Harper A, Kim R, Kamath P, Kremers W, Lake J, Howard T, Merion RM, Wolfe RA, Krom R. Model for end-stage liver disease (MELD) and allocation of donor livers. *Gastroenterology* 2003; **124**: 91-96 [PMID: 12512033 DOI: 10.1053/gast.2003.50016]
- 4 **Maluf DG**, Edwards EB, Kauffman HM. Utilization of extended donor criteria liver allograft: Is the elevated risk of failure independent of the model for end-stage liver disease score of the recipient? *Transplantation* 2006; **82**: 1653-1657 [PMID: 17198254 DOI: 10.1097/01.tp.0000250571.41361.21]
- 5 **Bonney GK**, Aldersley MA, Asthana S, Toogood GJ, Pollard SG, Lodge JP, Prasad KR. Donor risk index and MELD interactions in predicting long-term graft survival: a single-centre experience. *Transplantation* 2009; **87**: 1858-1863 [PMID: 19543065 DOI: 10.1097/TP.0b013e3181a75b37]
- 6 **Weismüller TJ**, Negrn A, Becker T, Barg-Hock H, Klempnauer J, Manns MP, Strassburg CP. The introduction of MELD-based organ allocation impacts 3-month survival after liver transplantation by influencing pretransplant patient characteristics. *Transpl Int* 2009; **22**: 970-978 [PMID: 19619170 DOI: 10.1111/j.1432-2277.2009.00915.x]
- 7 **Schlitt HJ**, Loss M, Scherer MN, Becker T, Jauch KW, Nashan B, Schmidt H, Settmacher U, Rogiers X, Neuhaus P, Strassburg C. [Current developments in liver transplantation in Germany: MELD-based organ allocation and incentives for transplant centres]. *Z Gastroenterol* 2011; **49**: 30-38 [PMID: 21225535 DOI: 10.1055/s-0029-1245946]
- 8 **Lock JF**, Reinhold T, Malinowski M, Pratschke J, Neuhaus P, Stockmann M. The costs of postoperative liver failure and the economic impact of liver function capacity after extended liver resection--a single-center experience. *Langenbecks Arch Surg* 2009; **394**: 1047-1056 [PMID: 19533168 DOI: 10.1007/s00423-009-0518-4]
- 9 **Foxton MR**, Al-Freah MA, Portal AJ, Sizer E, Bernal W, Auzinger G, Rela M, Wendon JA, Heaton ND, O'Grady JG, Heneghan MA. Increased model for end-stage liver disease score at the time of liver transplant results in prolonged hospitalization and overall intensive care unit costs. *Liver Transpl* 2010; **16**: 668-677 [PMID: 20440776 DOI: 10.1002/lt.22027]
- 10 **Kaltenborn A**, Hartmann C, Salinas R, Ramackers W, Kleine M, Vondran FW, Barthold M, Lehner F, Klempnauer J, Schrem H. Risk factors for short- and long-term mortality in liver transplant recipients with MELD score ≥ 30 . *Ann Transplant* 2015; **20**: 59-69 [PMID: 25630462 DOI: 10.12659/AOT.892322]
- 11 **Sirivatanauksorn Y**, Taweerutchana V, Limsrichamrern S, Kositamongkol P, Mahawithitwong P, Asavakarn S, Tovikkai C. Recipient and perioperative risk factors associated with liver transplant graft outcomes. *Transplant Proc* 2012; **44**: 505-508 [PMID: 22410056 DOI: 10.1016/j.transproceed.2012.01.065]
- 12 **Chen XB**, Xu MQ. Primary graft dysfunction after liver transplantation. *Hepatobiliary Pancreat Dis Int* 2014; **13**: 125-137 [PMID: 24686540 DOI: 10.1016/S1499-3872(14)60023-0]
- 13 **Hayashi PH**, Forman L, Steinberg T, Bak T, Wachs M, Kugelmas M, Everson GT, Kam I, Trotter JF. Model for End-Stage Liver Disease score does not predict patient or graft survival in living donor liver transplant recipients. *Liver Transpl* 2003; **9**: 737-740 [PMID: 12827562 DOI: 10.1053/jlts.2003.50122]
- 14 **Jacob M**, Copley LP, Lewsey JD, Gimson A, Toogood GJ, Rela M, van der Meulen JH. Pretransplant MELD score and post liver transplantation survival in the UK and Ireland. *Liver Transpl* 2004; **10**: 903-907 [PMID: 15237375 DOI: 10.1002/lt.20169]
- 15 **Fikatas P**, Lee JE, Sauer IM, Schmidt SC, Seehofer D, Puhl G, Guckelberger O. APACHE III score is superior to King's College Hospital criteria, MELD score and APACHE II score to predict outcomes after liver transplantation for acute liver failure. *Transplant Proc* 2013; **45**: 2295-2301 [PMID: 23953541 DOI: 10.1016/j.transproceed.2013.02.125]
- 16 **Huo TI**, Wang YW, Yang YY, Lin HC, Lee PC, Hou MC, Lee FY, Lee SD. Model for end-stage liver disease score to serum sodium ratio index as a prognostic predictor and its correlation with portal pressure in patients with liver cirrhosis. *Liver Int* 2007; **27**: 498-506 [PMID: 17403190 DOI: 10.1111/j.1478-3231.2007.01445.x]
- 17 **Kim WR**, Biggins SW, Kremers WK, Wiesner RH, Kamath PS, Benson JT, Edwards E, Therneau TM. Hyponatremia and mortality among patients on the liver-transplant waiting list. *N Engl J Med* 2008; **359**: 1018-1026 [PMID: 18768945 DOI: 10.1056/NEJMoa0801209]
- 18 **Halldorson JB**, Bakthavatsalam R, Fix O, Reyes JD, Perkins JD. D-MELD, a simple predictor of post liver transplant mortality for optimization of donor/recipient matching. *Am J Transplant* 2009; **9**: 318-326 [PMID: 19120079 DOI: 10.1111/j.1600-6143.2008.02491.x]
- 19 **Sharma P**, Schaubel DE, Sima CS, Merion RM, Lok AS. Re-weighting the model for end-stage liver disease score components. *Gastroenterology* 2008; **135**: 1575-1581 [PMID: 18835388 DOI: 10.1053/j.gastro.2008.08.004]
- 20 **Feng S**, Goodrich NP, Bragg-Gresham JL, Dykstra DM, Punch JD, DeRoy MA, Greenstein SM, Merion RM. Characteristics associated with liver graft failure: the concept of a donor risk index. *Am J Transplant* 2006; **6**: 783-790 [PMID: 16539636 DOI: 10.1111/j.1600-6143.2006.01242.x]
- 21 **Cameron AM**, Ghobrial RM, Yersiz H, Farmer DG, Lipshutz GS, Gordon SA, Zimmerman M, Hong J, Collins TE, Gornbein J, Amersi F, Weaver M, Cao C, Chen T, Hiatt JR, Busuttil RW. Optimal utilization of donor grafts with extended criteria: a single-center experience in over 1000 liver transplants. *Ann Surg* 2006; **243**: 748-753; discussion 753-755 [PMID: 16772778 DOI: 10.1097/01.sla.0000219669.84192.b3]
- 22 **Schrem H**, Reichert B, Frühauf N, Becker T, Lehner F, Kleine M, Bektas H, Zachau L, Klempnauer J. The Donor-Risk-Index, ECD-Score and D-MELD-Score all fail to predict short-term outcome after liver transplantation with acceptable sensitivity and specificity. *Ann Transplant* 2012; **17**: 5-13 [PMID: 23018250]
- 23 **Rana A**, Hardy MA, Halazun KJ, Woodland DC, Ratner LE,

- Samstein B, Guarrera JV, Brown RS, Emond JC. Survival outcomes following liver transplantation (SOFT) score: a novel method to predict patient survival following liver transplantation. *Am J Transplant* 2008; **8**: 2537-2546 [PMID: 18945283 DOI: 10.1111/j.1600-6143.2008.02400.x]
- 24 **Rana A**, Jie T, Porubsky M, Habib S, Rilo H, Kaplan B, Gruessner A, Gruessner R. The survival outcomes following liver transplantation (SOFT) score: validation with contemporaneous data and stratification of high-risk cohorts. *Clin Transplant* 2013; **27**: 627-632 [PMID: 23808891 DOI: 10.1111/ctr.12181]
- 25 **Dutkowski P**, Oberkofler CE, Slankamenac K, Puhon MA, Schadde E, Müllhaupt B, Geier A, Clavien PA. Are there better guidelines for allocation in liver transplantation? A novel score targeting justice and utility in the model for end-stage liver disease era. *Ann Surg* 2011; **254**: 745-753; discussion 753 [PMID: 22042468 DOI: 10.1097/SLA.0b013e3182365081]
- 26 **Charlson ME**, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987; **40**: 373-383 [PMID: 3558716]
- 27 **Volk ML**, Hernandez JC, Lok AS, Marrero JA. Modified Charlson comorbidity index for predicting survival after liver transplantation. *Liver Transpl* 2007; **13**: 1515-1520 [PMID: 17969207 DOI: 10.1002/lt.21172]
- 28 **Wasilewicz M**, Raszeja-Wyszomirska J, Wunsch E, Wójcicki M, Milkiewicz P. Modified Charlson Comorbidity Index in predicting early mortality after liver transplantation. *Transplant Proc* 2009; **41**: 3117-3118 [PMID: 19857690 DOI: 10.1016/j.transproceed.2009.07.097]
- 29 **Leon-Justel A**, Noval-Padillo JA, Alvarez-Rios AI, Mellado P, Gomez-Bravo MA, Álamo JM, Porras M, Barrero L, Hinojosa R, Carmona M, Vilches-Arenas A, Guerrero JM. Point-of-care haemostasis monitoring during liver transplantation reduces transfusion requirements and improves patient outcome. *Clin Chim Acta* 2015; **446**: 277-283 [PMID: 25916692 DOI: 10.1016/j.cca.2015.04.022]
- 30 **Perilli V**, Aceto P, Modesti C, Ciocchetti P, Sacco T, Vitale F, Lai C, Magalini SC, Avolio AW, Sollazzi L. Low values of left ventricular ejection time in the post-anhepatic phase may be associated with occurrence of primary graft dysfunction after orthotopic liver transplantation: results of a single-centre case-control study. *Eur Rev Med Pharmacol Sci* 2012; **16**: 1433-1440 [PMID: 23104662]
- 31 **Ijtsma AJ**, van der Hilst CS, de Boer MT, de Jong KP, Peeters PM, Porte RJ, Slooff MJ. The clinical relevance of the anhepatic phase during liver transplantation. *Liver Transpl* 2009; **15**: 1050-1055 [PMID: 19718649 DOI: 10.1002/lt.21791]
- 32 **Briceño J**, Ciria R, de la Mata M, Rufián S, López-Cillero P. Prediction of graft dysfunction based on extended criteria donors in the model for end-stage liver disease score era. *Transplantation* 2010; **90**: 530-539 [PMID: 20581766 DOI: 10.1097/TP.0b013e3181e86b11]
- 33 **Zipprich A**, Kuss O, Rogowski S, Kleber G, Lotterer E, Seufferlein T, Fleig WE, Dollinger MM. Incorporating indocyanine green clearance into the Model for End Stage Liver Disease (MELD-ICG) improves prognostic accuracy in intermediate to advanced cirrhosis. *Gut* 2010; **59**: 963-968 [PMID: 20581243 DOI: 10.1136/gut.2010.208595]
- 34 **Zarrinpar A**, Lee C, Noguchi E, Yersiz H, Agopian VG, Kaldas FM, Farmer DG, Busuttil RW. A rapid, reproducible, noninvasive predictor of liver graft survival. *J Surg Res* 2015; **197**: 183-190 [PMID: 25940156 DOI: 10.1016/j.jss.2015.03.093]
- 35 **Olmedilla L**, Pérez-Peña JM, Ripoll C, Garutti I, de Diego R, Salcedo M, Jiménez C, Bañares R. Early noninvasive measurement of the indocyanine green plasma disappearance rate accurately predicts early graft dysfunction and mortality after deceased donor liver transplantation. *Liver Transpl* 2009; **15**: 1247-1253 [PMID: 19790138 DOI: 10.1002/lt.21841]
- 36 **Nishimura A**, Hakamada K, Narumi S, Totsuka E, Toyoki Y, Ishizawa Y, Umehara M, Yoshida A, Umehara Y, Sasaki M. Intraoperative blood lactate level as an early predictor of initial graft function in human living donor liver transplantation. *Transplant Proc* 2004; **36**: 2246-2248 [PMID: 15561207 DOI: 10.1016/j.transproceed.2004.08.051]
- 37 **Burns E**, Triger DR, Tucker GT, Bax ND. Indocyanine green elimination in patients with liver disease and in normal subjects. *Clin Sci (Lond)* 1991; **80**: 155-160 [PMID: 1848168]
- 38 **Hsieh CB**, Chen CJ, Chen TW, Yu JC, Shen KL, Chang TM, Liu YC. Accuracy of indocyanine green pulse spectrophotometry clearance test for liver function prediction in transplanted patients. *World J Gastroenterol* 2004; **10**: 2394-2396 [PMID: 15285026]
- 39 **von Spiegel T**, Scholz M, Wietasch G, Hering R, Allen SJ, Wood P, Hoeft A. Perioperative monitoring of indocyanine green clearance and plasma disappearance rate in patients undergoing liver transplantation. *Anaesthesist* 2002; **51**: 359-366 [PMID: 12125306 DOI: 10.1007/s00101-002-0290-0]
- 40 **Faybik P**, Krenn CG, Baker A, Lahner D, Berlakovich G, Steltzer H, Hetz H. Comparison of invasive and noninvasive measurement of plasma disappearance rate of indocyanine green in patients undergoing liver transplantation: a prospective investigator-blinded study. *Liver Transpl* 2004; **10**: 1060-1064 [PMID: 15390334 DOI: 10.1002/lt.20205]
- 41 **Vos JJ**, Wietasch JK, Absalom AR, Hendriks HG, Scheeren TW. Green light for liver function monitoring using indocyanine green? An overview of current clinical applications. *Anaesthesia* 2014; **69**: 1364-1376 [PMID: 24894115 DOI: 10.1111/anae.12755]
- 42 **Levesque E**, Saliba F, Benhamida S, Ichaï P, Azoulay D, Adam R, Castaing D, Samuel D. Plasma disappearance rate of indocyanine green: a tool to evaluate early graft outcome after liver transplantation. *Liver Transpl* 2009; **15**: 1358-1364 [PMID: 19790157 DOI: 10.1002/lt.21805]
- 43 **Schneider L**, Spiegel M, Latanowicz S, Weigand MA, Schmidt J, Werner J, Stremmel W, Eisenbach C. Noninvasive indocyanine green plasma disappearance rate predicts early complications, graft failure or death after liver transplantation. *Hepatobiliary Pancreat Dis Int* 2011; **10**: 362-368 [PMID: 21813383]
- 44 **Olmedilla L**, Lisbona CJ, Pérez-Peña JM, López-Baena JA, Garutti I, Salcedo M, Sanz J, Tisner M, Ascencio JM, Fernández-Quero L, Bañares R. Early Measurement of Indocyanine Green Clearance Accurately Predicts Short-Term Outcomes After Liver Transplantation. *Transplantation* 2016; **100**: 613-620 [PMID: 26569066 DOI: 10.1097/TP.0000000000000980]
- 45 **Klinzing S**, Brandi G, Stehberger PA, Raptis DA, Béchir M. The combination of MELD score and ICG liver testing predicts length of stay in the ICU and hospital mortality in liver transplant recipients. *BMC Anesthesiol* 2014; **14**: 103 [PMID: 25844060 DOI: 10.1186/1471-2253-14-103]
- 46 **Hori T**, Iida T, Yagi S, Taniguchi K, Yamamoto C, Mizuno S, Yamagiwa K, Isaji S, Uemoto S. K(ICG) value, a reliable real-time estimator of graft function, accurately predicts outcomes in adult living-donor liver transplantation. *Liver Transpl* 2006; **12**: 605-613 [PMID: 16555326 DOI: 10.1002/lt.20713]
- 47 **Levesque E**, Hoti E, Azoulay D, Adam R, Samuel D, Castaing D, Saliba F. Non-invasive ICG-clearance: a useful tool for the management of hepatic artery thrombosis following liver transplantation. *Clin Transplant* 2011; **25**: 297-301 [PMID: 20412097 DOI: 10.1111/j.1399-0012.2010.01252.x]
- 48 **Janssen MW**, Druckrey-Fiskaaen KT, Omid L, Sliwinski G, Thiele C, Donaubauer B, Polze N, Kaisers UX, Thiery J, Wittekind C, Hauss JP, Schön MR. Indocyanine green R15 ratio depends directly on liver perfusion flow rate. *J Hepatobiliary Pancreat Sci* 2010; **17**: 180-185 [PMID: 19760140 DOI: 10.1007/s00534-009-0160-0]
- 49 **Stockmann M**, Malinowski M, Lock JF, Seehofer D, Neuhaus P. Factors influencing the indocyanine green (ICG) test: additional impact of acute cholestasis. *Hepatogastroenterology* 2009; **56**: 734-738 [PMID: 19621693]
- 50 **Bärthel E**, Rauchfuss F, Hoyer H, Habrecht O, Jandt K, Götz M, Voigt R, Heise M, Marx G, Settmacher U. Impact of stable PGI₂ analog iloprost on early graft viability after liver transplantation: a pilot study. *Clin Transplant* 2012; **26**: E38-E47 [PMID: 21919966 DOI: 10.1111/j.1399-0012.2011.01516.x]

- 51 **Cui Y**, König J, Leier I, Buchholz U, Keppler D. Hepatic uptake of bilirubin and its conjugates by the human organic anion transporter SLC21A6. *J Biol Chem* 2001; **276**: 9626-9630 [PMID: 11134001 DOI: 10.1074/jbc.M004968200]
- 52 **Kimura S**, Yoshioka T, Shibuya M, Sakano T, Tanaka R, Matsuyama S. Indocyanine green elimination rate detects hepatocellular dysfunction early in septic shock and correlates with survival. *Crit Care Med* 2001; **29**: 1159-1163 [PMID: 11395594]
- 53 **Stockmann M**, Lock JF, Malinowski M, Neuhaus P. Evaluation of early liver graft performance by the indocyanine green plasma disappearance rate. *Liver Transpl* 2010; **16**: 793-794; author reply 795-796 [PMID: 20517918 DOI: 10.1002/lt.22068]
- 54 **Maring JK**, Klompmaker IJ, Zwaveling JH, Kranenburg K, Ten Vergert EM, Slooff MJ. Poor initial graft function after orthotopic liver transplantation: can it be predicted and does it affect outcome? An analysis of 125 adult primary transplantations. *Clin Transplant* 1997; **11**: 373-379 [PMID: 9361926]
- 55 **Stockmann M**, Lock JF, Riecke B, Heyne K, Martus P, Fricke M, Lehmann S, Niehues SM, Schwabe M, Lemke AJ, Neuhaus P. Prediction of postoperative outcome after hepatectomy with a new bedside test for maximal liver function capacity. *Ann Surg* 2009; **250**: 119-125 [PMID: 19561474 DOI: 10.1097/SLA.0b013e3181ad85b5]
- 56 **Jara M**, Reese T, Malinowski M, Valle E, Seehofer D, Puhl G, Neuhaus P, Pratschke J, Stockmann M. Reductions in post-hepatectomy liver failure and related mortality after implementation of the LiMAX algorithm in preoperative work-up: a single-centre analysis of 1170 hepatectomies of one or more segments. *HPB (Oxford)* 2015; **17**: 651-658 [PMID: 26058324 DOI: 10.1111/hpb.12424]
- 57 **Stockmann M**, Lock JF, Malinowski M, Niehues SM, Seehofer D, Neuhaus P. The LiMAX test: a new liver function test for predicting postoperative outcome in liver surgery. *HPB (Oxford)* 2010; **12**: 139-146 [PMID: 20495659 DOI: 10.1111/j.1477-2574.2009.00151.x]
- 58 **Lock JF**, Schwabauer E, Martus P, Videv N, Pratschke J, Malinowski M, Neuhaus P, Stockmann M. Early diagnosis of primary nonfunction and indication for reoperation after liver transplantation. *Liver Transpl* 2010; **16**: 172-180 [PMID: 20104485 DOI: 10.1002/lt.21973]
- 59 **Stockmann M**, Lock JF, Malinowski M, Seehofer D, Puhl G, Pratschke J, Neuhaus P. How to define initial poor graft function after liver transplantation? - a new functional definition by the LiMAX test. *Transpl Int* 2010; **23**: 1023-1032 [PMID: 20444241 DOI: 10.1111/j.1432-2277.2010.01089.x]
- 60 **Lock JF**, Malinowski M, Schwabauer E, Martus P, Pratschke J, Seehofer D, Puhl G, Neuhaus P, Stockmann M. Initial liver graft function is a reliable predictor of tacrolimus trough levels during the first post-transplant week. *Clin Transplant* 2011; **25**: 436-443 [PMID: 20482563 DOI: 10.1111/j.1399-0012.2010.01264.x]
- 61 **Parker BM**, Cywinski JB, Alster JM, Irefin SA, Popovich M, Beven M, Fung JJ. Predicting immunosuppressant dosing in the early postoperative period with noninvasive indocyanine green elimination following orthotopic liver transplantation. *Liver Transpl* 2008; **14**: 46-52 [PMID: 18161838 DOI: 10.1002/lt.21308]
- 62 **Potter JM**, Oellerich M. The use of lidocaine as a test of liver function in liver transplantation. *Liver Transpl Surg* 1996; **2**: 211-224 [PMID: 9346651]
- 63 **Potter JM**, Hickman PE, Henderson A, Balderson GA, Lynch SV, Strong RW. The use of the lidocaine-monoethylglycinexylidide test in the liver transplant recipient. *Ther Drug Monit* 1996; **18**: 383-387 [PMID: 8857555]
- 64 **Redaelli CA**, Dufour JF, Wagner M, Schilling M, Hüsler J, Krähenbühl L, Büchler MW, Reichen J. Preoperative galactose elimination capacity predicts complications and survival after hepatic resection. *Ann Surg* 2002; **235**: 77-85 [PMID: 11753045]
- 65 **Armuzzi A**, Candelli M, Zocco MA, Andreoli A, De Lorenzo A, Nista EC, Miele L, Cremonini F, Cazzato IA, Grieco A, Gasbarrini G, Gasbarrini A. Review article: breath testing for human liver function assessment. *Aliment Pharmacol Ther* 2002; **16**: 1977-1996 [PMID: 12452932]
- 66 **Pereboom IT**, Lismann T, Porte RJ. Platelets in liver transplantation: friend or foe? *Liver Transpl* 2008; **14**: 923-931 [PMID: 18581510 DOI: 10.1002/lt.21510]
- 67 **Nascimbene A**, Iannacone M, Brando B, De Gasperi A. Acute thrombocytopenia after liver transplant: role of platelet activation, thrombopoietin deficiency and response to high dose intravenous IgG treatment. *J Hepatol* 2007; **47**: 651-657 [PMID: 17716776 DOI: 10.1016/j.jhep.2007.06.012]
- 68 **Chang FY**, Singh N, Gayowski T, Wagener MM, Mietzner SM, Stout JE, Marino IR. Thrombocytopenia in liver transplant recipients: predictors, impact on fungal infections, and role of endogenous thrombopoietin. *Transplantation* 2000; **69**: 70-75 [PMID: 10653383]
- 69 **de Boer MT**, Christensen MC, Asmussen M, van der Hilst CS, Hendriks HG, Slooff MJ, Porte RJ. The impact of intraoperative transfusion of platelets and red blood cells on survival after liver transplantation. *Anesth Analg* 2008; **106**: 32-44, table of contents [PMID: 18165548 DOI: 10.1213/01.ane.0000289638.26666.ed]
- 70 **Li L**, Wang H, Yang J, Jiang L, Wang J, Wang W, Yan L, Wen T, Li B, Xu M. Immediate Postoperative Low Platelet Counts After Living Donor Liver Transplantation Predict Early Allograft Dysfunction. *Medicine (Baltimore)* 2015; **94**: e1373 [PMID: 26313775 DOI: 10.1097/md.0000000000001373]
- 71 **Chatzipetrou MA**, Tsaroucha AK, Weppler D, Pappas PA, Kenyon NS, Nery JR, Khan MF, Kato T, Pinna AD, O'Brien C, Viciano A, Ricordi C, Tzakis AG. Thrombocytopenia after liver transplantation. *Transplantation* 1999; **67**: 702-706 [PMID: 10096525]
- 72 **Lesurtel M**, Raptis DA, Melloul E, Schlegel A, Oberkofler C, El-Badry AM, Weber A, Mueller N, Dutkowski P, Clavien PA. Low platelet counts after liver transplantation predict early posttransplant survival: the 60-5 criterion. *Liver Transpl* 2014; **20**: 147-155 [PMID: 24123804 DOI: 10.1002/lt.23759]
- 73 **Kim J**, Yi NJ, Shin WY, Kim T, Lee KU, Suh KS. Platelet transfusion can be related to liver regeneration after living donor liver transplantation. *World J Surg* 2010; **34**: 1052-1058 [PMID: 20151125 DOI: 10.1007/s00268-010-0464-x]
- 74 **Han S**, Park HW, Song JH, Gwak MS, Lee WJ, Kim G, Lee SK, Ko JS. Association Between Intraoperative Platelet Transfusion and Early Graft Regeneration in Living Donor Liver Transplantation. *Ann Surg* 2015; Epub ahead of print [PMID: 26720430 DOI: 10.1097/SLA.0000000000001526]
- 75 **Elinav E**, Ben-Dov I, Hai-Am E, Ackerman Z, Ofra Y. The predictive value of admission and follow up factor V and VII levels in patients with acute hepatitis and coagulopathy. *J Hepatol* 2005; **42**: 82-86 [PMID: 15629511 DOI: 10.1016/j.jhep.2004.09.009]
- 76 **Zulian MC**, Chedid MF, Chedid AD, Grezzana Filho TJ, Leipnitz I, de Araujo A, Alvares-da-Silva MR, Cardoni MG, Guimaraes LS, Krul CD, Krul CR. Low serum factor V level: early predictor of allograft failure and death following liver transplantation. *Langenbecks Arch Surg* 2015; **400**: 589-597 [PMID: 25708642 DOI: 10.1007/s00423-015-1290-2]
- 77 **Remien CH**, Adler FR, Waddoups L, Box TD, Sussman NL. Mathematical modeling of liver injury and dysfunction after acetaminophen overdose: early discrimination between survival and death. *Hepatology* 2012; **56**: 727-734 [PMID: 22331703 DOI: 10.1002/hep.25656]
- 78 **Robertson FP**, Bessell PR, Diaz-Nieto R, Thomas N, Rolando N, Fuller B, Davidson BR. High serum Aspartate transaminase levels on day 3 postliver transplantation correlates with graft and patient survival and would be a valid surrogate for outcome in liver transplantation clinical trials. *Transpl Int* 2016; **29**: 323-330 [PMID: 26615011 DOI: 10.1111/tri.12723]
- 79 **den Dulk AC**, Sebik Korkmaz K, de Rooij BJ, Sutton ME, Braat AE, Inderson A, Dubbeld J, Verspaget HW, Porte RJ, van Hoek B. High peak alanine aminotransferase determines extra risk for nonanastomotic biliary strictures after liver transplantation with donation after circulatory death. *Transpl Int* 2015; **28**: 492-501 [PMID: 25601020 DOI: 10.1111/tri.12524]
- 80 **Wagener G**, Raffel B, Young AT, Minhaz M, Emond J. Predicting

- early allograft failure and mortality after liver transplantation: the role of the postoperative model for end-stage liver disease score. *Liver Transpl* 2013; **19**: 534-542 [PMID: 23576469 DOI: 10.1002/lt.23634]
- 81 **Olthoff KM**, Kulik L, Samstein B, Kaminski M, Abecassis M, Emond J, Shaked A, Christie JD. Validation of a current definition of early allograft dysfunction in liver transplant recipients and analysis of risk factors. *Liver Transpl* 2010; **16**: 943-949 [PMID: 20677285 DOI: 10.1002/lt.22091]
- 82 **Jochmans I**, Monbaliu D, Pirenne J. The beginning of an end point: peak AST in liver transplantation. *J Hepatol* 2014; **61**: 1186-1187 [PMID: 25051295 DOI: 10.1016/j.jhep.2014.07.021]
- 83 **Nguyen HB**, Rivers EP, Knoblich BP, Jacobsen G, Muzzin A, Ressler JA, Tomlanovich MC. Early lactate clearance is associated with improved outcome in severe sepsis and septic shock. *Crit Care Med* 2004; **32**: 1637-1642 [PMID: 15286537]
- 84 **Wu JF**, Wu RY, Chen J, Ou-Yang B, Chen MY, Guan XD. Early lactate clearance as a reliable predictor of initial poor graft function after orthotopic liver transplantation. *Hepatobiliary Pancreat Dis Int* 2011; **10**: 587-592 [PMID: 22146621 DOI: 10.1016/S1499-3872(11)60100-8]
- 85 **Assy N**, Pruzansky Y, Gaitini D, Shen Orr Z, Hochberg Z, Baruch Y. Growth hormone-stimulated IGF-1 generation in cirrhosis reflects hepatocellular dysfunction. *J Hepatol* 2008; **49**: 34-42 [PMID: 18456366 DOI: 10.1016/j.jhep.2008.02.013]
- 86 **Wu YL**, Ye J, Zhang S, Zhong J, Xi RP. Clinical significance of serum IGF-I, IGF-II and IGFBP-3 in liver cirrhosis. *World J Gastroenterol* 2004; **10**: 2740-2743 [PMID: 15309731]
- 87 **Jara M**, Schulz A, Malinowski M, Puhl G, Lock JF, Seehofer D, Neuhaus P, Stockmann M. Growth hormone/insulin-like growth factor 1 dynamics in adult living donor liver transplantation. *Liver Transpl* 2014; **20**: 1118-1126 [PMID: 24889799 DOI: 10.1002/lt.23922]
- 88 **Bassanello M**, De Palo EF, Lancerin F, Vitale A, Gatti R, Montin U, Ciarleglio FA, Senzolo M, Burra P, Brolese A, Zanusi G, D'Amico DF, Cillo U. Growth hormone/insulin-like growth factor 1 axis recovery after liver transplantation: a preliminary prospective study. *Liver Transpl* 2004; **10**: 692-698 [PMID: 15108263 DOI: 10.1002/lt.20111]
- 89 **Nicolini D**, Mocchegiani F, Palmonella G, Coletta M, Brugia M, Montalti R, Fava G, Taccaliti A, Risaliti A, Vivarelli M. Postoperative Insulin-Like Growth Factor 1 Levels Reflect the Graft's Function and Predict Survival after Liver Transplantation. *PLoS One* 2015; **10**: e0133153 [PMID: 26186540 DOI: 10.1371/journal.pone.0133153]
- 90 **Salso A**, Tisone G, Taricciotti L, Lenci I, Manzia TM, Baiocchi L. Relationship between GH/IGF-1 axis, graft recovery, and early survival in patients undergoing liver transplantation. *Biomed Res Int* 2014; **2014**: 240873 [PMID: 24804205 DOI: 10.1155/2014/240873]
- 91 **Toshima T**, Ikegami T, Kimura K, Harimoto N, Yamashita Y, Yoshizumi T, Soejima Y, Ikeda T, Shirabe K, Maehara Y. Application of postoperative Model for End-Stage Liver Disease scoring system for evaluating liver graft function after living donor liver transplantation. *Transplant Proc* 2014; **46**: 81-86 [PMID: 24507030 DOI: 10.1016/j.transproceed.2013.09.034]
- 92 **Cardoso NM**, Silva T, Basile-Filho A, Mente ED, Castro-e-Silva O. A new formula as a predictive score of post-liver transplantation outcome: postoperative MELD-lactate. *Transplant Proc* 2014; **46**: 1407-1412 [PMID: 24935305 DOI: 10.1016/j.transproceed.2013.12.067]
- 93 **Knaus WA**, Zimmerman JE, Wagner DP, Draper EA, Lawrence DE. APACHE-acute physiology and chronic health evaluation: a physiologically based classification system. *Crit Care Med* 1981; **9**: 591-597 [PMID: 7261642]
- 94 **Knaus WA**, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. *Crit Care Med* 1985; **13**: 818-829 [PMID: 3928249]
- 95 **Knaus WA**, Wagner DP, Draper EA, Zimmerman JE, Bergner M, Bastos PG, Sirio CA, Murphy DJ, Lotring T, Damiano A. The APACHE III prognostic system. Risk prediction of hospital mortality for critically ill hospitalized adults. *Chest* 1991; **100**: 1619-1636 [PMID: 1959406]
- 96 **Zimmerman JE**, Kramer AA, McNair DS, Malila FM. Acute Physiology and Chronic Health Evaluation (APACHE) IV: hospital mortality assessment for today's critically ill patients. *Crit Care Med* 2006; **34**: 1297-1310 [PMID: 16540951 DOI: 10.1097/01.CCM.0000215112.84523.F0]
- 97 **Angus DC**, Clermont G, Kramer DJ, Linde-Zwirble WT, Pinsky MR. Short-term and long-term outcome prediction with the Acute Physiology and Chronic Health Evaluation II system after orthotopic liver transplantation. *Crit Care Med* 2000; **28**: 150-156 [PMID: 10667515]
- 98 **Oliveira VM**, Brauner JS, Rodrigues Filho E, Susin RG, Draghetti V, Bolzan ST, Vieira SR. Is SAPS 3 better than APACHE II at predicting mortality in critically ill transplant patients? *Clinics (Sao Paulo)* 2013; **68**: 153-158 [PMID: 23525309]
- 99 **Sawyer RG**, Durbin CG, Rosenlof LK, Pruett TL. Comparison of APACHE II scoring in liver and kidney transplant recipients versus trauma and general surgical patients in a single intensive-care unit. *Clin Transplant* 1995; **9**: 401-405 [PMID: 8541634]
- 100 **Keegan MT**, Gali B, Findlay JY, Heimbach JK, Plevak DJ, Afessa B. APACHE III outcome prediction in patients admitted to the intensive care unit after liver transplantation: a retrospective cohort study. *BMC Surg* 2009; **9**: 11 [PMID: 19640303 DOI: 10.1186/1471-2482-9-11]
- 101 **Basile-Filho A**, Nicolini EA, Auxiliadora-Martins M, Alkmim-Teixeira GC, Martinez EZ, Martins-Filho OA, de Castro e Silva O. Comparison of acute physiology and chronic health evaluation II death risk, Child-Pugh, Charlson, and model for end-stage liver disease indexes to predict early mortality after liver transplantation. *Transplant Proc* 2011; **43**: 1660-1664 [PMID: 21693253 DOI: 10.1016/j.transproceed.2010.11.029]
- 102 **Vincent JL**, Moreno R, Takala J, Willatts S, De Mendonça A, Bruining H, Reinhart CK, Suter PM, Thijs LG. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. *Intensive Care Med* 1996; **22**: 707-710 [PMID: 8844239]
- 103 **Moreau R**, Jalan R, Gines P, Pavesi M, Angeli P, Cordoba J, Durand F, Gustot T, Saliba F, Domenicali M, Gerbes A, Wendon J, Alessandria C, Laleman W, Zeuzem S, Trebicka J, Bernardi M, Arroyo V. Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. *Gastroenterology* 2013; **144**: 1426-1437, 1426-137, [PMID: 23474284 DOI: 10.1053/j.gastro.2013.02.042]
- 104 **Pan HC**, Jenq CC, Lee WC, Tsai MH, Fan PC, Chang CH, Chang MY, Tian YC, Hung CC, Fang JT, Yang CW, Chen YC. Scoring systems for predicting mortality after liver transplantation. *PLoS One* 2014; **9**: e107138 [PMID: 25216239 DOI: 10.1371/journal.pone.0107138]
- 105 **Elsayed FG**, Sholkamy AA, Elshazli M, Elshafie M, Naguib M. Comparison of different scoring systems in predicting short-term mortality after liver transplantation. *Transplant Proc* 2015; **47**: 1207-1210 [PMID: 26036555 DOI: 10.1016/j.transproceed.2014.11.067]
- 106 **Pareja E**, Cortes M, Hervás D, Mir J, Valdivieso A, Castell JV, Lahoz A. A score model for the continuous grading of early allograft dysfunction severity. *Liver Transpl* 2015; **21**: 38-46 [PMID: 25204890 DOI: 10.1002/lt.23990]
- 107 **Broering DC**, Topp S, Schaefer U, Fischer L, Gundlach M, Sterneck M, Schoder V, Pothmann W, Rogiers X. Split liver transplantation and risk to the adult recipient: analysis using matched pairs. *J Am Coll Surg* 2002; **195**: 648-657 [PMID: 12437252]
- 108 **Nanashima A**, Pillay P, Verran DJ, Painter D, Nakasuji M, Crawford M, Shi L, Ross AG. Analysis of initial poor graft function after orthotopic liver transplantation: experience of an Australian single liver transplantation center. *Transplant Proc* 2002; **34**: 1231-1235 [PMID: 12072325]
- 109 **Heise M**, Settmacher U, Pfitzmann R, Wünsch U, Müller AR,

- Jonas S, Neuhaus P. A survival-based scoring-system for initial graft function following orthotopic liver transplantation. *Transpl Int* 2003; **16**: 794-800 [PMID: 12844216 DOI: 10.1007/s00147-003-0625-z]
- 110 **Tekin K**, Imber CJ, Atli M, Gunson BK, Bramhall SR, Mayer D, Buckels JA, McMaster P, Mirza DF. A simple scoring system to evaluate the effects of cold ischemia on marginal liver donors. *Transplantation* 2004; **77**: 411-416 [PMID: 14966416 DOI: 10.1097/01.TP.0000110318.70879.20]
- 111 **Ben-Ari Z**, Weiss-Schmilovitz H, Sulkes J, Brown M, Bar-Nathan N, Shaharabani E, Yussim A, Shapira Z, Tur-Kaspa R, Mor E. Serum cholestasis markers as predictors of early outcome after liver transplantation. *Clin Transplant* 2004; **18**: 130-136 [PMID: 15016125 DOI: 10.1046/j.1399-0012.2003.00135.x]
- 112 **Kremers WK**, van IJperen M, Kim WR, Freeman RB, Harper AM, Kamath PS, Wiesner RH. MELD score as a predictor of pretransplant and posttransplant survival in OPTN/UNOS status 1 patients. *Hepatology* 2004; **39**: 764-769 [PMID: 14999695 DOI: 10.1002/hep.20083]
- 113 **Pokorny H**, Langer F, Herkner H, Schernberger R, Plöchl W, Soliman T, Steininger R, Muehlbacher F. Influence of cumulative number of marginal donor criteria on primary organ dysfunction in liver recipients. *Clin Transplant* 2005; **19**: 532-536 [PMID: 16008601 DOI: 10.1111/j.1399-0012.2005.00384.x]
- 114 **Monbaliu D**, Libbrecht L, De Vos R, Vekemans K, Walter H, Liu Q, Heedfeld V, Goossens V, Pirenne J, Roskams T. The extent of vacuolation in non-heart-beating porcine donor liver grafts prior to transplantation predicts their viability. *Liver Transpl* 2008; **14**: 1256-1265 [PMID: 18756467 DOI: 10.1002/lt.21513]
- 115 **Cieślak B**, Lewandowski Z, Urban M, Ziarkiewicz-Wróblewska B, Krawczyk M. Microvesicular liver graft steatosis as a risk factor of initial poor function in relation to suboptimal donor parameters. *Transplant Proc* 2009; **41**: 2985-2988 [PMID: 19857657 DOI: 10.1016/j.transproceed.2009.08.019]
- 116 **Dhillon N**, Walsh L, Krüger B, Ward SC, Godbold JH, Radwan M, Schiano T, Murphy BT, Schröppel B. A single nucleotide polymorphism of Toll-like receptor 4 identifies the risk of developing graft failure after liver transplantation. *J Hepatol* 2010; **53**: 67-72 [PMID: 20400193 DOI: 10.1016/j.jhep.2009.12.044]
- 117 **Nemes B**, Gelley F, Zádori G, Piros L, Perneczky J, Kóbori L, Fehérvári I, Görög D. Outcome of liver transplantation based on donor graft quality and recipient status. *Transplant Proc* 2010; **42**: 2327-2330 [PMID: 20692473 DOI: 10.1016/j.transproceed.2010.05.018]
- 118 **Máthé Z**, Paul A, Molmenti EP, Vernadakis S, Klein CG, Beckebaum S, Treckmann JW, Cicinnati VR, Kóbori L, Sotiropoulos GC. Liver transplantation with donors over the expected lifespan in the model for end-staged liver disease era: is Mother Nature punishing us? *Liver Int* 2011; **31**: 1054-1061 [PMID: 21733096 DOI: 10.1111/j.1478-3231.2011.02546.x]
- 119 **Hu Y**, Zhang X, Liu Y, Yan J, Li T, Hu A. APACHE IV is superior to MELD scoring system in predicting prognosis in patients after orthotopic liver transplantation. *Clin Dev Immunol* 2013; **2013**: 809847 [PMID: 24348682 DOI: 10.1155/2013/809847]
- 120 **Wong CS**, Lee WC, Jenq CC, Tian YC, Chang MY, Lin CY, Fang JT, Yang CW, Tsai MH, Shih HC, Chen YC. Scoring short-term mortality after liver transplantation. *Liver Transpl* 2010; **16**: 138-146 [PMID: 20104481 DOI: 10.1002/lt.21969]

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