Clinics and Research in Hepatology and Gastroenterology (2019) 43, 730—737

Available online at ScienceDirect www.sciencedirect.com

Elsevier Masson France EM|consulte www.em-consulte.com/en

ORIGINAL ARTICLE

Impact of early remote organ dysfunction on long-term survival after liver transplantation

Camille Besch[a], **Baptiste Michard**[a], **Pietro Addeo**[a], **Constantin Oncioiu**[a], **Bernard Ellero**[a], **Marie-Lorraine Woehl-Jaegle**[a], **Philippe Bachellier**[a], **François Faitot**[a,b,*]

[a] *Hepato-pancreato-biliary surgery and liver transplantation, hopitaux universitaires de Strasbourg, hopital de Hautepierre, 1 avenue Molière, 67000 Strasbourg, France*
[b] *Laboratoire ICube, UMR7357, university of Strasbourg, 300, boulevard Sébastien Brandt, 67200 Illkirch-Graffenstaden, France*

Available online 4 April 2019

KEYWORDS
Early allograft dysfunction;
Inflammation;
Renal failure;
Cardiovascular complications;
Interleukin-6

Summary
Background: Attention is focused on graft function although extrahepatic organ dysfunction often occurs. Renal failure, cardiovascular events and sepsis have individually shown a significant impact on short- and long-term outcomes. The aim of the study was to identify how extrahepatic organ dysfunction (EROD) and allograft dysfunction (EAD) may be associated and their relative impact on long-term survival.
Methods: A retrospective study was conducted in a unicentric cohort of 294 patients transplanted between 2009 and 2014. The composite endpoint EROD was defined as requirement during the hospitalization of de novo renal replacement therapy, reintubation/ventilation > 7 days or cardiovascular event. Donor and recipient characteristics were evaluated as predictive of EROD in uni- and multivariate analysis. Main endpoint was overall survival evaluated by Kaplan—Meier method.
Results: EROD occurred in 91 patients (31%) among whom 42 also experienced EAD (46%). Predicting factors associated with EROD were IL6 level ($P = 0.002$) and lab-MELD ($P < 0.001$). Only patients experiencing both EAD and EROD had a worse survival ($P = 0.001$). In patients without EAD, time to normalization of bilirubin and INR were longer in patients with EROD compared to those without EROD ($P = 0.002$ and $P = 0.008$ respectively).

* Corresponding author at: Hepato-pancreato-biliary surgery and liver transplantation department, hopitaux universitaires de Strasbourg, 1, avenue Molière, 67000 Strasbourg, France.
E-mail address: francois.faitot@chru-strasbourg.fr (F. Faitot).

https://doi.org/10.1016/j.clinre.2019.02.016

Conclusions: The composite endpoint described as early remote organ dysfunction could be used as a predictive factor after transplantation and should be included in future studies together with early allograft dysfunction. Identifying patients in whom EROD and EAD occur together or one after the other could help to better predict long-term outcomes.

EROD	early remote organ dysfunction
EAD	early allograft dysfunction
CIT	cold ischemia time
IRI	ischemia-reperfusion injury
RPS	reperfusion syndrome
RRT	renal replacement therapy
ECD	extended criteria donor
LRC	liver-related complications

Introduction

Short- and long-term outcome after liver transplantation is the result of complex interactions between donor and recipient. Early predictors for liver transplantation have mainly focused on liver related complications such as graft function. Early allograft dysfunction (EAD) has been defined as an abnormal biological postoperative course with significant impact on outcome [1,2]. Ischemia-reperfusion injury (IRI) plays a central role in the early outcomes of LT as suggested by the prognostic impact of cold ischemia time (CIT) [3,4] and recent studies evaluating histological reperfusion biopsies [5]. However, even in cases of standard CIT, EAD may occur because of recipient's status, infection or technical complications.

On the other hand, remote organ dysfunctions have shown to have a significant impact on long-term survival especially renal failure. Calcineurin-inhibitor induced renal insufficiency as well as cardiovascular diseases are the leading causes of patient's death past the first year of transplantation but they also represent one of the main cause of early mortality along with infections [4].There are few studies evaluating the impact of early remote organ dysfunction on the outcome of liver transplantation. Recent works have underlined the significant impact of early renal failure [6], cardiovascular [7] or pulmonary complications [8]. As for liver dysfunction, some authors have shown the significant impact of SIRS on the occurrence of these complications without being considered in relation to liver related complications [9].

The working hypothesis of this study was that remote organ injuries significantly impact long-term results independently of early allograft dysfunction and may eventually impact on graft function after day 7.

Patients and method

From 2009 to 2014, all adult patients consecutively transplanted with a liver graft were retrospectively analyzed. Patients receiving a combined kidney, heart or lung with a liver graft were excluded. All patients gave informed consent for the study and the study was approved by the local University ethical committee.

Patients were listed after discussion in multi-disciplinary meeting including surgeons, transplant physicians and anesthesiologists, according to standard LT guidelines. Patients with hepatocellular carcinoma were selected according to the Milan criteria and received preoperative treatment whenever possible.

All donors were deceased donors whose consent was obtained either through absence of opposition during life or after family consent. LT was performed using the piggy-back technique in the vast majority of cases. Portal decompression was rarely used during the study period and left at the surgeon's discretion. Liver graft was rinsed with albumin just before reperfusion and portal reperfusion was realized just after caval unclamping. IL6 has been measured as a routine blood examination before, during and after LT since a decade. The reperfusion value reported in this study was measured within the 30 minutes after reperfusion.

Post-operative immunosuppression consisted of triple regimen immunosuppression (calcineurin inhibitors, steroids and mycophenolate mofetil). The corticosteroid dosage was reduced during the first 3 months and calcineurin inhibitor doses were adapted according to trough level and renal function. Induction immunosuppression with anti-IL2 antibodies was used in patients with severely altered renal function before transplantation as a renal function sparing strategy.

Definitions

A composite criteria was used to define early remote organ dysfunction (EROD) as any requirement during the initial post-LT hospitalization of de novo renal replacement therapy (pre-LT ICU RRT and kidney-liver transplantation excluded) OR reintubation/ventilation time over 7 days OR significant cardiovascular event necessitating ICU or cardiologic intervention (i.e. myocardial infarction, acute cardiac failure, adrenergic cardiopathy, non-tolerated arrhythmia).

EAD was defined according to the Olthoff's criteria: ASAT or ALAT > 2000 UI/L within the first 7 days, day7 bilirubin $\geq$ 171 mmol/L (10 mg/dL) or day7 INR $\geq$ 1.6 [10]. In order

Table 1 Predicting factors of EROD in the whole population and in EAD-free patients.

	No EROD $n=199$	EROD $n=86$	*P*-value	No EROD $n=157$	EROD $n=48$	*P*-value
Recipient's characteristics						
Age	53 ± 11	54 ± 10	0.264	53 ± 11	55 ± 10	0.127
Male gender	71%	77%	0.463	72%	71%	0.878
BMI	26.6 ± 5	25.7 ± 5	0.267	25.9 ± 4	26.2 ± 5	0.698
Diabetes mellitus	31%	22%	0.218	28%	24%	0.645
Etiology of cirrhosis						
Alcohol	96	44	0.651	75	30	0.074
HCV	37	11	0.229	29	3	0.041
HBV	14	6	0.986	9	4	0.517
Fulminant hepatitis	7	3	0.990	4	3	0.216
HCC	32%	24%	0.190	31%	33%	0.718
Lab-MELD Score at listing	19.6 ± 10	26 ± 11	<0.001‡	19.5 ± 9	26.6 ± 12	<0.001
Albumin	33 ± 7	32 ± 7	0.286	33 ± 7	32 ± 7	0.324
Sodium	137 ± 5	136 ± 5	0.204	137 ± 5	136 ± 5	0.374
PreLT ACLF 0/1/2/3	146/28/16/9	46/11/16/13	0.0004‡	119/23/11/4	25/7/9/7	0.0004
IL6 before incision	23.9 ± 3	83.4 ± 28	0.001‡	23.9 ± 3	87.4 ± 50	0.018
Portal thrombosis	11%	27%	0.007	10%	22%	0.072
Ascitis at LT (mL)	2317 ± 241	2934 ± 373	0.155	2509 ± 286	2491 ± 511	0.974
Donor characteritics						
Age	55 ± 20	52 ± 20	0.179	48 ± 21	55 ± 19	0.034
Cold ischemia time (minutes)	509 ± 127	520 ± 123	0.500	501 ± 111	514 ± 107	0.476
BAR Score	7.8 ± 5	11 ± 6	<0.0001	7.6 ± 4	11 ± 6	<0.0001
Operative characteristics						
Anhepatic duration (minutes)	95 ± 34	92 ± 35	0.649	93 ± 34	87 ± 32	0.310
Portal decompression	21%	20%	0.904	31%	27%	0.375
Reperfusion syndrome	39%	69%	0.007	30%	70%	0.002
IL6 at reperfusion (ng/mL)	1221 ± 280	2632 ± 1119	0.098	1028 ± 333	1268 ± 270	0.700
IL6 > 1000 at reperfusion	21%	42%	0.0002‡	15%	40%	0.0003
ASAT at reperfusion (UI/L)	1402 ± 100	1342 ± 145	0.739	1122 ± 919	987 ± 101	0.375
ALAT at reperfusion (UI/L)	964 ± 74	853 ± 77	0.370	761 ± 42	693 ± 71	0.43

BMI: body mass index; HCV: hepatitis C virus; HBV: hepatitis B virus; HCC: hepatocellular carcinoma; ACLF: acute-on-chronic liver failure; BAR: balance of risk; IL6: interleukin 6; LT: liver transplantation; ‡: parameters used in the multivariate analysis; *: factors significantly associated to EROD in multivariate analysis.

to take in consideration liver complications occurring after day 7 for the impact on long-term survival, a composite criteria was used to define Liver Related Complications (LRC) as EAD and/or vascular or biliary complications.

Postoperative mortality was considered at day 90. Extended criteria liver donors (ECD) were defined according to the EASL definition [11].

Liver biopsy was not systematically performed in case of suspicion of acute rejection. Therefore it was not possible to accurately predict the correlation between EROD and acute rejection.

Reperfusion syndrome was defined as a significant > 30% fall in mean arterial pressure compared to the pressure observed during anhepatic phase for more than 1 minute within the 5 minutes following reperfusion [12] or the need for vasopressors administration.

EASL definition of Extended criteria donor [10] was used to evaluated graft quality. Balance of risk (BAR) score were used to assess the donor-recipient matching as described by Dutkowski et al. [13].

Statistical analysis

Continuous variables are expressed as mean ± SD or median and range as appropriate according to distribution. They are compared using two-ways Student *t*-test or Mann-Whitney as appropriate. Qualitative variables are compared using Chi^2 test. Overall (OS) and graft (GS) survival probabilities were calculated using Kaplan–Meier method from the time of transplantation. A multivariate analysis using logistic regression or a Cox-Model (for OS and GS) was performed on factors identified in univariate analysis with a *P*-value < 0.1. Statistical studies were performed on StatView 5.0 for Windows (SAS) or SPSS for ROC curve.

Results

During the study period, 285 patients were included. The main indication for LT was alcoholic cirrhosis ($n=143$) followed by post-hepatitis C cirrhosis ($n=50$). Median MELD

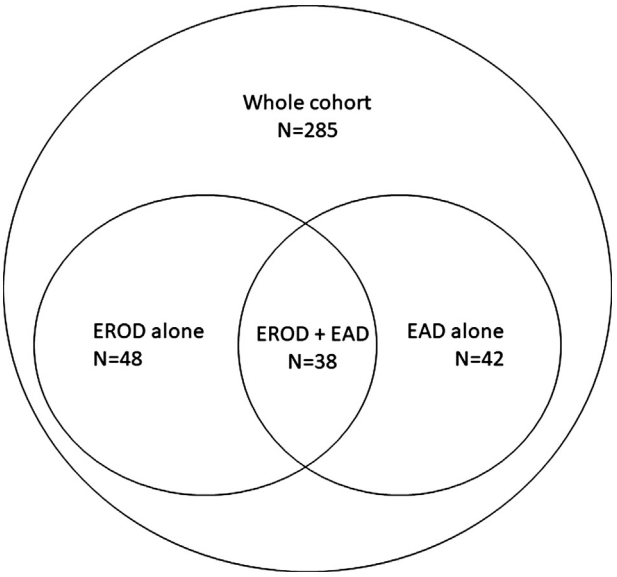

Figure 1 Distribution of patients according to the occurrence of EAD, EROD or both.

score was 20 with 69 patients (23%) having a MELD higher than 30. HCC was present in 85 patients (29%). ECD were used in 159 cases (54%) and median cold ischemia time was 507 minutes (75-1022).

Occurrence and risk factors for early remote organ dysfunction

EROD occurred in 86 patients (30%). The risk factors associated with EROD were pre-LT IL6 level, MELD Score at listing, portal vein thrombosis, BAR Score and IL6 level at reperfusion (Table 1). In multivariate analysis, only one independent factors was associated to EROD: IL6 level at reperfusion ($P = 0.015$). MELD Score at listing and portal vein thrombosis were marginally significant ($P = 0.051$ and 0.052 respectively).

EAD occurred in 80 patients (28%) with high bilirubin at day7 in 38 patients (45%), high INR at day 7 in 31 patients (36%) and high transaminases peak in 30 patients (35%). EAD occurred without EROD in 42 patients. Among patients experiencing EROD, 38 patients (44%) also experienced EAD. (Fig. 1) EROD was mainly associated to high INR and bilirubin.

EAD was significantly more frequent in patients presenting EROD (44% vs. 21%; $P < 0.0001$). EROD was associated to longer hospital stay. EROD was associated to reperfusion syndrome ($P = 0.002$) and correlated with a significantly longer hospital stay ($P < 0.0001$). The risk factors for EROD were found to be identical to those in the whole cohort. Donor age was also significantly associated to EROD ($P = 0.042$) (Table 2). EROD was associated to a significantly higher risk of graft loss at 3 year (40% vs. 14%; $P < 0.0001$).

A subgroup analysis was conducted on patients not experiencing EAD to evaluate whether EROD and its consequence were secondary to EAD or if it had its proper impact ($n = 205$). Interestingly, the time to normalization of bilirubin and INR was longer in patients with EROD ($P = 0.002$ and 0.008 respectively) (Fig. 2).

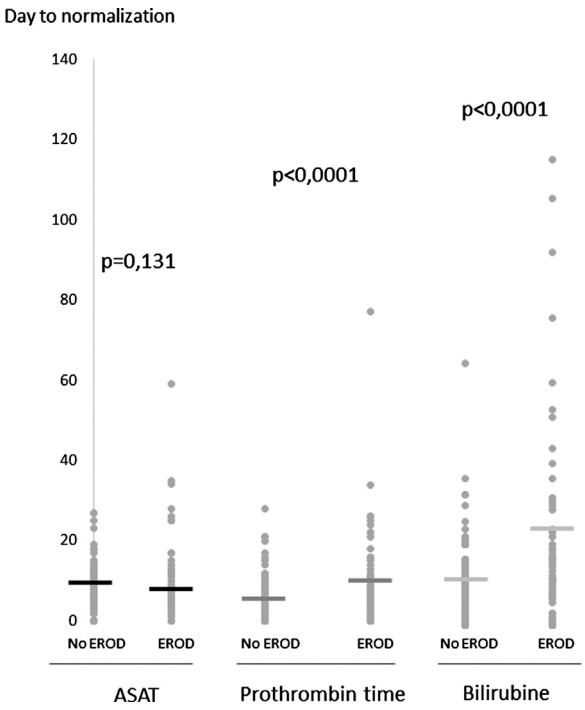

Figure 2 Day to normalization for aspartate aminotransferase (ASAT), prothrombin time and bilirubin in patients not experiencing EAD according to the occurrence of EROD or not. Patients experiencing EROD have a significantly longer time to normalization for prothrombin time ($P < 0.001$) and bilirubin ($P < 0.001$) although their liver function do not define allograft dysfunction.

Survival analysis

One- and 3-year patient and graft survival were 88%, 81% and 83%, 77% respectively.

Graft's survival were significantly lower in patients experiencing LRC ($P < 0.0001$) and in patients experiencing EROD ($P < 0.0001$) (Fig. 3a). A subgroup analysis evaluating the impact of extrahepatic organ failures in patients not exerting pretransplant organ failures confirmed the significant impact of EROD on survival (Fig. 3b). There was no difference in survival according to the type of extrahepatic organ failure.

Patients experiencing only LRC without EROD did not have lower graft's survival than patients with neither EAD nor EROD ($P = 0.311$). Indeed graft survival was impacted by LRC only when EROD occurred. Patients experiencing both EROD and LRC presented a significantly altered 3-year graft survival (38%; $P = 0.001$) (Fig. 4a). All these results were confirmed when analyzing EAD instead of LRC.

Prognostic factors for graft survival were EROD, LRC, septicemia, labMELD at listing over 30, donor age > 70 years-old, ECD, ACLF grade at transplantation and portal vein thrombosis. Logistic regression analysis for graft survival identified EROD and ACLF grade at the time of transplantation as independent predicting factors (Table 3) with no independent impact of LRC. The causes of graft loss were graft failure in 18 patients (primary non function in 4 (1.3%), vascular complications in 14 (4.7%)), and patient's death in 56 (mainly

Table 2 Impact of EROD on the early liver-related outcomes in the whole population ($n = 285$) and in EAD-free patients ($n = 205$).

	No EROD $n = 199$	EROD $n = 86$	*P*-value	No EROD $n = 157$	EROD $n = 48$	*P*-value
EAD	21%	42%	< 0.0001			
90-day patient's death	5%	23%	< 0.0001	3%	9%	0.124
Length of hospital stay	21 ± 10	51 ± 38	< 0.0001	21 ± 10	47 ± 41	< 0.0001
Rehospitalization within 90 days	38%	41%	0.663	36%	33%	0.711
Retransplantation	4%	10%	0.058	4%	2%	0.457
Day of ASAT normalization	10 ± 9	8 ± 4	0.133	8 ± 4	8 ± 6	0.628
Day of INR normalization	5 ± 1	10 ± 1	< 0.0001	5 ± 2	8 ± 2	0.006
Day of bilirubin normalization	10 ± 1	24 ± 4	< 0.0001	9 ± 7	16 ± 3	0.001

EAD: early allograft dysfunction; ASAT: aspartate aminotransferase; INR: international normalized ratio.

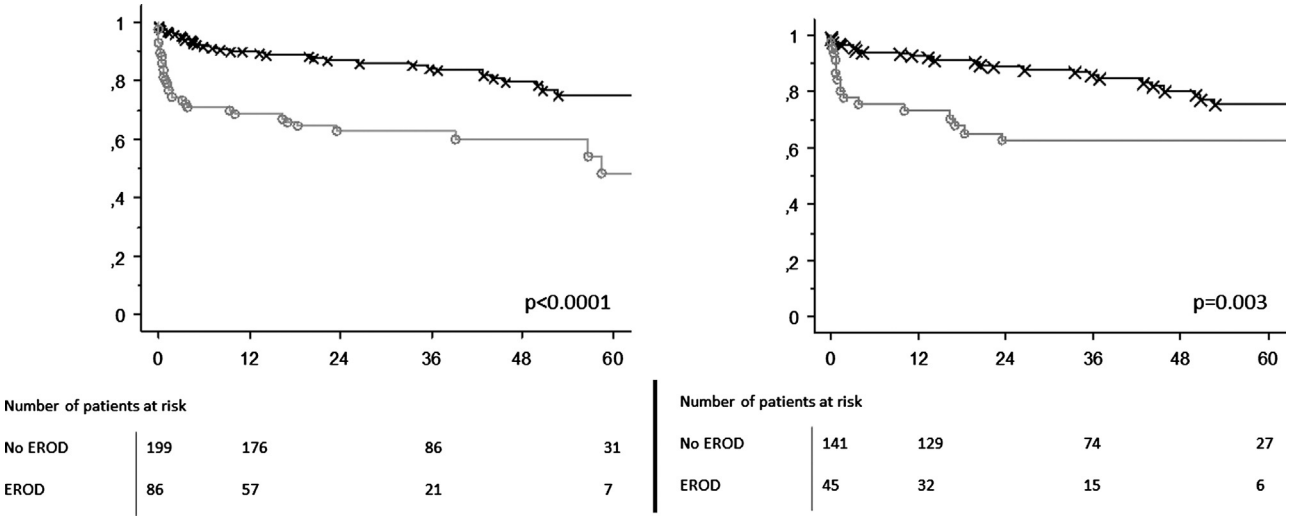

Figure 3 Graft survival according to the occurrence of EROD: Right panel: EROD is an independent factor for graft survival ($P < 0.0001$); Left panel: prognostic value of EROD in patients transplanted from home (UNOS status 4); black line with circles (o) represents patients without EROD, grey line with crosses (x) represents patients with EROD ($P < 0.0001$).

cardiac failure ($n = 7$), neurologic complications ($n = 7$), cancer ($n = 9$), sepsis ($n = 10$), vascular complications ($n = 11$)).

Discussion

Long-term outcome after liver transplantation is the result of the complex interactions between graft function, recipient's status at transplantation and postoperative complications due to surgery and immunosuppression. Many studies have focused on the impact of graft function and few have considered extrahepatic dysfunctions as being cause and/or consequence of graft dysfunction.

This study underlines the importance of evaluating and reporting the occurrence of extrahepatic organ dysfunction together with early allograft as they both have significant impact on outcomes.

De novo extrahepatic organ dysfunction may play a significant role in long-term results. In the current series, EAD and EROD were associated to survival in an independent way, validating many data from the literature regarding EAD. However, patients experiencing either EAD or EROD alone did not present a lower survival compared to patients experiencing neither complications. On the contrary, patients experiencing both EAD and EROD had a low graft survival. The major insight of this study is to emphasize the importance of extrahepatic organ dysfunction after LT. The incidence of EROD (31%) was close to that of EAD although patients experiencing EAD and EROD were not necessarily the same. Hence, it is mandatory to distinguish among patients experiencing EAD those who develop EROD in order to correctly predict long-term outcomes.

Many studies have shown the impact of individual EROD mainly renal failure [14] (especially in case of RRT need) [15] and cardiovascular complications. Acute kidney injury may significantly impact the outcome of LT through hemodynamic and metabolic derangements. Inversely hepatic IRI may significantly impact the function of remote organs as already shown for kidney [16]. In the same way, cardiac and pulmonary injury may induce a significant impairment of graft oxygenation with subsequent aggravation of the ischemia-reperfusion injury. This observation may also be attributed to the status of the recipient as cirrhotic patients with advanced disease often present with clinically significant or silent cardiac, renal or pulmonary impairment. In the era of MELD Score, the impact of renal impairment has been

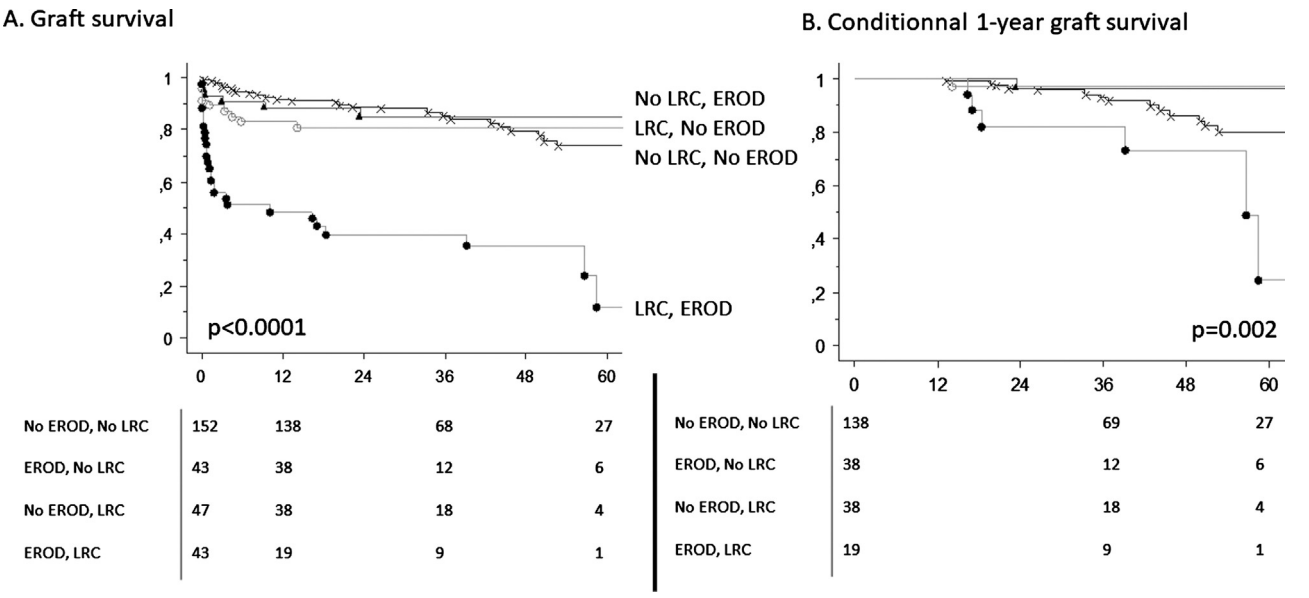

Figure 4 Graft survival according to concomitant EROD and EAD: Right panel: graft survival ($P < 0.0001$); Left panel: conditional 1-year graft survival ($P = 0.002$). Only patients experiencing both EAD and EROD have a significantly lower graft survival. Black line with crosses (x) for patients experiencing neither LRC nor EROD; black line with open circles (o) for patients experiencing LRC without EROD; grey line with black triangles for patients experiencing no LRC but EROD; grey line with dark circles (•) for patients experiencing both EROD and EAD.

Table 3 Predictive factors of graft survival in the studied population.

	Graft survival		Uni *P*-value	RR	95% IC	Multivariate *P*-value
	1-year	3-years				
Early liver-related complications			< 0.0001	2.25	1.35—3.76	0.797
Yes	67%	61%				
No	91%	85%				
Septicemia[a]			0.007	1.01	0.99—1.05	0.303
Yes	74%	66%				
No	87%	82%				
Early remote organ dysfunction			< 0.000	2.51	1.14—5.52	0.013
Yes	70%	62%	1			
No	90%	84%				
MELD > 30 at listing			0.029	0.98	0.96—1.003	0.342
Yes	74%	70%				
No	86%	80%				
Portal vein thrombosis			0.024	1.80	0.79—4.13	0.164
Yes	77%	62%				
No	88%	84%				
Pretransplant ACLF grade			< 0.000	4.01	1.6—10.1	0.006
Grade 0	89%	81%				
Grade 1	85%	81%	1			
Grade 2	78%	78%				
Grade 3	45%	45%				
Extended criteria donor			0.043	1.69	1.02—2.79	0.067
Yes	81%	72%				
No	86%	83%				

[a] Documented septicemia.

a growing issue. Systemic and regional circulatory insufficiency is well described in this setting. It has already been shown that cirrhotic cardiomyopathy may become clinically significant after LT [17,18].

This concept of extrahepatic dysfunction after LT may be put in parallel to acute-on-chronic liver failure where extrahepatic organ failure(s) may impact the outcome [19]. It has been shown that SOFA Score after LT is associated to short-term outcomes [20]. This is in line with the findings that ACLF Scores after liver transplantation may be good predictors of the early outcomes [21,22]. Indeed ACLF grade 3 was associated to an increased risk of de novo extrahepatic organ dysfunction and EAD and was a major determinant of long-term graft survival together with EROD. These ACLF patients present with a higher risk of prolonged ventilation or renal replacement therapy after LT as well as altered long-term outcome [23].

Interestingly both renal failure [24] and cardiovascular complications [25] have been recently shown to be associated to significant elevation of cytokines or acute-phase response confirming the data presented herein. Indeed one of the major determinants of EROD is the systemic inflammatory response as defined by high IL6 level. This latter finding is particularly interesting in view to understand whether hepatic or extrahepatic dysfunctions come first. Even though the retrospective aspect of the study does not enable to draw straightforward conclusions, some hypotheses can made. One of the most interesting hypotheses is that remote organ injury, either preexisting (in ACLF patients) or developing in the first postoperative week (due to the systemic inflammatory response), can significantly impact graft function even in the absence of genuine EAD. This is well shown by longer time to normalization of INR and bilirubin in patients with EROD, when studying only the population without EAD.

In some cases, EAD may induce extrahepatic organ dysfunction. This may be true in case of severe portal hypertension with portosystemic collaterals and/or portal thrombosis when the significant hemodynamic impairment may favour postoperative persistent ascites and subsequent renal failure. The observation that portal thrombosis is linked to extrahepatic dysfunction only when there is an associated EAD is in favour of this hypotheses. However, it should be underlined that neither portal vein thrombosis nor liver-related complications are independent predictors of survival contrary to EROD.

Significant systemic inflammatory response may induce remote organ injury which in turn induces graft dysfunction. In a recent work, the use of polyethyleneglycol (PEG)-containing reduced IL6 secretion and extrahepatic complications [26]. Therapeutic actions aiming at reducing the inflammatory response from the graft could have a direct beneficial impact on extrahepatic organ dysfunction.

The retrospective aspect of this study surely limits some conclusions. It was not possible to properly assess the timing of graft and extrahepatic dysfunction, which could have oriented towards the hypotheses stated above. Larger prospective observational studies should be led to validate this hypothesis and help better define the predictive factors. Graft characteristics, such as degree of steatosis were not available for many patients, limiting the possibility to further define grafts at risk of EROD. However, only de novo remote organ injuries were considered in order to limit the impact of pre-transplant status on the occurrence of these complications.

In conclusion, early remote organ dysfunction should be taken in consideration as a predictive factor in the same way as early allograft dysfunction does. It could be an original new endpoint in future studies to define extended graft criteria and for the evaluation of newer treatments and techniques.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

Disclosure of interest

The authors declare that they have no competing interest.

References

[1] Lai Q, Molinaro A, Mennini G, et al. Preoperative donor scores and postoperative early measures of graft function: relevance to the outcome of liver transplantation. Transpl Proc 2010;42(4):1209—11.
[2] Hudcova J, Scopa C, Rashid J, et al. Effects of early allograft dysfunction on outcomes following liver transplantation. Clin Transplan 2017;31, http://dx.doi.org/10.1111/ctr.12887.
[3] Burroughs AK, Sabin CA, Rolles K, et al. 3-month and 12-month mortality after first liver transplant in adults in Europe: predictive models for outcome. Lancet 2006;367:225—32.
[4] Gonzalez FX, Rimola A, Grande L, et al. Predictive factors of early postoperative graft function in human liver transplantation. Hepatology 1994;20:565—73.
[5] Ali JM, Davies SE, Brais RJ, et al. Analysis of ischemia/reperfusion injury in time-zero biopsies predicts liver allograft outcomes. Liver Transpl 2015;21:487—99.
[6] Hilmi IA, Damian D, Al-Khafaji A, et al. Acute kidney injury following orthotopics liver transplantation: incidence, risk factors and effects on patient and graft outcome. Br J Anaesth 2015;114:919—26.
[7] VanWagner LB, Serper M, Kang R, et al. Factors associated with major adverse cardiovascular events after liver transplantation among a national sample. Am J Transpl 2016;16:2684—94.
[8] Aydin C, Otan E, Akbulut S, et al. Postoperative pulmonary complications after liver transplantation: assessment of risk factors for mortality. Transpl Proc 2015;47:1488—94.
[9] Hassan L, Bueno P, Ferron-Celma I, et al. Early postoperative response of cytokines in liver transplant recipients. Transpl Proc 2006;38(8):2488—91.
[10] Olthoff KM, Kulik L, Samstein B, et al. Validation of current definition of early allograft dysfunction in liver transplant recipients and analysis of risk factors. Liver Transpl 2010;16(8):943—9.
[11] European Association for the Study of the Liver. EASL Clinical Practive Guidelines: Liver Transplantation. J Hepatol 2016;64(2):433—85.
[12] Paugam-Burtz C, Kvafyan J, Merckx P, et al. Postrepserfusion syndrome during liver transplantation for cirrhosis: outcome and predictors. Liver Transpl 2009;15(5):522—9.
[13] Dutkowski P, Oberkofler CE, Slankamenac K, et al. Are there better guidelines for allocation in liver transplantation? A novel score targeting justice and utility in the model foe end-stage liver disease era. Ann Surg 2011;245(5):745—53.

[14] Zhu M, Li Y, Xia Q, et al. Strong impact of acute kidney injury on survival after liver transplantation. Transpl Proc 2010;42(9):3634—8.
[15] Klaus F, Keitel da Silva C, Meinerz G, et al. Acute kidney injury after liver transplantation: incidence and mortality. Transpl Proc 2014;46(6):1819—21.
[16] Jochmans I, Meurisse N, Neirynck A, et al. Hepatic ischemia-reperfusion injury associates with acute kidney injury in liver transplantation: prospective cohort study. Liver Transpl 2017, http://dx.doi.org/10.1002/lt.24728 [epub].
[17] Liu H, Jayakumar S, Traboulsi M, et al. Cirrhotic cardiomyopathy: implications for liver transplantation. Liver Transpl 2017;23(6):826—35.
[18] Sonny A, Ibrahim A, Schuster A, et al. Impact and persistence of cirrhotic cardiomyopathy after liver transplantation. Clin Transplant 2016;30(9):986—93.
[19] Artru F, Louvet A, Ruiz I, et al. Liver transplantation in the most severly ill cirrhotic patients; a multicenter study in acute-on-chronic liver failure grade3. J Hepatol 2017;67(4):708—15.
[20] Schrem H, Reichert M, Reichert B, et al. Value of the SOFA score as a predictive model for short-term survival in high-risk liver transplant recipients with a pre-transplant labMELD score >30. Langenbecks Arch Surg 2012;397(5):717—26.
[21] Lee M, Lee JH, Oh S, et al. CLIF-SOFA scoring system accurately predicts short-term mortality in acutely decompensated patients with alcoholic cirrhosis: a retrospective analysis. Liver Int 2015;35(1):46—57.
[22] Pan HC, Jeng CC, Lee WC, et al. Scoring systems for predicting mortality after liver transplantation. PloS One 2014;9(9):e107138.
[23] Levesque E, Winter A, Noorah Z, et al. Impact of acute-on-chronic liver failure on 90-day mortality following a first liver transplantation. Liver Int 2017, http://dx.doi.org/10.1111/liv.13355.
[24] Teppo AM, Thornroth T, Honkanen E, et al. Elevated C-reactive protein associates with deterioration of renal function in transplant recipients. Clin Nephrol 2003;60(4):248—56.
[25] Watt KD, Fan C, Therneau T, et al. Serum adipokine and inflammatory markers before and after liver transplantation in reciepients with major cardiovascular events. Liver Transpl 2014;20:791—7.
[26] Brisson H, Arbelot C, Monsel A, et al. Impact of graft preservation solutions for liver transplantation on early cytokine release and postoperative organ dysfunction. A pilot study. Clin Res Hepatol Gastroenterol 2017;41(5):564—74.