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Liver Transplantation outcome prediction - A retrospective analysis on donor and recipient factors

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Abstract

Introduction: Primary graft dysfunction (PGD) can significantly impact graft and patient outcomes. However, we are still lacking a consensual definition of PGD. The aims of this study were to validate proposed PGD definitions in our centre population and to find methods to predict post-transplant complications requiring intervention.

Methods: We analysed 93 patients transplanted in our centre between May 2012 and December 2014. Patients aged less than 18 years old, retransplantations, split liver transplants and acute liver failure were excluded. First year follow-up data were collected on donor, preoperative, intraoperative and post-operative periods of all patients. Previously described D-MELD, Model for Early Allograft Function (MEAF) Score, MELD-Lactate, Nanashima's, Olthoff's and Rosen's IPGF scores were applied to all patients. All post-transplant complications were classified according to Dindo *et al.* classification.

Results: In our series, D-MELD was shown to be a good pre-transplant graft outcome predictor (p=0.009). MEAF Score (AUC = 0.886, Cut-off value = 7.368, p=0.025) was proven to have a significant association with patient mortality. Hepatic artery resistance index below 0.55 on any of the first five postoperative days was also shown to have a significant association with early post-transplant mortality (p=0.016). Through multivariate analysis preoperative AST, postoperative CRP and AST, recipient body mass index and CMV status were also shown to be independent risk factors for post-transplant intervention-requiring complications. CMV positive graft transplantation to CMV negative recipients was shown to be independently associated with a nine-fold increase in intervention-requiring post-transplant complications.

Conclusion: D-MELD was shown to be a solid pre-transplant graft outcome predictor aiding in the refinement of donor-recipient matching. MEAF score was found to be highly predictive

of patient mortality and should be routinely included in the clinical management of post-transplant periods. Clinical strategies should be reinforced in order to avoid donor-recipient CMV mismatch-related complication risk increase. Clinical results after liver transplantation should include not only patient and graft survival, but also the incidence of intervention-requiring complications. Clinical scores should, in the near-future, be adapted to accurately predict these complications.

Keywords:

Liver transplantation; Postoperative complications; Predictive models; Primary graft dysfunction;

Glossary

AUC - Area under the receiver-operating-characteristic curve

BD - Brain dead

BMI - Body mass index

CKD - Chronic kidney disease

CMV - Cytomegalovirus

CRP - c-reactive protein

DCD - Donation after circulatory death

ERCP - Endoscopic retrograde cholangiopancreatography

GRBW - Graft weight-to-recipient body weight

HARI - Hepatic artery resistance index

HCC - Hepatocellular carcinoma

INR - International normalized ratio

IPGF- Initial poor graft function

LT- Liver transplantation

MEAF - Model for early allograft function

MELD - Model for end stage disease

PGD - Primary graft dysfunction

PNF - Primary non function

UTHPA - Unidade de Transplantação Hepática Pediátrica e de Adultos

Introduction

Despite significant improvements over the years in the results of liver transplantation (LT) [1], primary graft dysfunction (PGD) remains, to this day, one of the most important prognostic factors for early patient outcome [2,3]. Primary non function (PNF), the early irreversible failure of the graft, represents the most serious form of PGD, leading to need for retransplantation in order to avoid patient death. On the other hand, initial poor graft function (IPGF) completes the PGD spectrum as a milder borderline form of PGD with recovery potential, and is associated with a myriad of risk factors ranging from graft quality, long ischemic times and medical status of the recipient [2,4,5]. Interestingly, even though its importance for the individual LT prognosis is widely recognized, we are yet to achieve consensus about the definition and diagnostic criteria of IPGF [5]. Thus, the literature remains inconclusive with different studies using different endpoints and variant clinical criteria, usually liver-related laboratory parameters or symptoms such as aminotransferase levels, prothrombin time, bile output, bilirubin levels, international normalized ratio (INR) or the presence of encephalopathy [1,2,6–11]. These multiple and sometimes discrepant criteria [1], in turn undermine the development of novel ways to approach this issue and the potential for early diagnosis to allow more aggressive treatment leading to better clinical outcomes.

The present study was undertaken at a single transplant centre in Coimbra, Portugal, as a retrospective analysis of recipient and donor parameters in an effort to reach a definition of IPGF that would predict the patient and graft survival in the first year following LT. As a secondary objective, we intended to go further and determine whether post-transplant complications requiring reintervention, in the same time period, could be predicted through preoperative, intraoperative and post-transplant parameters of both the recipient and the donor.

Methods

Study Design

We conducted a retrospective analysis of all patients who underwent LT at Unidade de Transplantação Hepática Pediátrica e de Adultos (UTHPA) from Centro Hospitalar e Universitário de Coimbra (Head of Department: Dr. Emanuel Furtado, Coimbra, Portugal) between May 2012 and December 2014. Exclusion criteria adopted were: patients aged less than 18 years old, retransplantation, split liver transplants and acute liver failure **(Figure 1)**. All grafts were from brain dead (BD) donors and no donation after circulatory death (DCD) was registered. The present study was approved by the ethics committee of Faculty of Medicine, University of Coimbra, Portugal.

Study Population

The study population consisted of 93 patients undergoing LT, 75 men (80.6%) and 18 women (19.4%), with a mean age of 54 ± 9.7 years (range 23 – 69 years), with a minimum follow-up of one year.

A summary of demographic, clinical and surgical information of all 93 patients included in this study is shown on **Table 1**. In our series, a predominance of male gender was shown (75/18) with a mean age of 54.03 ± 9.68 years. The majority of

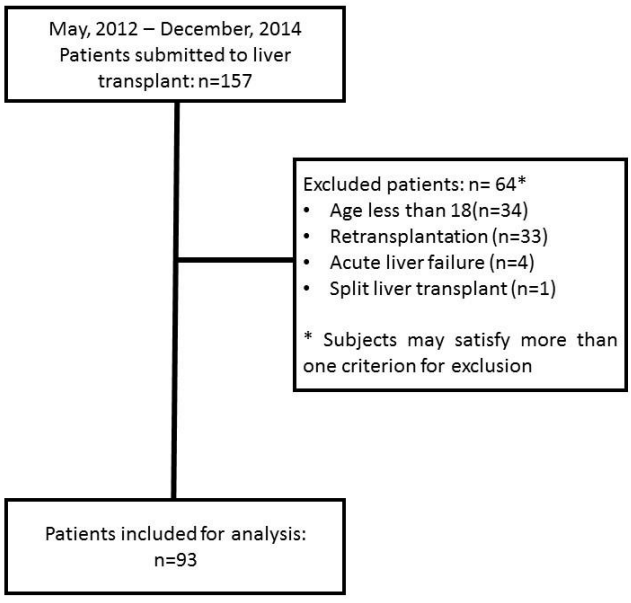

Figure 1. Flow diagram. Patients included in the study

patients (80.7%) were selected for alcoholic cirrhosis or hepatocellular carcinoma (HCC).

Median Model for End Stage Disease (MELD) score prior to LT was 16 with an interquartile range of 9 (no extra MELD points were assigned for patients with HCC on the waiting list). Patients were selected for transplant according to MELD, Child-Pugh scores and in accordance with our department policy.

Table 1. Population Summary

Variables	Mean ± SD
Age	54.03 ± 9.68
Gender (male/female)	75/18
Cause of end-stage liver disease	
Alcoholic Cirrhosis	40.9% (38/93)
Hepatocellular carcinoma	39.8% (37/93)
PBC/PSC	8.6% (8/93)
HCV	3.2% (3/93)
AIH	1.1% (1/93)
Other	6.4% (6/93)
Pre-LT MELD[a]	16 (9)
Donor Age	51.53 ± 15.9
Donor Risk Index	1.63 ± 0.38
Cold Ischemia (min)	330.76 ± 69.25
Graft Fibrosis	8.3% (7/84[b])

[a]Displayed as median and interquartile range. [b]Number of Patients with available data. PBC/PSC: primary biliary cirrhosis/primary sclerosing cholangitis; HCV: hepatitis C virus; AIH: autoimmune hepatitis;

Clinical Data Collection

The variables included in the analysis were chosen according to clinically plausible hypothesis of increased risk of graft injury and previous literature reports of strong clinical correlation with graft and patient outcome in the MELD era.

Data was collected on the first year follow-up period of pre-transplant, intraoperative and post-transplant parameters related to donor, recipient and surgical procedure.

The recipient and donor background, surgical information, anaesthetic records and follow-up data were retrieved from patient records, anaesthetic charts, surgical individual reports and UTHPA database. D-MELD score was calculated according to Halldorson *et al.* [12].

Outcome Analysis

Outcome analysis in the present study was divided in primary and secondary outcomes.

Primary outcomes were defined as patient mortality and graft failure in the first 90 days and 360 days after LT. Previously described IPGF definition tested in our study are shown in **Table 2**. In order to find the best fitting IPGF definition for clinical use in our study population, sensitivity, specificity and overall correctness of all statistically relevant IPGF definitions were compared**.**

Table 2. Previously reported definitions of Initial Poor Graft Function

Authors	n	Parameters	Time Frame (days)	Graft Dysfunction [a]	
				PNF	Total
Rosen *et al.* [9]	213	AST	3	7.6%	-
Nanashima *et al.* [4]	93	AST/ALT	3	4.3%	18.3%
Olthoff et al. [11]	300	AST/ALT, Bilirubin, INR	7	1.7%	23.2%
Cardoso *et al.* [13]	58	MELD-Lactate – MELD, Lactate 1st hour	1	-	-
Pareja *et al.* [14]	829	Model for Early Allograft Function Scoring (MEAF) – ALT, Bilirubin, INR	3	2.1%	-

[a] As reported in the original series. NOTE: The definitions were chosen according to an unsystematic PubMed search with the terms: *liver transplantation*, *initial poor function* and *primary graft dysfunction*. Only original criteria with parameters fitting the variables collected and with n≥50 were included.

As secondary outcome measure, multivariate analysis was used to find post-transplant reintervention predictors.

Therefore**,** post-transplant complications were graded according to Dindo *et al.* [15], and tested outcome was defined as Dindo grade ≥ III (complications requiring reintervention and\or associated with organ dysfunction) in the first year of follow-up. Deceased patients were excluded from the analysis.

Statistical Analysis

All data was summarized as mean ± standard deviation for continuous variables and as absolute and relative frequency for categorical variables. Univariate analysis was conducted using chi-squared tests for categorical variables, and Mann-Whitney U tests for continuous variables (after testing for normality). Area under the receiver-operating-characteristic curve (AUC) was used in quantitative IPGF definitions to analyse accuracy of outcome prediction. IPGF definitions' sensitivity and specificity were calculated and used alongside overall correctness for comparison. All statistically relevant variables in univariate testing were analysed through binary logistic regression modelling in order to construct a predicting model for reintervention in post-transplant patients. All statistical analysis was performed using IBM SPSS Statistics version 24 software.

Results

Post-transplant mortality and graft failure

In this series, 90-day post-transplantation mortality rate was 3.2% (3/93) with a one-year survival of 88.2% (82/93). According to UNOS criteria [16], 1.08% (1/93) were classified as PNF and underwent retransplantation during the first 90 days. Three patients (3.2%) were submitted to retransplantation during the first year. Mean graft survival was 148.33 ± 132.35 days (range 4 - 254 days).

Post-Transplant mortality and graft failure risk factors

Regarding donor parameters, univariate analysis showed donor peak INR value to be associated (p=0.046) with one-year mortality rate (**Table 3)**, while also trending towards association with 90-day mortality (p=0.054). D-MELD was shown to be a statistically strong predictor (p=0.009) for one-year graft failure. Furthermore, donor age (p=0.013), and graft liver weight (p=0.036) were also shown to have a significant association with one-year graft failure (**Table 4)**.

As for recipient variables, chronic kidney disease (CKD) was present in all 90-day deceased patients, proving a statistically significant association (p=0.036) with 90-day mortality rate. Both preoperative c-reactive protein (CRP) (p=0.031) and haemoglobin levels (p=0.048) were also shown to be correlated with one-year graft failure (**Table 4)**, with preoperative CRP additionally trending towards association (p=0.065) with one-year mortality (**Table 3**).

Duration of surgical procedure was the only statistically significant intraoperative value in our analysis, showing an association (p=0.044) with one-year patient survival (**Table 3**). Nevertheless, cold ischemia time also trended for significance (p=0.069) with one-year patient survival.

In regard to postoperative parameters, AST values from day 1 to day 7 were shown to be statistically significant ($p<0.05$) predictors of 90-day patient mortality. Concomitantly, ALT values were also shown to be significant 90-day patient mortality predictors ($p<0.05$), albeit only from day 1 to day 6, with day 7 ALT values trending towards significance (p=0.053). Univariate analysis also showed INR values from days 4 and 5 to be statistically significant to 90-day (p=0.036 and p=0.031, respectively) and one-year patient survival (p=0.036 and p=0.018, respectively), while day 6 platelet counts and day 1 bilirubin levels proving to be significantly associated (p=0.030 and p=0.027) with only 90-day patient mortality (**Table 3**).

Interestingly, 24^{th} hour lactate clearance was found to be statistically significant to one-year mortality as well as one-year graft survival (p=0.037 and p=0.043) while higher clearance values were observed in the non-survivor and graft loss groups. Additionally, an important association was found between hepatic artery resistance index (HARI) below 0.55 on any of the first five postoperative days and early 90-day mortality (p=0.016), this association could not, however, be proven to one-year survival or graft failure (**Tables 3 and 4**).

Day 6 and 7 AST values were concurrently associated (p=0.026 and p=0.035) with one-year graft survival, while day 6 and 7 ALT values only trended towards association (p=0.060 and p=0.054, respectively). Furthermore, day 7 platelet count proved to be associated (p=0.013) with one-year graft survival (**Table 4**), while bilirubin day 1 levels were also proven to be trending towards association (p=0.066).

No other donor, recipient, intraoperative or postoperative parameters were significant.

A multivariate analysis was tried, however, due to low case number on the positive endpoint groups, the statistically criteria for analysis could not be met.

Table 3.1 Survivor vs. non-survivor comparison

Variables	Mortality (90 days)			Mortality (360 days)		
	Survivors	Nonsurvivors	P	Survivors	Nonsurvivors	P
Donor parameters						
Age (years)	51.14 ± 15.86	62.67 ± 15.18	.255	50.51 ± 16.00	59.50 ± 13.18	.100
Donor Peak INR	1.53 ± 1.54	1.05 ± 0.03	.054	1.56 ± 1.61	1.20 ± 0.39	**.046**
Graft Liver Weight (gr)	1464.69 ± 288.94	1201.33 ± 290.28	.102	1453.61 ± 267.12	1473.45 ± 446.38	.784
Graft-to-Recipient Body Weight (%)	1.99 ± 0.51	1.64 ± 0.46	.246	1.97 ± 0.50	2.05 ± 0.61	.626
Recipient parameters						
Preoperative Haemoglobin (g/dL)	11.82 ± 2.35	10.97 ± 4.19	.463	11.80 ± 2.30	11.69 ± 3.17	.898
Preoperative CRP (mg/L)	1.64 ± 3.34	2.29 ± 3.36	.918	1.30 ± 2.67	4.18 ± 5.80	.065
Chronic Kidney Disease	31% (28/89)	100% (3/3)	**.036**	32% (26/81)	45% (5/11)	.498
MELD [a]	16 (9)	18 (-)	.601	16 (9)	14 (11)	.721
D-MELD [a]	800 (457)	1422 (-)	.202	810 (475.5)	859 (834.75)	.327
Intraoperative parameters						
Cold Ischemia (min)	329.18 ± 69.56	378.33 ± 41.63	.181	325.63 ± 69.45	369.00 ± 56.72	.069
Surgery Duration (min)	480.42 ± 86.42	557.00 ± 54.62	.073	473.99 ± 77.72	548.64 ± 119.57	**.044**
Postoperative parameters						
1st day Bilirubin (mg/dL)	2.32 ± 2.03	4.77 ± 2.12	**.027**	2.36 ± 2.12	2.70 ± 1.79	.255
1st day AST (IU/L)	990.10 ± 1419.45	2104.00 ± 465.50	**.028**	1000.83 ± 1469.72	1213.91 ± 891.63	.191
1st day ALT (IU/L)	854.30 ± 816.09	1765.67 ± 672.05	**.035**	861.40 ± 834.69	1049.91 ± 762.33	.338
2nd day AST (IU/L)	550.23 ± 776.18	2083.67 ± 1249.62	**.014**	564.48 ± 802.69	862.27 ± 1024.35	.419
2nd day ALT (IU/L)	725.50 ± 717.63	1926.33 ± 1142.95	**.027**	736.55 ± 725.54	970.64 ± 972.77	.681
3rd day AST (IU/L)	262.09 ± 301.11	1445.00 ± 1643.72	**.018**	268.13 ± 305.27	539.64 ± 962.94	.826
3rd day ALT (IU/L)	544.48 ± 516.24	1640.67 ± 1435.89	**.036**	551.79 ± 501.80	789.64 ± 1018.39	.861

[a]Displayed as median and interquartile range. CRP = c-reactive protein; INR = international normalized ratio.

Table 3.2 Survivor vs. non-survivor comparison

Variables	Mortality (90 days)			Mortality (360 days)		
	Survivors	Nonsurvivors	P	Survivors	Nonsurvivors	P
Postoperative parameters (continued)						
4th day INR	1.26 ± 0.18	3.51 ± 2.42	**.036**	1.25 ± 0.17	1.94 ± 1.49	**.036**
4th day AST (IU/L)	134.46 ± 115.51	1502.33 ± 957.86	**.004**	136.18 ± 117.68	495.18 ± 781.28	.423
4th day ALT (IU/L)	424.00 ± 369.75	1485.67 ± 1253.75	**.027**	428.32 ± 359.80	682.55 ± 865.96	.825
5th day INR	1.24 ± 0.16	2.88 ± 1.63	**.031**	1.23 ± 0.15	1.74 ± 1.04	**.018**
5th day AST (IU/L)	97.98 ± 68.98	1098.67 ± 1022.62	**.003**	98.59 ± 69.08	366.36 ± 658.80	.255
5th day ALT (IU/L)	331.04 ± 256.17	1196.00 ± 750.93	**.012**	333.59 ± 245.80	548.00 ± 616.50	.647
6th day Platelet Count (x1000/µL)	82.89 ± 59.35	29.00 ± 13.45	**.030**	82.87 ± 60.96	66.90 ± 42.94	.501
6th day AST (IU/L)	79.14 ± 51.66	839.00 ± 644.53	**.006**	78.53 ± 51.51	337.67 ± 497.32	.070
6th day ALT(IU/L)	280.04 ± 194.47	1082.33 ± 874.46	**.015**	275.95 ± 189.48	582.89 ± 613.19	.106
7th day Platelet Count (x1000/µL)	102.50 ± 74.15	56.00 ± 53.33	.367	101.13 ± 75.44	103.10 ± 64.31	.681
7th day AST (IU/L)	71.54 ± 54.68	236.50 ± 177.48	**.043**	72.93 ± 55.38	94.40 ± 104.84	.944
7th day ALT (IU/L)	230.74 ± 156.38	1004.50 ± 928.43	.053	234.30 ± 153.92	359.20 ± 488.17	.967
HARI <0.55 1st - 5th days	23% (21/90)	100% (3/3)	**.016**	23% (19/82)	45% (5/11)	.144
6th hour Lactate Clearance	15.39 ± 43.40	2.97 ± 59.76	.727	13.98 ± 44.56	21.77 ± 38.01	.637
12th hour Lactate Clearance	41.64 ± 37.18	60.75 ± 28.88	.443	40.19 ± 38.08	54.75 ± 26.85	.351
24th hour Lactate Clearance	35.95 ± 54.25	52.39 ± 39.46	.710	32.54 ± 55.98	63.87 ± 19.27	**.037**
48th hour Lactate Clearance	44.50 ± 44.88	49.66 ± 19.00	.881	42.85 ± 46.58	57.79 ± 17.18	.542

[a]Displayed as median and interquartile range. INR = international normalized ratio; HARI = hepatic artery resistance index

Table 4.1 Graft survival vs. graft loss comparison

Variables	Graft Failure (90 days)			Graft Failure (360 days)		
	Graft survival	Graft Loss	P	Graft survival	Graft Loss	P
Donor parameters						
Age (years)	51.22 ± 15.71	79 [b]	.094	50.81 ± 15.66	72.00 ± 7.00	**.013**
Donor Peak INR	1.52 ± 1.52	1.08 [b]	.400	1.53 ± 1.54	1.11 ± 0.07	.263
Graft Liver Weight (gr)	1460.03 ± 290.30	1094 [b]	.183	1467.08 ± 289.65	1131.33 ± 59.54	**.036**
Graft-to-Recipient Body Weight (%)	1.98 ± 0.51	1.76 [b]	.533	1.99 ± 0.51	1.71 ± 0.59	.388
Recipient parameters						
Preoperative Haemoglobin (g/dL)	11.82 ± 2.39	8.5 [b]	.138	11.88 ± 2.39	9.23 ± 1.10	**.048**
Preoperative CRP (mg/L)	1.61 ± 3.30	6.16 [b]	.111	1.59 ± 3.32	4.83 ± 1.89	**.031**
Chronic Kidney Disease	33% (30/91)	100% (1/1)	.337	33% (29/89)	67% (2/3)	.262
MELD [a]	16 (9)	18 [b]	.731	16 (9)	22 (-)	.073
D-MELD [a]	800 (460)	1422 [b]	.174	792 (444.5)	1430 (-)	**.009**
Intraoperative parameters						
Cold Ischemia (min)	329.74 ± 68.91	425 [b]	.215	330.41 ± 69.52	341.33 ± 72.95	.943
Surgery Duration (min)	482.47 ± 86.83	523 [b]	.463	483.82 ± 87.29	456.00 ± 60.60	.590
Postoperative parameters						
1st day Bilirubin (mg/dL)	2.38 ± 2.07	4.2 [b]	.235	2.29 ± 1.89	5.63 ± 4.52	.066
1st day AST (IU/L)	1012.34 ± 1413.25	2286 [b]	.192	1025.53 ± 1426.05	1041.00 ± 1087.06	.744
1st day ALT (IU/L)	865.96 ± 811.29	2516 [b]	.109	871.07 ± 818.67	1262.67 ± 1116.83	.373
2nd day AST (IU/L)	568.82 ± 780.31	3441 [b]	.101	577.46 ± 785.75	1267.00 ± 1884.04	.811
2nd day ALT (IU/L)	737.71 ± 715.69	3205 [b]	.094	742.38 ± 721.64	1420.00 ± 1573.47	.466
3rd day AST (IU/L)	267.17 ± 299.76	3343 [b]	.087	270.74 ± 302.08	1185.33 ± 1868.95	.811
3rd day ALT (IU/L)	550.59 ± 513.27	3277 [b]	.087	553.89 ± 517.52	1361.67 ± 1673.38	.448

[a]Displayed as median and interquartile range. [b]Only one patient. CRP = c-reactive protein; INR = international normalized ratio.

Table 4.2 Graft survival vs. graft loss comparison

Variables	Graft Failure (90 days)			Graft Failure (360 days)		
	Graft survival	Graft Loss	P	Graft survival	Graft Loss	P
Postoperative parameters (continued)						
4th day INR	1.29 ± 0.28	6.07 [b]	.087	1.29 ± 0.28	3.60 ± 3.49	.592
4th day AST (IU/L)	163.17 ± 264.24	1683 [b]	.094	161.21 ± 265.69	726.67 ± 845.78	.118
4th day ALT (IU/L)	431.78 ± 371.01	2917 [b]	.087	430.07 ± 371.63	1309.67 ± 1431.74	.238
5th day INR	1.26 ± 0.23	4.5 [b]	.087	1.26 ± 0.24	2.29 ± 1.91	.565
5th day AST (IU/L)	125.15 ± 239.61	627 [b]	.094	124.00 ± 241.71	326.67 ± 279.20	.079
5th day ALT (IU/L)	341.04 ± 265.16	2006 [b]	.087	336.04 ± 258.96	1046.00 ± 924.35	.145
6th day Platelet Count (x1000/µL)	81.75 ± 59.12	18 [b]	.121	82.54 ± 59.59	38.67 ± 20.50	.077
6th day AST (IU/L)	96.33 ± 157.59	898 [b]	.095	95.55 ± 159.40	385.00 ± 444.54	**.026**
6th day ALT(IU/L)	287.19 ± 199.52	2072 [b]	.087	281.49 ± 192.91	1041.67 ± 949.13	.060
7th day Platelet Count (x1000/µL)	102.38 ± 73.30	19 [b]	.104	104.05 ± 73.84	30.67 ± 15.31	**.013**
7th day AST (IU/L)	72.02 ± 54.52	362 [b]	.087	71.13 ± 54.63	192.67 ± 150.54	**.035**
7th day ALT (IU/L)	232.16 ± 155.95	1661 [b]	.087	226.78 ± 148.62	853.67 ± 744.22	.052
HARI <0.55 1st - 5th days	25% (23/92)	100% (1/1)	.258	26% (23/90)	33% (1/3)	.596
6th hour Lactate Clearance	14.50 ± 43.70	55.11 [b]	.248	14.57 ± 44.20	25.98 ± 26.62	.780
12th hour Lactate Clearance	41.63 ± 36.92	81.17 [b]	.198	41.29 ± 37.26	62.68 ± 24.20	.331
24th hour Lactate Clearance	35.79 ± 53.89	80.3 [b]	.200	35.06 ± 53.91	84.06 ± 5.31	**.043**
48th hour Lactate Clearance	44.38 ± 44.54	63.09 [b]	.618	45.02 ± 44.58	33.02 ± 42.53	.525

[a]Displayed as median and interquartile range. INR = international normalized ratio; HARI = hepatic artery resistance index

IPGF definitions

In our study, according to Nanashima's *et al.* definition, 23 patients were classified as IPGF, compared to 32 patients according to Olthoff's *et al.* definition. MEAF scored our population with a mean of 6.33 (± 1.64) (**Table 5)**.

A significant association (p=0.002, **Figure 2**) with 90-day mortality was found in Nanashima's IPGF group**.** Furthermore, both Olthoff's definition (p=0.015, **Figure 3**) and MEAF score were also proven to be significant 90-day patient survival predictors (p=0.025). An area under receiver operating curve (AUC) of 0.886 was reported for MEAF, with a significant cut-off value of 7.368 (**Figure 4**). Additionally, Rosen's definition did not show any association with either patient survival or graft failure. No association with either one-year survival or graft failure was observed in any of the tested definitions.

Table 5. Analysis of IPGF definitions according to primary outcomes

Definitions	n	Mortality (90 days)		Mortality (360 days)		Graft Failure (90 days)		Graft Failure (360 days)	
		p	OR (CI)	p	OR (CI)	p	OR (CI)	p	OR (CI)
Rosen *et al.*	8% (7/93)	.619	-	.314	-	.774	-	.615	-
Nanashima *et al.*	25% (23/93)	**.002**	**1.150 (0.982 – 1.335)**	.090	-	.079	-	.726	-
Olthoff *et al.*	34% (32/93)	**.015**	**1,103 (0.987 – 1.234)**	.134	-	.165	-	.232	-
MEAF	6.33 ± 1.64	**.025**	**3,843 (0.846 – 17.46)**	.258	-	.118	-	.164	-
MELD - Lactate	18.93 ± 5.93	.256	-	.671	-	.184	-	.086	-

OR = Odds ratio; CI = Confidence interval;

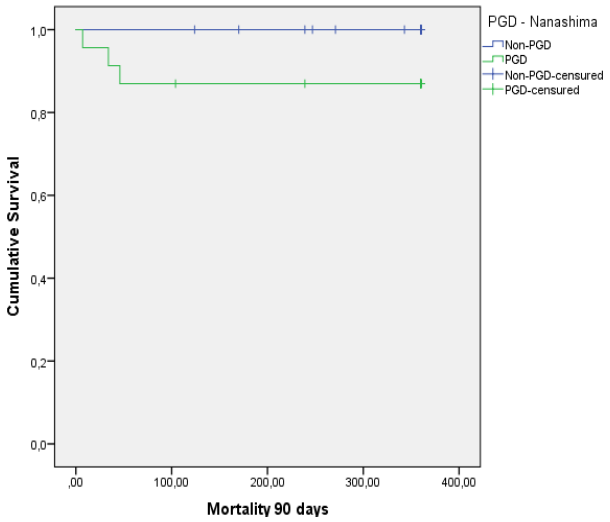

Figure 2. *Nanashima et al. (Mortality 90 days)*

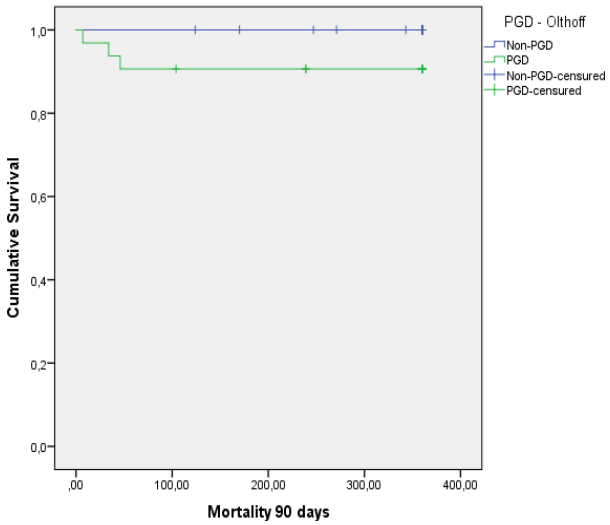

Figure 3. *Olthoff et al. (Mortality 90 days)*

The sensitivity, specificity, cut-off value and overall correctness of each statistical significant definition are displayed on **Table 6**.

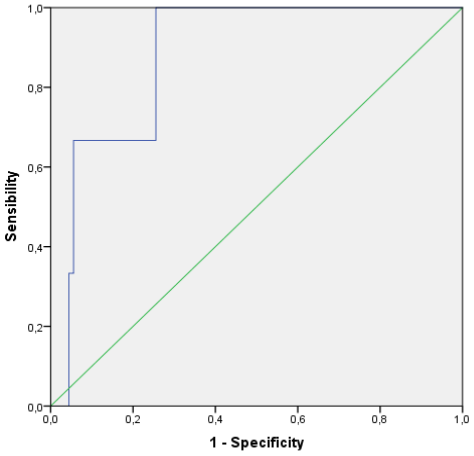

Figure 4. *MEAF ROC Curve (Mortality 90 days)*

Table 6. Statistical significant IPGF definitions' sensitivity, specificity and overall correctness.

Definitions	Cut-off value	Sensitivity (%)	Specificity (%)	Overall Correctness (%)	p-value
Nanashima *et al.* (**90th day mortality**)	NA	100	77.8	78.49	**.002**
Olthoff *et al.* (**90th day mortality**)	NA	100	67.78	68.82	**.015**
MEAF (**90th day mortality**)	7.368	100	74.4	75.27	**.025**

NA = not applicable

Post-transplant need for reintervention

Since one-year survival was high, we analysed first year complications according to Dindo *et al.* as shown in **Figures 5 and 6**.

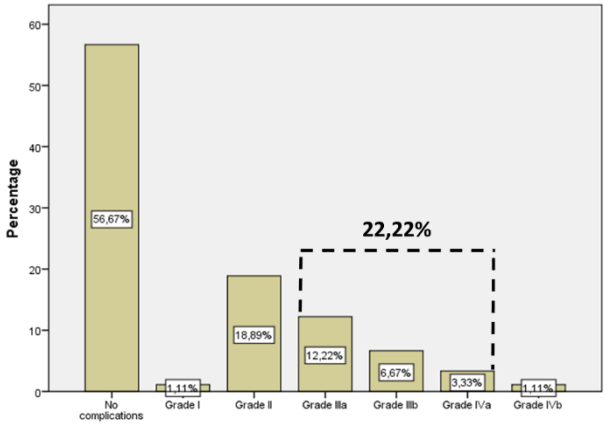

Figure 5. *90-Day Dindo Grade*

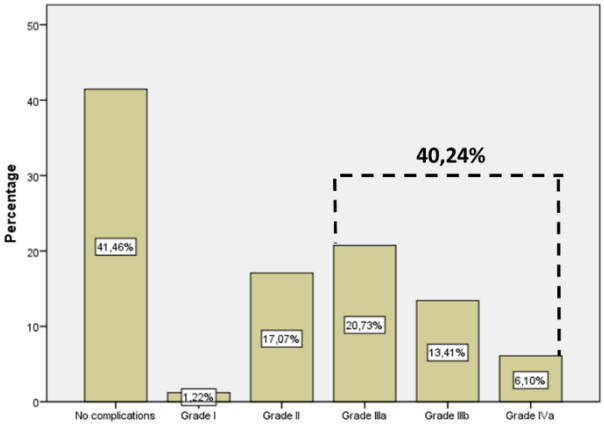

Figure 6. *360-Day Dindo Grade*

In our series, 34.4% (32/93) had a postoperative infection, 40.63% of which were multi-drug resistant pathogens.

In the first 90 days, vascular complications were present in two patients (2.2%) and biliary complications occurred in 14%, while 3.2% had simultaneously vascular and biliary

Table 7. Post-transplant complication analysis

Complications	90-Day Follow-up	360-Day Follow-up
Positive microbiology cultures	34.4% (32/93)	NDA
Multi-drug resistant infections	40.63% (13/32)	NDA
Vascular complications	2.2% (2/93)	0%
Biliary complications	14.0% (13/93)	31.7% (26/82)
Biliary + Vascular complications	3.2% (3/93)	6.1% (5/82)
ERCP	11.8% (11/93)	28% (26/93)
Reoperation	10.8% (10/93)	15.1% (14/93)
Post-transplant Biliary Reinterventions	NDA	0.73 ± 1.13
Dindo grade ≥ III [a]	22.22% (20/90)	40.24% (33/82)
Survival	96.8% (90/93)	88.2% (89/93)

[a] Deceased patients excluded. ERCP = Endoscopic retrograde cholangiopancreatography; NDA = No data available

complications. Eleven patients (11.8%) had been submitted to Endoscopic retrograde cholangiopancreatography (ERCP) while ten (10.8%) were submitted to surgery. A Dindo grade ≥ III was found in 20 patients (22.22%) out of the 90 survivors (**Table 7**).

After one-year of follow-up, 40.24% (33/82) of our patients were classified as grade ≥ III and 11 deceased were excluded. Biliary complications were present in 31.7% (26/82) of our population, while 6.1% had concomitant vascular and biliary complications. ERCP had been performed in 28% of our study population (in comparison to 11.8% on the first 90 days) and 15.1% had been submitted to surgery (**Table 7**).

Using a stepwise logistic regression model, the following factors were found to be significant: Cytomegalovirus (CMV) D+/R- (positive graft in negative recipient), recipient body mass index, preoperative AST value, peak AST^{1-3} (post-operative days 1-3) and peak CRP^{1-3} (post-operative days 1-3). No influence from any other factors was observed. The model was statistically significant, X^2 (5) = 31.933 ($p < 0.001$), explained 44.7% (Nagelkerke R^2) of the observed variance and correctly identified 77.5% of the patients (results are shown in **Table 8**). CMV negative patients who received a positive graft were almost nine times more likely to need reintervention procedures (Dindo grade ≥ III) on the first 360 days. Higher postoperative AST (AUC = 0.656, Cut-off = 62.5, p=0.017), CRP (AUC = 0.645, Cut-off = 8.08, p=0.027), preoperative AST (AUC = 0.657, Cut-off = 67.5, p=0.017) and recipient body mass index were also associated with higher risk of reintervention.

Table 8. Risk factors identified in stepwise multiple logistic regression model.

Variables	B[a]	SE	Wald test	p-Value	OR[b] (95% CI)
CMV (D+/R-)	2.175	0.928	5.490	**.019**	8.800 (1.427 – 54.264)
Recipient BMI	0.181	0.070	6.756	**.009**	1.198 (1.045 – 1.373)
Preoperative AST	0.013	0.006	5.420	**.020**	1.013 (1.002 – 1.025)
Peak AST[d]	4.52×10^{-4}	2.06×10^{-4}	4.803	**.028**	1.000 (1.000 – 1.001)
Peak CRP[d]	0.276	0.095	8.427	**.004**	1.318 (1.094 – 1.589)
Constant	-10.045	2.779	13.068	**.000**	-

$X^2(5) = 31.933$, $p < 0.001$. Nagelkerke $R^2 = .447$. Overall correctness = 77.5% [a]β values are the estimated unstandardized regression coefficients. [b] OR indicates likelihood of Dindo Grade ≥ III. [d] Maximum value in the first 4 postoperative days (day 0 excluded). CRP = C-reactive protein; BMI = body mass index; CMV = cytomegalovirus.

When applied to a follow-up period of just 90 days, CMV (D+/R-), peak AST^{1-3} (post-operative days 1-3) and peak CRP^{1-3} (post-operative days 1-3) were still proven to be independent risk factors ($p < 0.05$), with CMV (D+/R-) patients more than seven times more likely to need reintervention (Dindo grade ≥ III).

Discussion

The aim of this study was to validate previously proposed definitions of IPGF in our population, as well as correctly identify risk factors for intervention-requiring complications, morbidity and mortality.

In our study, very low mortality and graft failure rates were observed in comparison to other studies, a mortality rate of 11.8% on the first year post-LT diverged from usually reported mortality rates of 14.4 to 18% [17–20]. Interestingly, while one-year graft failure was also considerably reduced compared to other reported studies (3.2% versus 9.5 to 17.4%) [21], we found a PNF prevalence of 1.8% which is in line with those (1.7% to 7.6%) found in most studies (**Table 1**) [9–11,14]. This finding might reflect the single centre nature of our study as well as the strict exclusion criteria we employed.

In their series, Feng *et al.* [22] described seven donor characteristics to be associated with graft failure. Donor age was shown to have a particularly strong negative impact on graft survival. A similar result was found in our series with consistent association between older donors and poorer one-year graft outcomes, however, none of the other parameters reported by Feng *et al.* were shown to be significant in our analysis. The importance of donor age is further confirmed by a very strong statistical association (AUC = 0.945, p=0.009) between D-MELD and one-year graft survival. Although our study reported a low incidence of graft failure (3/93 patients), our analysis suggests D-MELD will improve graft-recipient match by complementing MELD scores with graft outcome predicting capability.

Interestingly, we also found heavier grafts to be associated with better one-year graft outcomes, which would otherwise suggest transplantation with small-for-functional-needs livers to be common, however graft weight-to-recipient body weight (GRBW) analysis

showed all patients' to be above the 0.8% threshold, effectively ruling out small-for-size syndrome [23]. Lower peak donor INR values' association with poorer outcomes further raises questions about how to correctly determine the graft liver's functional capabilities prior to LT, while simultaneously reaffirming the need for more complex methodologies such as D-MELD to be applied in graft-donor selection.

In our study, chronic kidney disease was also shown to be a significant 90-day mortality predictor. Similar results have been reported by other series [24,25] which showed CKD to be associated with higher short-term mortality and morbidity following LT. Moreover, preoperative CRP and haemoglobin levels were shown to be predictive of one-year graft failure, this result further adds to the importance of preoperative patient status in the prediction of patient and graft outcomes, as well as suggest that the improvement of patient optimization protocols might directly benefit patient and graft outcome.

In our population, the only intra-operative parameter found to influence patient outcome was surgery duration. Higher surgery duration has previously been linked to poorer patient outcome, particularly longer hospital stays and infectious complications [26], however, in our study a direct association to one-year mortality was found. On the other hand, Rana *et al.* [20] described a correlation between cold ischemia time and recipient survival which, while trending towards significance (p=0.069), could not be confirmed in our series. This result is likely explained by low variance and short overall cold ischemia times found in our study.

Unsurprisingly, immediate postoperative AST, ALT, INR, platelet count and bilirubin levels were found to be significant predictors of both patient and graft outcomes. These results are similar and further reinforce the findings of many other studies [9–11,14], which described these variables as important predictors of mortality and graft outcome.

According to Sanyal *et al.* [27], an HARI >0.8 is a common finding in post LT patients without any association with initial poor function. However, a HARI <0.55 is usually associated with more ominous findings. In our study, we found an association between an HARI below 0.55 on any of the first 5 postoperative days and 90-day mortality (p=0.016). Although this association could not be found in either 360-day mortality or graft failure, more studies should be performed as HARI measurements could be used alongside IPGF definitions for early prediction of short-term mortality and implementation of more aggressive care protocols.

Very clear disagreements in the number of patients classified as IPGF by each definition (Rosen *et al.* – 8%, Nanashima *et al.* – 25% and Olthoff *et al.* – 34%) were found. This observation confirms previously stated need for harmonization and validation of one universal IPGF definition. Furthermore, only Nanashima's definition, Olthoff's and MEAF were able to predict 90-day mortality. In his series, Pareja *et al.* reported MEAF score to be significantly associated with graft and patient survival in the first 3, 6 and 12 months, however, in our series MEAF score (AUC = 0.886, Cut-off value = 7.368, p=0.025) only showed statistical significance with 90-day patient mortality, showing no association with 12-month mortality or graft outcome.

Analysis of sensitivity and specificity of all three definitions found a 100% sensitivity for all definitions, but a slightly higher specificity for both Nanashima's and MEAF score (77.8% and 74.4%, respectively) compared to Olthoff's definition (67.78%). With these results in mind, although none of the PGD definitions successfully predicted both mortality and graft failure, we believe MEAF score to be the best candidate for clinical practice adoption. MEAF not only permits an early classification of IPGF (first 3 postoperative days), but it also relies on a quantitative nature, allowing dysfunction severity based clinical decision.

The second objective of this study was to analyse risk factors for reintervention, while grading complications with Dindo *et al.* classification. We showed that nearly half of the patients needed reintervention in the first follow-up year (Dindo grade ≥ III in 40.24%). To our knowledge no such analysis was reported before. Multivariate analysis identified CMV D+/R- (positive graft in negative recipient), recipient BMI, preoperative AST value, peak AST^{1-3} (post-operative days 1-3) and peak CRP^{1-3} (post-operative days 1-3). The model constructed (**Table 7**) explained 44.7% of the observed variance and correctly predicted 77.5% of the patients needing reintervention in the first follow-up year.

CMV has already been defined as a major cause of morbidity and mortality in post-transplantation patients [28], however, with reported incidences as high as 44-65%, CMV replication effect in D+/R- transplantation patients' outcome remains subject of controversy [29–31]. CMV liver infection is clinically manifested through either tissue-invasive CMV infection, usually indistinguishable from acute allograft rejection and often requiring liver biopsy for distinction, or through indirect CMV effects, believed to be related with the virus immune system modulation capabilities, ranging from acute or chronic allograft rejection induction, to vanishing bile duct syndrome or even higher incidence of vascular or hepatic artery complications [31]. Meije *et. al.* [29] reported the development of CMV replication to be a risk factor for 5-year graft failure, but found no differences in patient mortality. Interestingly, no difference in graft or patient outcome was found in our population, however, a nine-fold increase in reintervention risk was seen in non-immune patients receiving a CMV positive graft. This constitutes an important finding as the implementation of universal prophylaxis or other CMV morbidity decreasing strategies, such as valganciclovir and oral ganciclovir prophylaxis, were shown to reduce CMV infection incidence in transplant recipients [31]. Preventive strategy development and implementation might therefore help reduce the incidence of intervention-requiring complications in LT patients.

In a large multicentre study, Ayloo *et al.* [32] found no association between BMI and patient or graft survival, in a similar UK single centre large study Hakeem *et al.* [33] also reported no association with patient or graft survival. In our series, similar results were obtained, with no association between BMI and patient or graft survival, however, a higher BMI proved to be an independent risk factor for postoperative morbidity and consequent need for reintervention. With that in mind, early identification of overweight patients might help reduce post-operative morbidity, need for endoscopic or surgical reintervention and potentially allow adoption of beneficial risk reducing strategies. The importance of preoperative patient status was additionally reinforced with the association of preoperative AST.

Postoperative AST and CRP have also been widely described as reliable predictors of patient and graft outcome [9–11,14,34], however, the concept that early post-transplant levels also pose as important risk factors for post-transplant complications further reinforces the importance of ischemic/reperfusion mechanisms [9,35] in development of PGD and later complications.

Further studies with a larger sample are needed in order to validate the model and risk factors, meanwhile, the harmonization of IPGF definition is capital and will significantly improve clinical post-transplant morbidity and mortality enhancing protocols, as well as facilitate future research on the subject.

Conclusion

Both donor, preoperative, intraoperative and postoperative parameters are significant predictors of patient and graft outcome in liver-transplantation. D-MELD substantially improves MELD's LT outcome prediction capability and should be adopted into clinical practice. Hepatic artery resistance index below 0.55 on any of the first 5 postoperative days provides a fast early supplemental method of predicting 90-day mortality risk. Moreover, MEAF score was statistically associated with 90-day mortality, even though we were unable to find 360-day mortality or graft failure associations. CMV status (D+/R-), recipient body mass index, pre-operative AST, postoperative AST and postoperative CRP values are independent risk factors for post-transplant need for reintervention. Harmonization of IPGF definitions remains of paramount importance.

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