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How to define initial poor graft function after liver transplantation? – a new functional definition by the LiMAx test

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Summary

Initial poor function (IPF) is a frequent complication after liver transplantation, but there is no consensus on its definition. Ninety-nine patients undergoing primary deceased-donor liver transplantation were examined in a prospective clinical trial. A new functional classification for initial graft function was developed based on two LiMAx readouts during 24 h after transplantation with a cutoff LiMAx of 60 and 120 μg/kg/h using a simple algorithm. Patients were classified as non- (3/99), poor- (23/99) and immediate function (73/99). The functional regeneration of IPF grafts was delayed until day 28 ($P < 0.05$). Significant differences were observed for postoperative maximal transaminase activity, bilirubin, albumin, coagulation and creatinine. Recipients' MELD score, the donor risk index and donor age were increased in the IPF group. Incidence of haemodialysis ($P = 0.003$) and catecholamine support ($P < 0.0001$) was higher for IPF, resulting in higher therapy costs ($P = 0.049$). However, IPF did not influence either the length of stay ($P = 0.434$) or 2-year recipient ($P = 0.415$) or graft survival ($P = 0.495$). In conclusion, the LiMAx test might provide the first adequate functional parameter to assess and classify liver graft performance from the beginning. Patients with IPF frequently suffer from secondary complications, but ultimately develop satisfactory outcome and thus worth intensive and expensive therapy.

Introduction

Early graft function after liver transplantation (LT) is an important prognostic parameter for the individual outcome [1–3]. Initial poor function (IPF) has been described as a borderline dysfunction with the potential to recover [4], which appears as a form of temporary/reversible liver insufficiency. IPF is a multifactorial event, which is related to different risk factors, such as marginal donors, severe ischaemia-reperfusion injuries, acute rejection episodes or vascular complications [5]. Nevertheless, the question how to define exactly graft function and dysfunction has not been ultimately answered yet. For reasons of lack of appropriate tests, which could accurately quantify the grafts' performance, a number of models and scoring systems have been developed to classify early graft function [6]. Different, partially contradictory definitions of IPF have been provided in literature and no final consensus has been reached for its diagnosis [7]. Various parameters, such as laboratory readouts from clinical chemistry or clinical data like bile output or the grade of encephalopathy have been used for this purpose. However, the selection of parameters and cut points has been somehow arbitrary and does not provide a generally applicable classification of graft dysfunction. Ploeg *et al.* [2] primarily defined IPF as serum aspartate-aminotransferase activity >2000 U/l, prothrombin time (PT) >16 s and ammonia level >50 μmol/l during postoperative days 2–7. Deschênes *et al.* defined IPF as presence of serum bilirubin >10 mg/dl, PT >17 s and hepatic encephalopathy during days 2–7 [8]. Pokorny *et al.* [3] replaced PT and ammonia by clotting factor

support and bile production on days 1–3. Ultimately, Nanashima *et al.* [9] simplified the classification criteria to the level of aminotransferase >1500 U/l on two consecutive measurements within 72 h after LT. Therefore, it is not surprising that a prospective comparison of different scoring systems revealed only a poor concordance in-between each other [7]. Moreover, no evidence concerning the long-term impact and the recovery from IPF is currently available. It has been suggested that the initial function could have a significant impact on the patients' individual prognosis [10]. Thus, IPF is potentially associated with secondary complications, such as renal failure, severe bleeding or septic infections [7,11], and might have a negative effect on long-term health and employment [12]. However, the individual impact of IPF on the postoperative recovery, the occurrence of secondary complications and the graft survival cannot be sufficiently predicted yet [7,13].

A new dynamic liver function test, the LiMAx test, was developed at our Department. Its prognostic validity during the postoperative monitoring of liver function was recently shown in hepatectomy [14,15] and LT [6]. The aim of this study was the development of a simple decision tree algorithm for effective classification of initial graft performance based on initial LiMAx test readouts. Risk factors for IPF, including donor and recipient characteristics and the clinical consequences of IPF were analysed.

$$\text{LiMAx} = \frac{\text{DOB}_{\max} \cdot \frac{^{13}CO_2}{^{12}CO_2}\,[\text{standard}] \cdot CO_2\ \text{production} \cdot \text{molar mass}^{13}\text{C} - \text{methacetin}}{\text{body weight}}.$$

Methods

Study design

Patients receiving deceased-donor LT were enrolled into a prospective noninterventional study. The study protocol had received official approval by the faculty's review board. All patients provided written informed consent before LT. Assessment of graft function was first scheduled 6 h after graft reperfusion and analogously on postoperative days 1, 3, 5, 10, 14 and 28 (at 06:00 AM). Besides standard postoperative monitoring by clinical biochemistry, the graft performance (functional capacity) was directly measured by the LiMAx test. The LiMAx readouts were compared with standard graft function scores by Ploeg *et al.* [2] and Deschênes *et al.* [8]. A new algorithm was developed to classify patients exclusively by LiMAx readouts during 24 h after LT. An arbitrary cut point of 120 μg/kg/h was chosen for this purpose (Fig. 1). The new classification was compared with recipient and donor characteristics, including the donor risk index (DRI) described by Feng *et al.* [16]. In addition, post-transplant complications were prospectively assessed and documented during the hospitalization. Patient and graft survival was followed up for 2 years.

Performance of LiMAx test

LiMAx test was applied by intravenous bolus injection of 2 mg/kg ^{13}C-labbeled methacetin (Euriso-top, Saint-Aubin Cedex, France), as a substrate for the hepatic cytochrome P450 1A2 enzyme family. Metabolism of ^{13}C-methacetin leads to hepatic production and thus exhalation of ^{13}C-carbon dioxide, which was consecutively measured in an online breath analysis over 60 min by nondispersive isotope-selective infrared spectrometry (NDIRS). Breath was collected by a face mask or if patients were mechanically ventilated by direct connection to the ventilator circuit. Ventilated patients received 100% oxygen to avoid interference with NDIRS [17]. No tests were performed during haemodialysis to avoid extrahepatic clearance. The LiMAx readout was calculated by

Readouts in a large group of healthy volunteers were found homogenously >315 μg/kg/h [14]. Prior reports had revealed certain cut points of postoperative LiMAx values for prediction of clinical outcome: Irreversible liver failure was indicated by LiMAx <74 μg/kg/h after hepatectomy [14] and initial graft dysfunction requiring surgical re-intervention or retransplantation was indicated by LiMAx <64 μg/kg/h after LT [6].

Parameters of graft dysfunction

LiMAx results were compared with standard laboratory readouts, in particular, aspartate-aminotransferase activity as a measure of ischaemia/preservation/reperfusion injury; bilirubin, albumin, and PT/INR as a measure of graft performance and creatinine as a measure of renal function. The laboratory tests were performed by hospital's facilities independent from the study.

Statistical analysis

Parametric data are presented as median with interquartile range, unless otherwise noted. Patients with primary nonfunction [5] were excluded from the analysis of IPF versus control group (immediate function). Univariate analysis was performed by Mann–Whitney *U*-test for

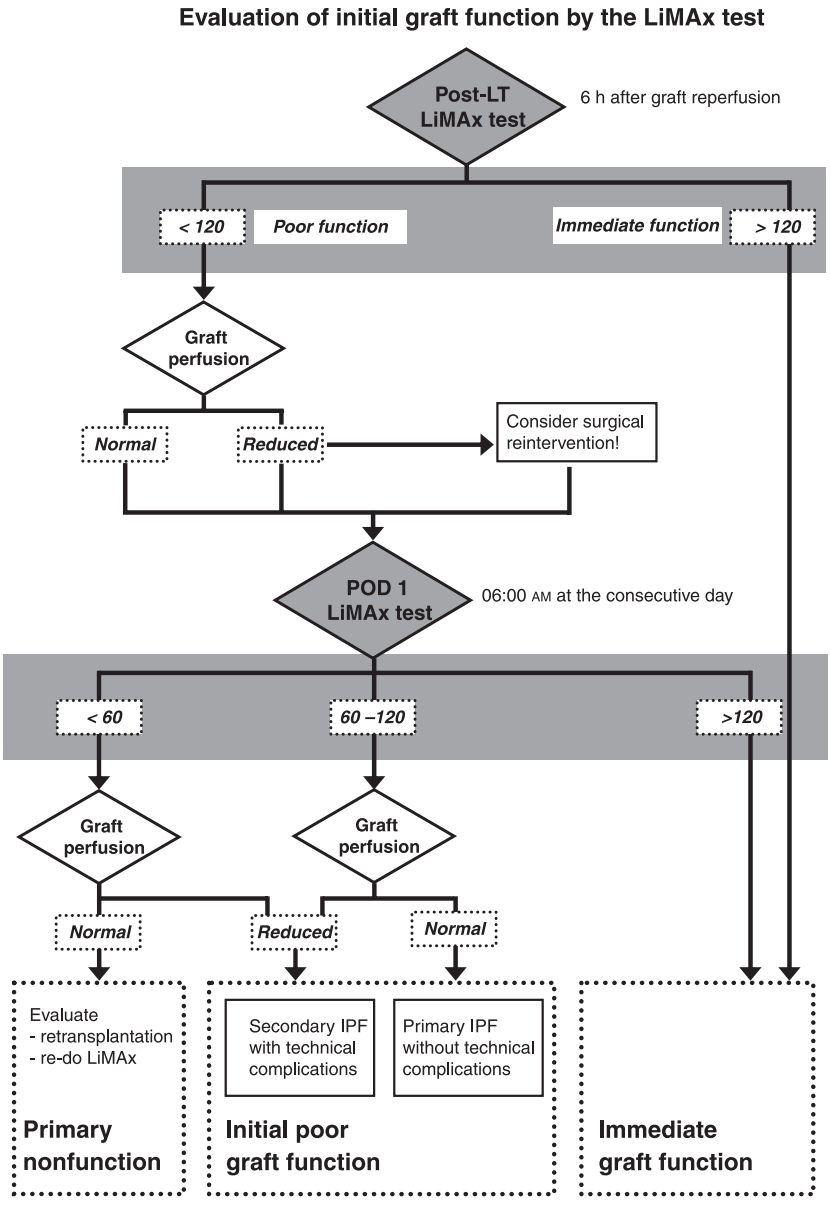

Figure 1 Classification of initial graft function. Patients classified as immediate function were applied as control group for the analysis of outcome for patients with initial poor function.

independent samples, by Wilcoxon test for paired samples, and chi-squared test according to the respective data distribution. Survival analysis was performed by Kaplan–Meier analysis with Logrank test. Statistical significance was accepted at $P < 0.05$ (two-sided). Calculations were performed with SPSS™ 15.0 (SPSS Inc., Chicago, IL, USA).

Results

A total of 99 patients were recruited and they received LT during 2005–2007. The indications for LT were alcoholic cirrhosis (30%), chronic hepatitis C infection (30%), carcinoma (10%), primary biliary cirrhosis/sclerosing cholangitis (14%) and other (16%). The age of recipients was 58 (49–61) years with 66% male gender. The direct preoperative labMELD score was 13 (7–18). The age of donors was 59 (42–67) years, with a DRI of 1.9 (1.6–2.2) (Table 1). All recipients underwent our standard surgical procedures [piggyback (85%) and vena cava replacement (15%)]. Immunosuppressive therapy was based mainly on prednisolone and tacrolimus.

Classification of initial graft function

The initial graft function was actually determined by LiMAx 6.8 (5.7–7.7) h after graft reperfusion. The initial readouts ranged between 8 and 504 μg/kg/h with a

Table 1. Pretransplant characteristics of recipients and donors.

	All*	IPF	Control	*P*-value†
Recipient characteristics				
labMELD	13 (7–19)	15 (8–22)	12 (7–16)	0.060
AST (U/l)	62 (42–86)	63 (45–96)	56 (42–84)	0.347
Bilirubin (mg/dl)	2.4 (1.0–5.2)	3.3 (1.3–9.1)	2.2 (0.8–4.7)	0.169
Albumine (g/dl)	3.4 (3.0–4.0)	3.1 (2.9–3.7)	3.4 (3.0–4.0)	0.136
INR	1.4 (1.2–1.8)	1.6 (1.2–2.1)	1.4 (1.2–1.7)	0.182
Creatinine	0.87 (0.71–1.11)	0.89 (0.68–1.58)	0.86 (0.72–1.01)	0.466
Donor characteristics				
Donor Risk Index[16]	1.9 (1.6–2.2)	2.1 (1.7–2.5)	1.8 (1.6–2.1)	**0.021**
Donor age (years)	58.5 (41.5–67.4)	67.0 (52.0–74.4)	54.0 (39.0–66.5)	**0.009**
Serum sodium (mmol/l)	147 (142–154)	148 (142–157)	147 (142–154)	0.397
Cold ischaemia (min)	604 (480–709)	618 (517–702)	602 (480–717)	0.942
Warm ischaemia (min)	44 (36–45)	45 (38–50)	44 (35–45)	0.390

IPF, initial poor function defined by LiMAx readouts according to Fig. 1; Control, control group of patients with immediate function.
Median values with interquartile range, analysed by Mann–Whitney *U*-test.
Bold values indicates significant values.
*Includes three patients with primary nonfunction that are not separately shown and were excluded from statistical analysis.
†IPF group versus control group.

median LiMAx of 166 (94–225) μg/kg/h. In seven cases, normal LiMAx values >315 μg/kg/h were determined already at that point. The second LiMAx test was performed consecutively at 06:00 AM, which was actually 20.9 (17.8–23.8) h after graft reperfusion. Overall, the individual readouts did not change significantly during 24 h ($P = 0.949$). Thirty-six patients had LiMAx <120 μg/kg/h at 6 h, but 10 of them increased up to >120 μg/kg/h at day 1. The time interval within both LiMAx tests was not correlated with the individual progression of LiMAx values ($r = 0.081$; $P = 0.447$). Normal LiMAx values (>315 μg/kg/h) were determined in nine patients at day 1. In some cases, technical (vascular) complications were evident, which explain poor graft performance in those patients as a secondary IPF. The graft performance homogenously increased after surgical re-intervention. Three cases with extremely low LiMAx readouts and without any technical complication were diagnosed as primary nonfunction and underwent retransplantation. The respective algorithm for classification of graft function based on LiMAx readouts is presented in Fig. 1. Patients were classified as initial non- (3/99), initial poor- (23/99) and immediate function (73/99).

LiMAx readouts at day 1 were compared with the IPF classification by Ploeg *et al.* [2] and Deschênes *et al.* [8] respectively. For both classifications, LiMAx readouts were significantly lower in the respective IPF group (Fig. 2). In addition, the IPF definitions by LiMAx, Ploeg and Deschênes were compared in two-by-two contingency tables and showed significant correlations (Table 2). The DRI in the LiMAx-IPF group was 2.1 (1.7–2.5) in comparison with the control group with 1.8 (1.6–2.1; $P = 0.002$). Especially, donor age was highly significantly different between IPF group and control group defined by LiMAx (Table 1). Interestingly, the DRI was not different between IPF group and control group defined by the classification of both Ploeg ($P = 0.927$) and Deschênes ($P = 0.516$). The preoperative labMELD score was higher for IPF with 15 vs. 12 ($P = 0.060$), but single biochemical parameters of recipients' liver function were merely different (Table 1).

Regeneration of graft function

The decision tree algorithm (Fig. 1) was *post hoc* applied to compare the developing of LiMAx and laboratory readouts during 4 weeks after LT. A homogenous recovery of LiMAx readouts were observed in all survivors after the first post-transplant day. The regeneration in IPF-classified grafts was significantly delayed until day 28 (always $P < 0.05$; Fig. 3a). While a majority of patients with immediate function (control group) had regained normal liver function at day 5, it took until day 28 for IPF-classified grafts to do so. Transaminase activity rose in IPF-classified grafts up to a maximum of 1802 (895–2910) U/l, in contrast to the control group with 922 (598–1756) U/l ($P = 0.016$). These levels resolved in both groups until day 5 (Fig. 3b). Bilirubin levels of 5.2 (4.0–8.2) mg/dl were initially determined in the IPF group in comparison with the control group with 3.7 (2.6–5.5) mg/dl ($P = 0.009$). The difference between both groups remained significant during follow-up (always $P < 0.05$; Fig. 3c) and hyperbiliru-

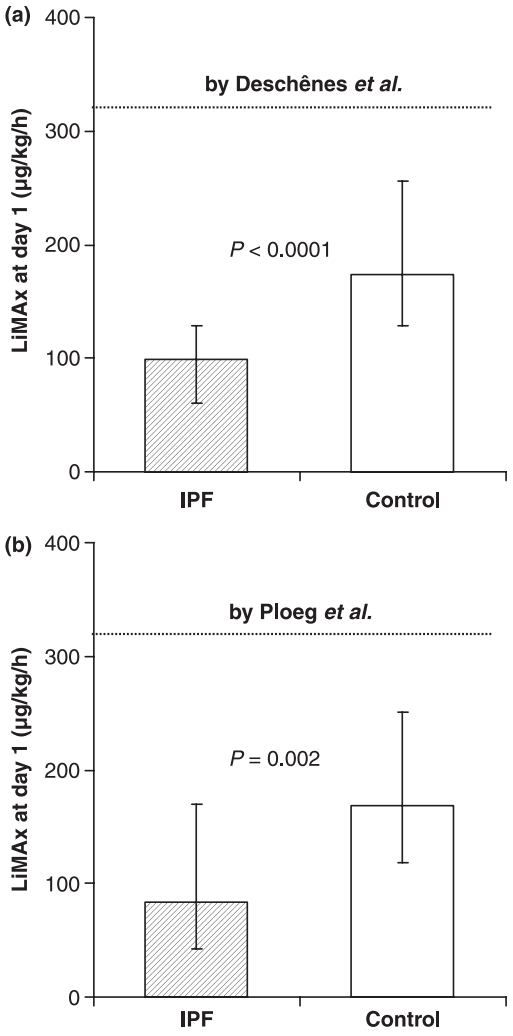

Figure 2 Post-transplant LiMAx and initial poor function, defined by Ploeg and Dêschenes. (a) IPF, initial poor function defined by Ploeg *et al.* as serum aspartate-aminotranferase activity >2000 U/l, prothrombin time (PT) >16 s, and ammonia level >50 µmol/l during postoperative days 2–7. Control, control group of patients with immediate function according to Ploeg *et al.* (b) IPF, initial poor function defined by Deschênes *et al.* as presence of serum bilirubin >10 mg/dl, PT >17 s, and hepatic encephalopathy during days 2–7. Control, control group of patients with immediate function according to Deschênes *et al.*

Table 2. Contingency tables for different IPF classifications.

	Ploeg *et al.* [2]		
P = 0.014	IPF	Control	∑
LiMAx			
IPF	**7**	**16**	23
Control	**7**	**66**	73
∑	14	82	96
	Deschênes *et al.* [8]		
P = 0.039	IPF	Control	∑
LiMAx			
IPF	**8**	**15**	23
Control	**11**	**62**	73
∑	19	77	96
	Ploeg *et al.* [2]		
P = 0.019	IPF	Control	∑
Deschênes *et al.* [8]			
IPF	**6**	**13**	19
Control	**8**	**69**	77
∑	14	82	96

IPF, initial poor function was either defined by Ploeg *et al.* as serum aspartate-aminotranferase activity >2000 U/l, prothrombin time (PT) >16 s, and ammonia level >50 µmol/l during postoperative days 2–7; by Deschênes *et al.* as presence of serum bilirubin >10 mg/dl, PT >17 s, and hepatic encephalopathy during days 2–7, and by LiMAx readouts according to Fig. 1. Control, control group of patients with immediate function. Three patients with primary nonfunction and early retransplantation were excluded from this analysis. Analysis by chi-squared test. Bold values indicates significant values.

binemia resolved in the control group within 4 weeks, while bilirubin remained slightly elevated in the IPF group. Analogously albumin levels were significantly different until day 14 and resolved until day 28 (Fig. 3d). Moreover, IPF-classified grafts revealed a certain coagulation deficit after surgery with an INR of 1.9 (1.7–2.1) vs. 1.6 (1.4–1.8) in the control group ($P < 0.0001$). Coagulation resolved within 3 days for the control group, but took 10 days for IPF (Fig. 3e). Finally, also parameters of renal function were different between both groups. Creatinine levels rose up to 1.9 (1.4–3.6) g/dl at day 3 in the IPF group in comparison to 1.1 (0.8–1.7) g/dl in the control group ($P < 0.0001$). Consequently, the values resolved until day 10 in both groups (Fig. 3f).

Clinical outcome and early complications

The intra-hospital mortality after LT was 5/99. One patient (4%) with IPF died of septic peritonitis during hospitalization. In contrast, three patients (4%) with immediate function deceased either of intracerebral infarction, acute hepatic artery bleeding or respiratory failure. Retransplantation was performed in 7/99 patients, in three of them for primary nonfunction. No single patient in the IPF group received retransplantation during hospitalization, but four did in the control group. The indications for retransplantation were secondary graft failure caused by hepatic artery thrombosis (three cases at days 2, 3 and 6) and one case of severe abdominal bleeding from hepatic artery (at day 6). The incidence of single or multiorgan failure (according to Dindo grade IVa+b [18]) was relatively higher for IPF with 26% vs. 12%.

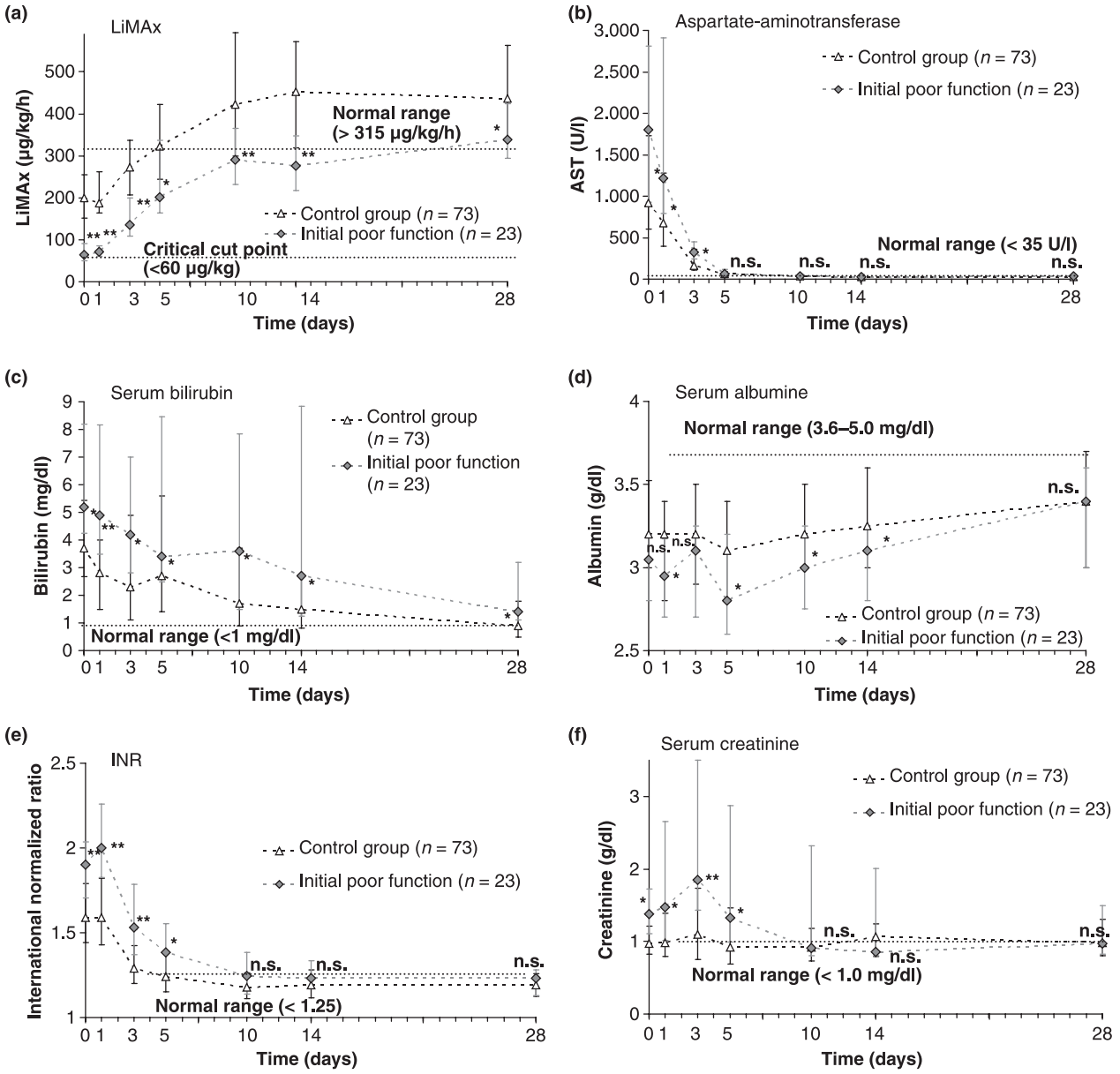

Figure 3 Regeneration of graft function. Patients were classified as initial poor function according to the classification in this figure (n = 23) and compared to patients with immediate function (control group; n = 73). The analysis included the following parameters: LiMAx test (a) as measure of the metabolic liver function capacity. Aspartate-aminotransferase activity (b) as a measure of ischaemia/preservation/reperfusion injury; bilirubin (c), albumin (d) and INR (e) as a measure of graft performance and creatinine (f) as a measure of kidney function. Group differences were calculated by Mann–Whiney *U*-test. Values are expressed as median with interquartile range as error bars. *P < 0.05; **P < 0.001; NS, not significant.

Other grades of complication were not different within the two groups. The total incidence of re-operation was 19/73 for immediate function and 6/23 for IPF (P = 0.943). Also, length of stay on intensive care and total hospitalization were not statistically different (Table 3). However, the incidence of acute renal failure and haemodialysis was higher in the IPF group (Fig. 4a and b). Respiratory function was also somehow impaired in the IPF group: 30% in IPF required mechanical ventilation for longer than 3 days vs. 14% in control (P = 0.067). The most significant difference was observed for initial haemodynamic stability after LT: 44% vs. 11% required catecholamine support (P < 0.0001; Table 3). Consequently, the total costs of treatment for the hospital were 39 000 (26 800–63 700) Euro for IPF vs. 28 700 (23 700–47 500) Euro (P = 0.049; Table 3). Interestingly, these early complications did not impair long-term graft survival: IPF did not influence the 2-year recipient

Table 3. Clinical outcome parameters.

	All*	IPF	Control	*P*-value†
Post-transplant complications (%)‡				
Acute renal failure	20/99 (20)	9/23 (39)	8/73 (11)	**0.002**
Requiring haemodialysis	15/99 (15)	7/23 (30)	5/73 (7)	**0.003**
Mechanical ventilation (>3 days post-transplant)	20/99 (20)	7/23 (30)	10/73 (14)	0.067
Hypotension requiring catecholamines	20/99 (20)	10/23 (44)	8/73 (11)	**<0.0001**
Retransplantation	7/99 (7)	0/23 (0)	4/73 (6)	0.251
Dindo classification (%)‡				
Grade 0–III	77/99 (78)	16/23 (70)	61/73 (83)	0.142
Grade IVa–IVb (single or multiorgan failure)	17/99 (17)	6/23 (26)	9/73 (12)	0.113
Grade V (death)	5/99 (5)	1/23 (4)	3/73 (4)	0.960
Hospitalization§				
On ICU (days)	8 (5–15)	10 (5–17)	7 (5–11)	0.207
Total (days)	26 (22–38)	27 (23–43)	26 (22–34)	0.434
Costs (1000 Euro)	29 (24–51)	39 (27–64)	29 (24–47)	**0.049**
Survival (%)¶				
2-year recipient survival	86/99 (87)	19/23 (83)	65/73 (89)	0.415
2-year graft survival	80/99 (81)	18/23 (78)	62/73 (85)	0.495

IPF, initial poor function defined by LiMAx readouts according to Fig. 1; Control, control group of patients with immediate function.
Bold values indicates significant values.
*Includes three patients with primary nonfunction that are not separately shown and were excluded from statistical analysis.
†IPF group versus control group.
‡Number of events, analysed by chi-squared test for homogeneity.
§Median values with interquartile range, analysed by Mann–Whitney *U*-test.
¶Analysed by Logrank test.

survival ($P = 0.415$; Fig. 5a) or 2-year graft survival ($P = 0.495$; Fig. 5b).

Discussion

This study provides the first definition of IPF that was exclusively based on a direct parameter of graft performance – the actual metabolic capacity. This approach includes several advantages in comparison with prior definitions of IPF: The LiMAx test determines the graft performance in real-time. Thus, the pretransplant liver function or general health condition does not influence the test result. Moreover, no serum half-lives of biochemical parameters or any interference from extrahepatic factors has to be taken into account. The direct postoperative bedside test provides the fastest diagnostic test result that is available and no scores need to be calculated. As a result, the definition of IPF can be reduced to one singe quantitative parameter determined within 24 h after LT.

The presented results point out that LiMAx readouts are a valuable surrogate parameter of graft performance, as they are highly correlated with the progression and recovery of conventional biochemical parameters. Moreover, LiMAx readouts were also different for the standard graft function scores that were applied as comparators [2,8]. The contingency between LiMAx, Ploeg's and Deschênes' graft classification was high for immediate function, but incongruence for IPF was evident – also in between the scores of Ploeg versus Deschênes. Interestingly, a significant difference in the DRI was observed between IPF and control for LiMAx, but not for the comparator scores (Ploeg/Deschênes). Furthermore, the IPF-classified group by LiMAx revealed significantly higher incidences of early post-transplant complications that are associated with liver function. But, at the end, the occurrence of IPF was not associated with the duration of hospitalization and the survival. This is in accordance with former classification scores that suggested the potential of grafts to overcome IPF without further impact on prognosis [7,13,19]. However, other authors had also suggested a negative impact on survival [2,3]. It is apparent that the fate of primary nonfunctioning grafts is irreversible and leads to either death or retransplantation [5]. Hence, these three cases were excluded from analysis of

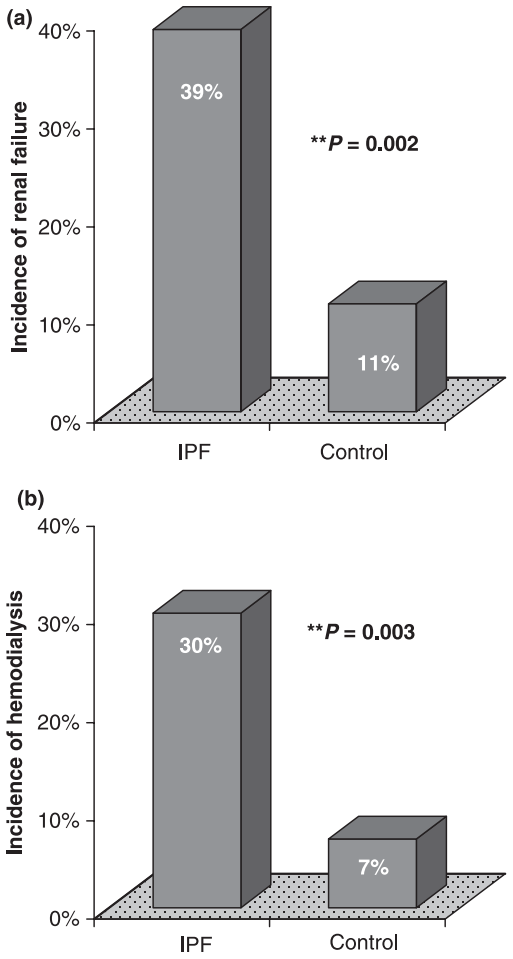

Figure 4 Incidence of renal dysfunction. Post-transplant incidences of (a) renal failure and (b) haemodialysis divided into patients with initial poor function (n = 23) versus patients with immediate function (control; n = 73; defined by the LiMAx algorithm). Group differences were calculated by Mann–Whiney U-test.

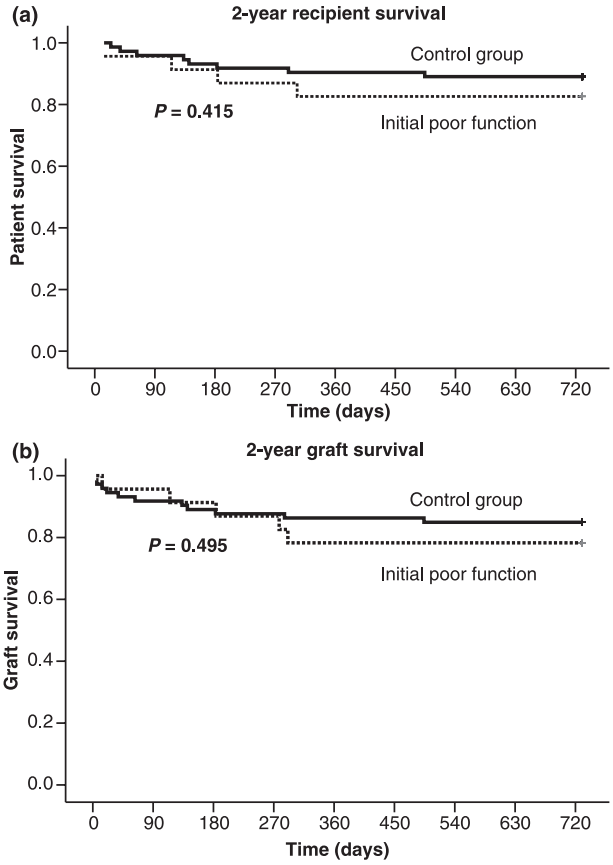

Figure 5 Survival curves. Kaplan–Meier curve for the patient survival (a) and graft survival (b) that was followed up for 2 years after LT. Logrank test was applied for analysis.

long-term survival. In contrast, borderline graft performance, or IPF, has an entirely different clinical impact and could be differentiated from PNF as recently shown [6]. The present results demonstrate complete functional regeneration of IPF-classified grafts within 4 weeks. Nevertheless, these patients frequently develop secondary complications and thus require additional care and a more intensified management, as shown by the significant increase in hospital charges.

A relevant number of studies tried to predict outcome after LT from preoperative variables, such as recipients and donor factors [8,20,21]. However, the potential of these strategies is limited because graft performance is also strongly dependent on organ preservation and pathophysiological effects during and after reperfusion. Therefore, effective evaluation of initial graft function remains an inevitable challenge. On the other hand, the clinical impact of initial graft performance is not exclusive. The outcome of LT is extremely multifactorial. Both immediate and poor function can develop technical or immunological complications, which could threaten graft survival. Nevertheless, the negative impact of additional complications is more critical in patients who already suffer from poor graft performance. Therefore, the diagnosis of IPF should imply a careful management and additional evaluation of graft perfusion. The decision and schedule for surgical re-intervention because of impaired graft perfusion could also be augmented by the LiMAx readouts.

However, this new classification algorithm might appear somehow academic, if no effective intervention strategies are available for IPF management. There is still a lack of interventional strategies to enhance graft regeneration to shorten recovery. The potential of liver support therapy to induce or enhance graft regeneration cannot be appraised yet [22,23]. Somehow, all patients recovered without IPF-specific therapy, but required intensive and expensive treatment. Nevertheless, the prediction of clinical recovery and secondary complications is extremely favourable to

prevent critical situations by adequate intensive care management. Moreover, patients with primary nonfunction clearly profit from an early and safe diagnosis of irreversible graft failure, because the decision-making for or against retransplantation is reached earlier [6]. Furthermore, LT recipients might also profit from early diagnosis, as this might identify the patient eligible for transfer to general ward, if an ICU bed is needed for another patient.

In conclusion, the initial graft performance – measured by the LiMAx test – is closely associated with early postoperative outcome after LT. In addition, a significant association with donor and recipient factors was shown. The LiMAx test enables the effective patient classification into non, poor and immediate function with in 24 h after LT with a single parameter. Patients with IPF frequently suffer from secondary complications, but ultimately develop satisfactory outcome and thus worth intensive and expensive therapy.

Authorship

MS and PN: designed the study, analysed data and contributed to the writing of the manuscript. JFL: performed the study, collected the data and contributed in the statistical analysis and the writing of the manuscript. MM: contributed to the data collection and assisted in the data analysis and the writing of the manuscript. DS and GP: contributed to the study performance and writing of the paper.

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