ORIGINAL ARTICLE

# Impact of the new MELD-based allocation system on waiting list and post-transplant survival—a cohort analysis using the French national CRISTAL database

Carine Jasseron[1], Claire Francoz[2,3], Corinne Antoine[4], Camille Legeai[1], François Durand[2,3] & Sébastien Dharancy[5,6,7] Collaborators*

[1] Direction Prélèvement Greffe Organes-tissus, Pôle Évaluation, Agence de la Biomédecine, Saint-Denis La Plaine cedex, France
[2] Hepatology and Liver Intensive Care Unit, Hospital Beaujon, Clichy, France
[3] INSERM U773, Centre de Recherche Biomédicale Bichat Beaujon CRB3, Clichy, France
[4] Direction Générale Médicale et Scientifique, Direction Prélèvement Greffe Organes-tissus, Pôle Stratégie Prélèvement Greffe, Agence de la Biomédecine, Saint-Denis-la-Plaine cedex, France
[5] Inserm, UMR995 – LIRIC, Lille, France
[6] UMR995 – LIRIC, Univ. Lille, Lille, France
[7] Service des Maladies de l'Appareil Digestif et de la Nutrition, CHRU Lille, Hôpital Huriez, Lille, France

**Correspondence**
Carine Jasseron, Direction Prélèvement Greffe Organes-tissus, Pôle Évaluation, Agence de la Biomédecine, 1 avenue du Stade de France, 93212 Saint-Denis La Plaine cedex, France.
Tel.: +33 1 55 93 64 04;
fax: +33 1 55 93 69 30;
e-mail: carine.jasseron@biomedecine.fr

*Liver transplant advisory group, clinical centers, and transplant unit surgical and medical supervisors (see the list of participants attached in Acknowledgements).

## SUMMARY

Concerns related to equity and efficacy of our previous center-based allocation system have led us to introduce a patient-based allocation system called the "Liver Score" that incorporates the model for end-stage liver disease (MELD) score. The main objective of this study was to compare waitlist and post-transplant survivals before and after implementation of the "Liver Score" using the French transplant registry (period before: 2004–2006 and period after: 2007–2012). Patients transplanted during the second period were sicker and had a higher MELD. One-year waitlist survival (74% vs. 76%; $P = 0.8$) and 1-year post-transplant survival (86.3% vs. 85.7%; $P = 0.5$) were similar between the 2 periods. Cirrhotic recipients with MELD $\geq$35 had lower 1-year post-transplant survival compared to those with MELD <35 (74.8% vs. 86.3%; $P < 0.01$), mainly explained by their higher intubation and renal failure rates. The MELD showed a poor discriminative capacity. In cirrhotic recipients with MELD $\geq$35, patients presenting 2 or 3 risk factors (dialysis, intubation, or infection) had a lower 1-year survival compared to those with none of these risk factors (61.2% vs. 92%; $P < 0.01$). The implementation of the MELD-based allocation system has led to transplant sicker patients with no impact on waitlist and post-transplant survivals. Nevertheless, selection of patients with MELD $\geq$35 should be completed to allow safe transplantation.

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**Key words**
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## Introduction

In France, up until March 2007, liver grafts were allocated to transplant centers by rotation, except for national priority status in emergency settings (fulminant liver failure and early retransplantation) after expert validation [1]. Consequently, in each LT center, patients usually underwent liver transplantation (LT) at the LT team's discretion, usually based on the time spent on the waiting list. However, this allocation system resulted in significant differences in waitlist survival rates between different geographic areas and between different centers in the same area [2,3].

These concerns related to equity and efficacy of this previous regional center-based allocation system led us to develop a nationwide "Liver Score," a patient-based allocation score. The model for end-stage liver disease (MELD) score initially developed to predict mortality in patients undergoing transjugular intrahepatic portosystemic shunt, and used as a disease severity index for patients with end-stage liver disease, is now a validated score to predict mortality in patients registered on the liver transplantation waiting list [4–6]. The MELD score for patients with cirrhosis and a combination of the MELD score and the time spent on the waiting list for patients with hepatocellular carcinoma (HCC) were consequently integrated into our "Liver score." Moreover, patients with a low MELD score (<15) but with decompensated cirrhosis (i.e., refractory ascites, chronic hepatic encephalopathy) are attributed additional "Liver Score" points, after agreement by independent experts, allowing time-dependent access to an organ (expert component) [7]. This "Liver Score" is calculated daily for each patient and ranges from 0 to a maximum of 1000 points. All transplant candidates are classified according to the "Liver Score" in a unique national waiting list. This new allocation system is designed to provide reasonable and fair nationwide access to organs for each indication. An initial limited evaluation based on the first months of practice showed that the "Liver Score" reduced the waiting list mortality and futile transplantation rates and also accelerated access to LT for the most severely ill patients [8]. The same strategy, adopted in the Eurotransplant zone in Germany, provided similar results. However, surprisingly, it was also associated with an unexpected decrease in post-transplant survival [9]. Indeed, a secondary underestimated consequence of this new allocation system was a marked increase in the number of patients with isolated cirrhosis presenting a MELD score greater than 30 registered on the waiting list because of an expected short transplant waiting time. For example, in France, the number of candidates with a MELD score greater than 30 increased from 120 in 2008 to 274 in 2013 (+128% in 5 years) [10]. Although a recent review of the literature suggested that the MELD score was not a reliable predictor of post-LT survival [11], the potential deleterious impact of a high MELD score on post-LT survival needs to be investigated.

The primary objective of this study was to determine the impact of the MELD-based "Liver Score" on waitlist and post-LT survivals. The secondary objectives of this study were to evaluate the discriminative capacity of the MELD score on post-LT survival and to determine factors associated with 1-year post-LT survival in patients transplanted for cirrhosis without HCC and MELD $\geq$35.

## Patients and methods

### Study population

This study was a cohort analysis using the French national CRISTAL database.

### Pretransplant cohort

The pretransplant cohort included all newly registered adult patients (≥18 years of age) on the French national waiting list for first single-organ liver transplantation between January 1, 2004, and December 31, 2012, in the 16 active liver transplant centers in France. A total of 12 664 patients were listed for transplantation during the study period. Candidates aged <18 years ($n$ = 771), as well as those listed for retransplantation ($n$ = 1081) or combined solid organ transplantation ($n$ = 385), recipients of living donor transplants ($n$ = 221), and patients transplanted with national priority status in an emergency setting ($n$ = 630) were excluded from the analysis (Fig. 1a). A total of 9576 patients were finally included in the pretransplant cohort.

Two cohorts of patients were constructed according to the date of implementation of the "Liver Score" in 2007: Cohort 1 corresponded to patients newly registered between 2004 and 2006 ($n$ = 2661), and cohort 2 corresponded to patients newly registered between 2007 and 2012 ($n$ = 6915).

### Post-transplant cohort

This post-transplant cohort included all consecutive patients aged 18 years or over undergoing liver



Transplant International 2019; 32: 1061–1073

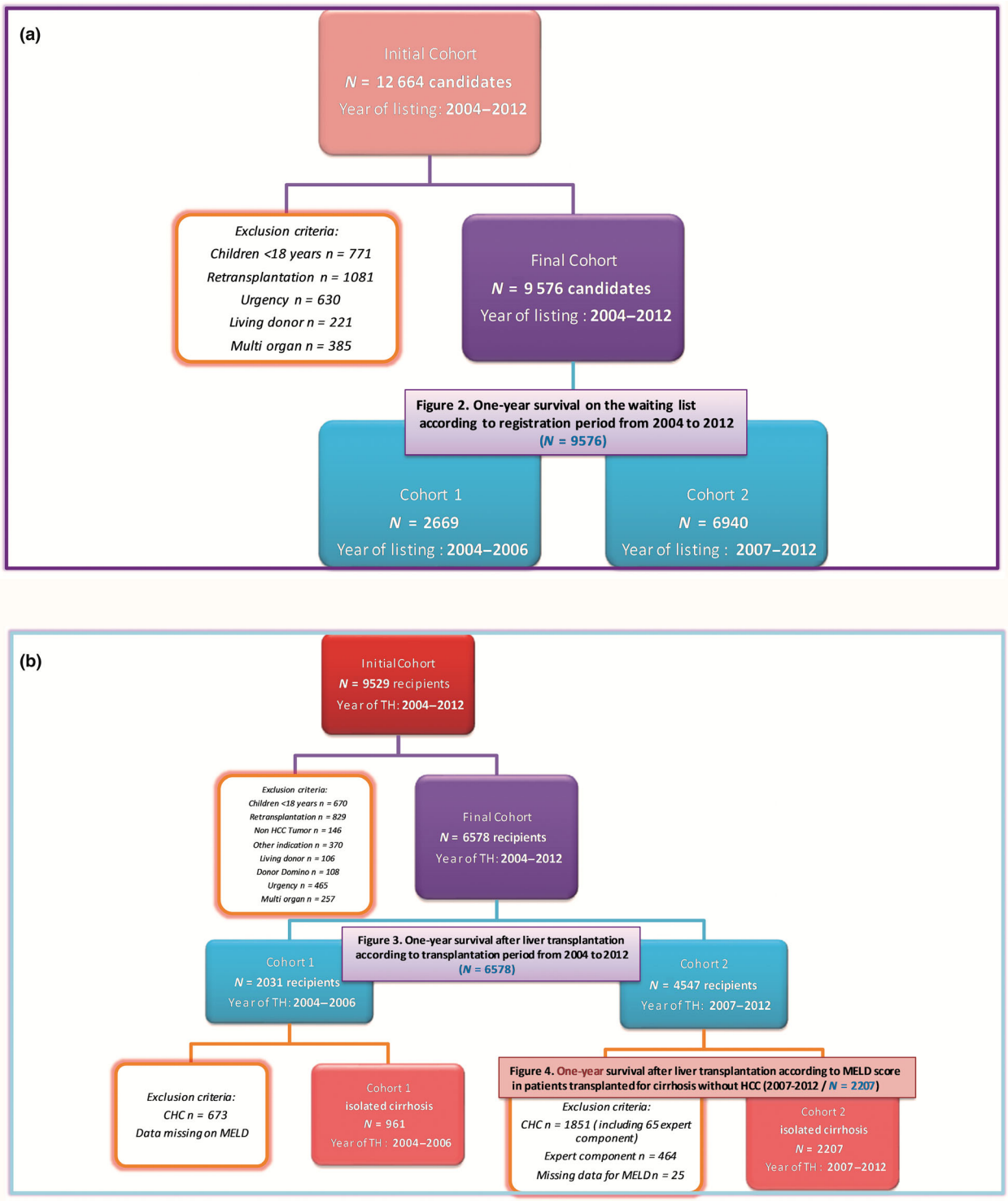



**Figure 1** Flowchart. (a) Candidate cohort. (b) Recipient cohort.

transplantation between January 1, 2004, and December 31, 2012, in the 16 accredited transplant centers in France. A total of 9529 patients were transplanted during the study period. In order to avoid recruitment bias, the following patients were excluded: (i) recipients of a living donor transplant ($n$ = 106), (ii) domino transplantation ($n$ = 108), (iii) patients transplanted with national priority status in an emergency setting ($n$ = 465), (iv) retransplantation ($n$ = 829), (v) multiorgan transplantation ($n$ = 257), and (vi) patients

transplanted for non-HCC tumor ($n = 146$) or for conditions other than HCC or cirrhosis ($n = 370$; Fig. 1b). A total of 6578 patients were finally included in the post-transplant cohort.

Two patient cohorts were constructed according to the date of implementation of the "Liver Score" in 2007: Cohort 1 corresponded to patients transplanted between 2004 and 2006 ($n = 2031$), and cohort 2 corresponded to patients transplanted between 2007 and 2012 ($n = 4547$) according to the "Liver Score." The characteristics of the recipients and 1-year post-transplant survivals were compared between the two cohorts.

The second part of the analysis exclusively concerned cohort 2 (year of LT: 2007–2012) restricted to isolated cirrhosis without HCC ($n = 2207$) in order to evaluate the impact of MELD on post-LT survival (exclusion of HCC, $n = 1851$; expert component, $n = 464$) and missing data for MELD ($n = 25$). Finally, the predictors of post-LT survival were determined in cohort 2 with MELD greater than 35.

### Data collection and variables recorded

CRISTAL is a national database initiated in 1996 and administered by the Agence de la biomédecine that prospectively collects data on all organ transplantation candidates, recipients, and donors in France together with candidate and recipient outcomes. The study was conducted in accordance with French legislation. According to French legislation, studies based on the national CRISTAL registry constitute part of the assessment of transplant outcomes and do not require ethics committee approval. Data are entered into the registry by each center. Data collection is mandatory. Variables potentially associated with outcomes were analyzed. Demographic, clinical, and laboratory data were collected at the time of listing, during pretransplant follow-up, at the time of transplant, and annually thereafter. Withdrawals from the waiting list and the deaths of patients were notified prospectively. Queries were performed to extract and subsequently analyze the following recipient characteristics at the time of transplantation: gender, age, indication for LT, pre-LT management, and MELD score at the time of LT. The main indication for LT was categorized into two groups: HCC and isolated cirrhosis.

The MELD score at the time of registration was considered for waitlist survival analysis, and the MELD score at the time of transplantation was considered for post-transplant survival analysis. The MELD score was calculated from laboratory parameters (INR, bilirubin, and creatinine) recorded on the day of registration or the day of LT. In the case of missing data at the time of transplantation, the variables recorded at registration or at last follow-up before LT were used. The following algorithm was used to calculate the MELD score: MIN (40,ROUND(10*(0.957*LOG(MIN(MAX (0.0113*CREAT,1),4)) + 0.378*LOG(MAX (0.06*BILI,1)) + 1.12*LOG(MAX(INR,1)) + 0.643))). The MELD score was categorized into 6 different groups of severity: <15, [15–20], [20–25], [25–30], [30–35], and [35–40]. The MELD [35–40] group was identified as a "high-risk group." MELD scores are only reported for the group of patients transplanted for cirrhosis without HCC, as the MELD score is less representative of the state of liver disease for the other indications for LT.

### Statistical analysis

Continuous variables are expressed as median and interquartile range. A chi-square test or two-sided Fisher's exact test was used to compare qualitative variables, and a Wilcoxon test was used to compare quantitative variables. Survival curves were estimated using the Kaplan–Meier method and were compared using the log-rank test.

The event assessed for the waitlist analysis was the 1-year waitlist mortality or delisting for worsening medical condition with censoring at transplantation, delisting for other reasons, or lost to follow-up. Survival time was defined as time between registration and the event. Cox proportional hazard models were performed to determine whether the period was associated with 1-year waitlist mortality.

The event assessed for the post-transplant analysis was the 1-year post-LT mortality, and survival time was defined as the time between transplantation and the event. To identify the predictors associated with 1-year post-transplant mortality, survival analysis was performed using a Cox proportional hazards model. Multivariate analysis included all variables associated with 1-year post-transplant mortality in univariate analysis at $P < 0.2$. The variables of the final model were selected by means of a backward stepwise procedure. Concordance probability estimation (CPE) was used to determine the discriminative capacity of the MELD score [12]. Observations with missing values for at least one of the predictive factors were excluded from the multivariate analysis. Statistical analyses were performed with SAS Enterprise Guide 7.1. $P < 0.05$ was considered to be statistically significant.

## Results

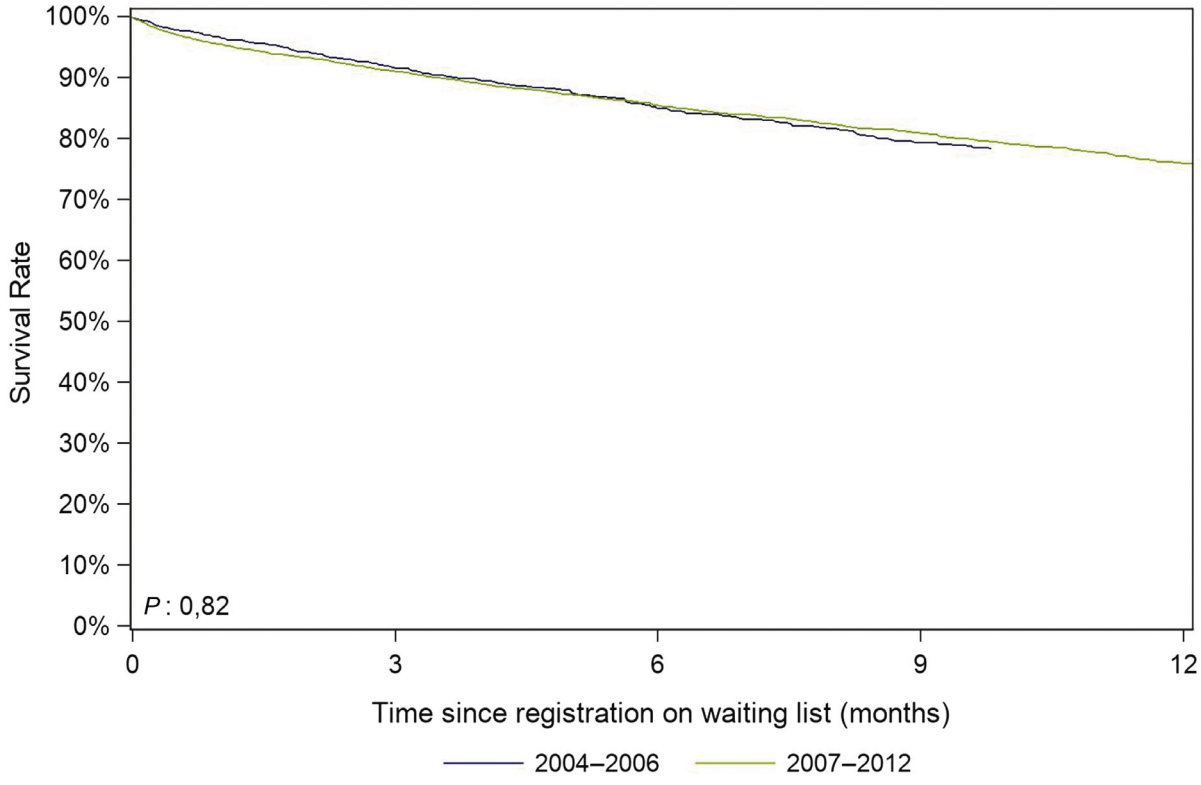
### Waitlist survivals

In patients with cirrhosis, the proportion of candidates with MELD < 15 at listing was lower in 2007–2012 than in 2004–2006 (24.4% vs. 63.8%; $P < 0.01$) and the proportion of MELD > 25 at listing was higher in 2007–2012 than in 2004–2006 (30.7% vs. 7.0%, $P < 0.01$).

The median waiting time was longer in 2007–2012 than in 2004–2006 (4.5 months vs. 2.9 months; $P < 0.01$). The overall 1-year waitlist survival was not significantly different between the two periods [76.0% (74.5–77.4%) in 2007–2012 vs. 74.0% (70.8–76.9%) in 2004–2006; $P = 0.82$] (Fig. 2). Similarly, in a univariate Cox model, the period was not associated with a higher risk of 1-year waitlist mortality or delisting for worsening medical condition [HR = 1.0 (0.9–1.1) $P = 0.9$]. In a bivariate Cox model with adjustment for the MELD score at listing that was strongly associated with 1-year waitlist mortality ($P < 0.0001$), the risk of 1-year waitlist mortality was significantly lower in 2007–2012: HR = 0.8 [0.7–0.9]; $P = 0.0002$.

### Comparison of the two cohorts at the time of LT

The main characteristics of the two cohorts at LT are presented in Table 1. Briefly, three-quarters of recipients were male in both cohorts ($P = 0.4$). The distribution of the two main indications for LT differed between the




| Period | N | 1-month survival | 3-month survival | 1-year survival |
|---|---|---|---|---|
| **2004–2006** | 2661 | 96.7% [95.9% – 97.3%] | 91.6% [90.3% – 92.7%] | 74.0% [70.8% – 76.9%] |
| Number of patients at risk* | | 2069 | 1308 | 295 |
| **2007–2012** | 6915 | 95.5% [94.9% – 96.0%] | 91.1% [90.3% – 91.8%] | 76.0% [74.5% – 77.4%] |
| Number of patients at risk* | | 5384 | 4139 | 1472 |

**Figure 2** One-year survival on the waiting list according to registration period from 2004 to 2012 ($N = 9576$).
*Number of patients not censored who are event free

**Table 1.** Patient characteristics in the two cohorts at the time of LT (2004–2012/*N* = 6578)

| Characteristics | Whole cohort (*N* = 6578) | | Cohort 1 2004–2006 (*N* = 2031) | | Cohort 2 2007–2011 (*N* = 4547) | | *P*-value |
|---|---|---|---|---|---|---|---|
| | *N* | % | *n* | % | *n* | % | |
| Gender | | | | | | | |
| Female | 1572 | 23.9 | 499 | 24.6 | 1073 | 23.6 | 0.4 |
| Male | 5006 | 76.1 | 1532 | 75.4 | 3474 | 76.4 | |
| Age at LT | | | | | | | |
| 18–29 | 151 | 2.3 | 51 | 2.5 | 100 | 2.2 | <0.01 |
| 30–55 | 3368 | 51.2 | 1161 | 57.2 | 2207 | 48.5 | |
| 56–65 | 2452 | 37.3 | 696 | 34.3 | 1756 | 38.6 | |
| ≥65 | 607 | 9.2 | 123 | 6.1 | 484 | 10.6 | |
| Indication for LT | | | | | | | |
| HCC | 2524 | 38.4 | 673 | 33.1 | 1851 | 40.7 | <0.01 |
| Cirrhosis | 4054 | 61.6 | 1358 | 66.9 | 2696 | 59.3 | |
| Management before LT[†] | | | | | | | |
| Outpatient | 5150 | 79.5 | 1749 | 86.1 | 3401 | 76.4 | <0.01 |
| Hospital | 754 | 11.6 | 190 | 9.4 | 564 | 12.7 | |
| Intensive care unit | 577 | 8.9 | 92 | 4.5 | 485 | 10.9 | |
| MELD score at LT[‡] | For isolated cirrhosis *n* = 3168 | | | | | | |
| <15 | 650 | 20.5 | 310 | 32.3 | 340 | 15.4 | <0.01 |
| 15–19 | 781 | 24.7 | 322 | 33.5 | 459 | 20.8 | |
| 20–24 | 710 | 22.4 | 194 | 20.2 | 516 | 23.4 | |
| 25–29 | 463 | 14.6 | 83 | 8.6 | 380 | 17.2 | |
| 30–34 | 267 | 8.4 | 33 | 3.4 | 234 | 10.6 | |
| ≥35 | 297 | 9.4 | 19 | 2.0 | 278 | 12.6 | |

[*]Ninety seven missing data.

[†]cf Flowchart (Fig. 1) cohort for analysis of MELD: period 1 *n* = 961 and period 2 *n* = 2207.

two cohorts with a higher rate of HCC in cohort 2 (40.7% vs. 33.1%; $P < 0.01$) and a lower rate of cirrhosis (59.3% vs. 66.9%). Patients of cohort 2 were significantly older (age >56 years: 49% vs. 40%; $P < 0.01$) and more severely ill with a higher hospitalization rate before LT (24% vs. 14%; $P < 0.01$) and higher mean MELD scores. In the group of patients transplanted for isolated cirrhosis, the proportion of recipients with MELD score at LT ≥ 35 increased from 2.0% in 2004–2006 to 12.6% in 2007–2012 ($P < 0.01$) with a median MELD score increasing from to 15 (range: 6–40) to 17 (range: 6–40; $P < 0.01$; data not shown). Ischemia time decreased in 2007–2012 [median 8.3 h (7–10) vs. 9 h (7–11) in 2004–2006; <0.01] (data not shown).

### Comparison of 1-year post-LT survivals between the two cohorts

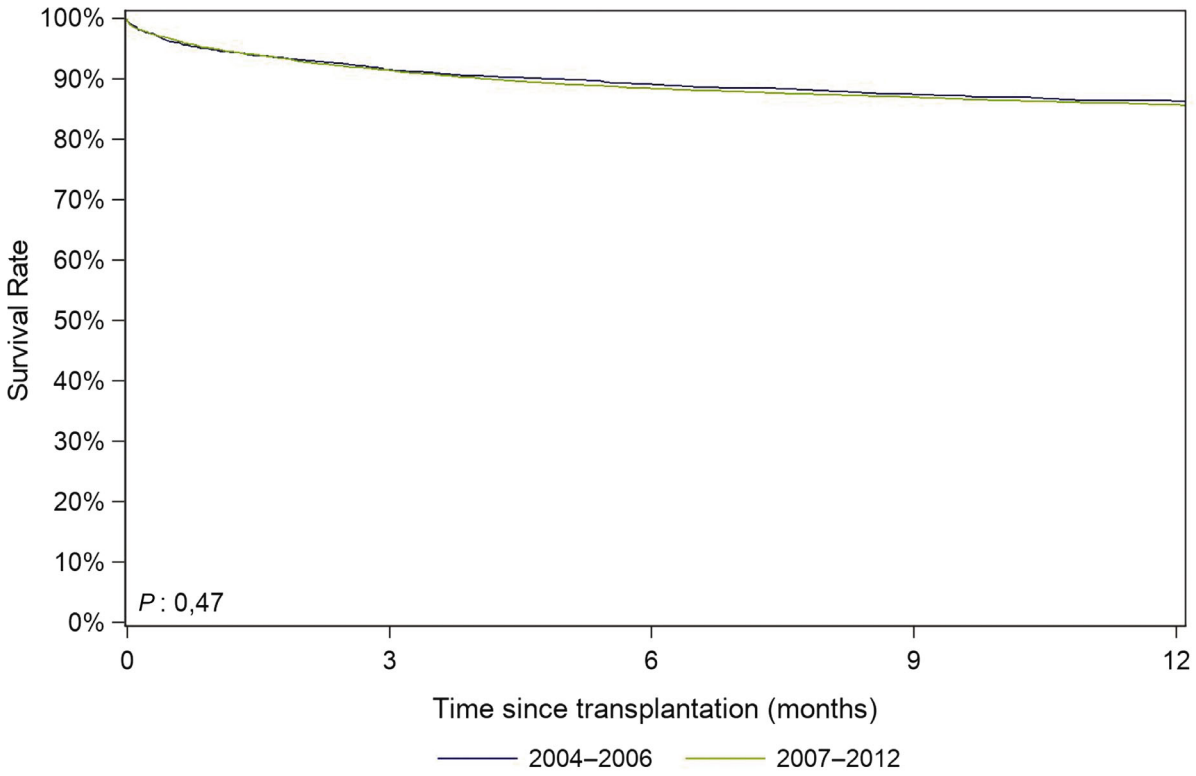
Despite the increased number of transplanted patients with higher MELD scores, 1-year post-LT survival was not significantly different between the two cohorts: 86.3% [84.8–87.8%] in cohort 1 vs. 85.7% [84.7–86.7%] in cohort 2; $P = 0.5$ (Fig. 3), and this result was also true in the subgroup of isolated cirrhosis without HCC. In multivariate Cox regression analysis including MELD score at the time of LT, recipient and donor age, waiting time, and indication for LT, the period of LT was not significantly associated with 1-year post-LT mortality [HRa: 1.0; 95% CI: (0.8–1.1), $P = 0.7$].

### Factors associated with 1-year post-LT survival: impact of MELD score

Secondary analysis was performed in cohort 2 (years 2007–2012) restricted to patients transplanted for isolated cirrhosis without HCC. Patients transplanted with a MELD score ≥35 had a lower 1-year post-LT survival than the other patients [74.8% (69.2–79.5%) vs. 86.3% (84.7–87.8%); $P < 0.01$] (Fig. 4a), as observed in a univariate Cox model for 1-year post-LT mortality HR = 2.1 (1.4–3.0; $P < 0.01$) (Table 2). However, the CPE was calculated in order to determine the general discriminative capacity of MELD score on post-LT survival and showed a poor discriminative capacity with a CPE of 0.57 (SD = 0.02).



Transplant International 2019; 32: 1061–1073



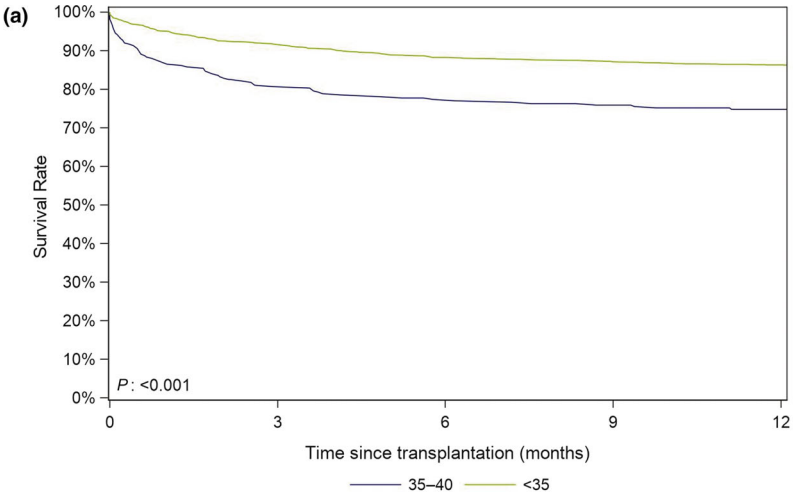

| Period | N | 1-month Survival | 3-month Survival | 1-year Survival |
|---|---|---|---|---|
| **2004–2006** | 2031 | 94.8% [93.8% – 95.7%] | 91.6% [90.3% – 92.7%] | 86.3% [84.8% – 87.8%] |
| Number of patients at risk* | | 1896 | 1827 | 1705 |
| **2007–2012** | 4547 | 95.0% [94.3% – 95.6%] | 91.4% [90.6% – 92.2%] | 85.7% [84.7% – 86.7%] |
| Number of patients at risk* | | 4233 | 4056 | 3715 |

**Figure 3** One-year survival after liver transplantation according to transplantation period from 2004 to 2012 (*N* = 6578).
*Number of patients not censored who are event free

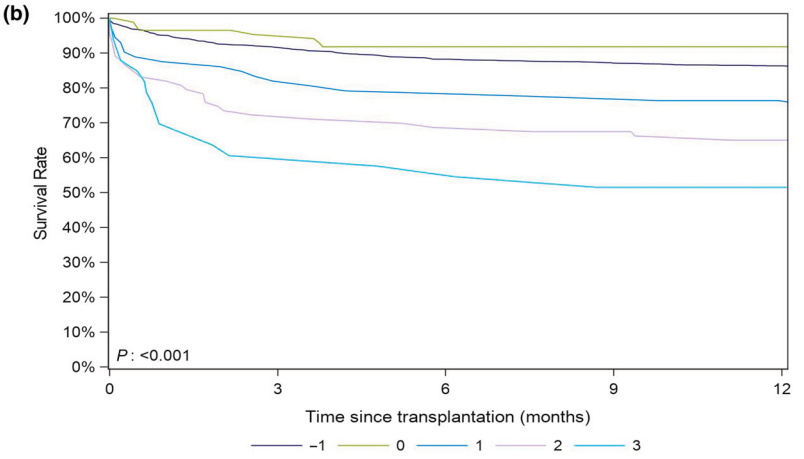
As expected, recipients with a MELD score ≥35 at LT had a poorer general status with higher hospitalization rates of 89% vs. 29% ($P < 0.01$) and a higher rate of intensive care unit admission (63% vs. 12%, $P < 0.01$), and a higher complication rate (58% vs. 30%, $P < 0.01$; data not shown). These patients also had higher dialysis rates before LT (35% vs. 1%, $P < 0.01$) and a lower glomerular filtration rate (GFR; 49 vs. 94, $P < 0.01$). Finally, they also more often required intubation and respiratory assistance (29% vs. 4%, $P < 0.01$; Table 3). Using a univariate Cox survival model, MELD score at LT >35, GFR <60, and intubation were significantly associated with higher 1-year post-LT mortality [HR = 2.1 (1.4–3.0), 3.7 (2.6–5.2), and 2.7 (2.1–3.7), respectively] (Table 2). Using a multivariate Cox survival model, only intubation and renal failure were independently associated with higher 1-year post-LT mortality [2.0 (1.4–2.8), $P < 0.01$ and 2.3 (1.1–3.8), respectively, $P < 0.01$], while a MELD score ≥35 was not associated with higher 1-year post-LT mortality [HR = 1.1 (0.8–1.7), $P = 0.5$; Table 2].

### Factors associated with 1-year post-LT survival in patients with isolated cirrhosis without HCC and MELD ≥35

In cohort 2, at least one complication at the time of transplantation was reported in 58% of patients with



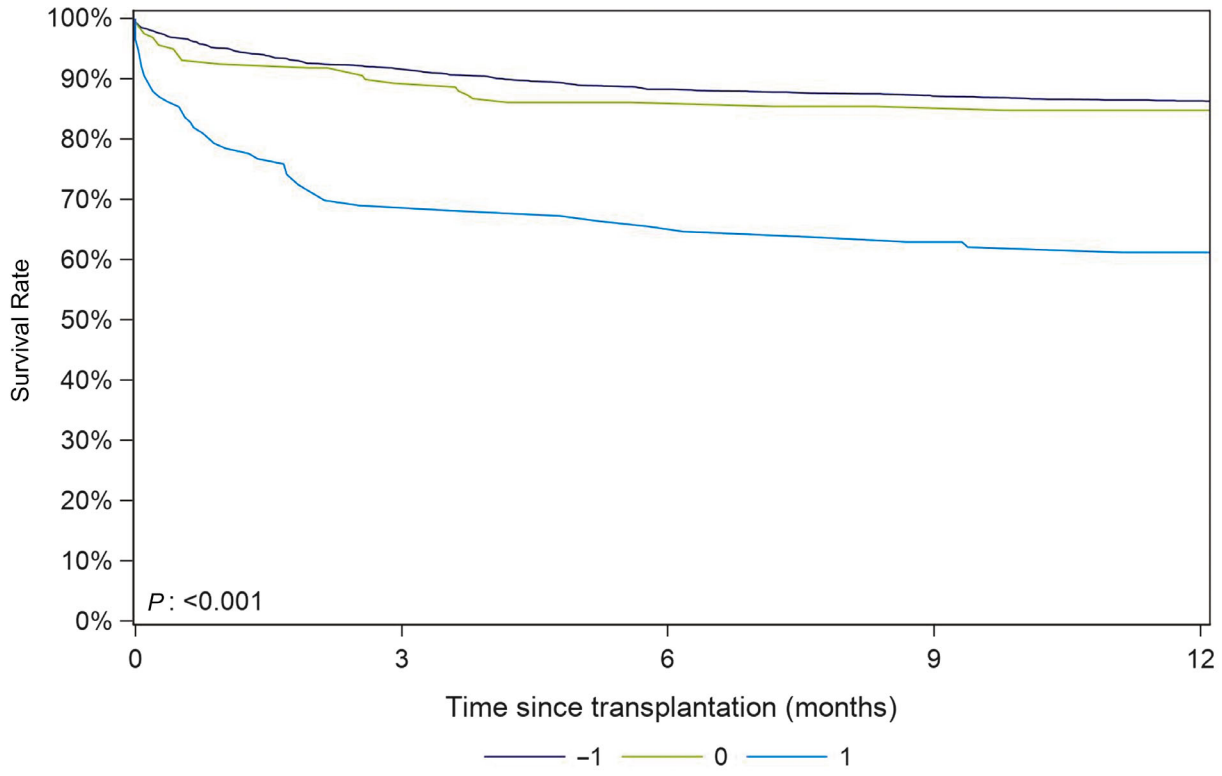

| MELD score | *N* | 1-month survival | 3-month survival | 1-year survival |
|---|---|---|---|---|
| MELD<35 | 1929 | 95.1% [94.0% – 96.0%] | 91.6% [90.3% – 92.8%] | 86.3% [84.7% – 87.8%] |
| Number of patients at risk* | | 1798 | 1724 | 1587 |
| MELD 35 — 40 | 278 | 86.9% [82.3% – 90.4%] | 80.7% [75.5% – 84.9%] | 74.8% [69.2% – 79.5%] |
| Number of patients at risk* | | 238 | 220 | 196 |




| MELD score and risk factors | *N* | 1-month survival | 3-month survival | 1-year survival |
|---|---|---|---|---|
| -1 MELD < 35 | 1929 | 95.1% [94.0% – 96.0%] | 91.6% [90.3% – 92.8%] | 86.3% [84.7% – 87.8%] |
| Number of patients at risk* | | 1798 | 1724 | 1587 |
| 0 MELD ≥ 35 and No intubation, no dialysis, no sepsis[1] | 90 | 96.5% [89.6% – 98.9%] | 95.3% [88.0% – 98.2%] | 91.8% [83.6% – 96.0%] |
| Number of patients at risk* | | 83 | 81 | 74 |
| 1 MELD ≥ 35 and One of these factors: intubation, dialysis, sepsis | 72 | 87.5% [77.4% – 93.3%] | 81.9% [70.9% – 89.1%] | 76.4% [64.8% – 84.6%] |
| Number of patients at risk* | | 63 | 59 | 53 |
| 2 MELD ≥ 35 and (Intubation and dialysis) or (sepsis and dialysis) | 83 | 83.1% [73.2% – 89.6%] | 72.3% [61.3% – 80.6%] | 65.0% [53.7% – 74.2%] |
| Number of patients at risk* | | 69 | 60 | 52 |
| 3 MELD ≥ 35 and Intubation and sepsis (+/– dialysis) | 33 | 69.7% [51.0% – 82.4%] | 60.6% [42.0% – 74.9%] | 51.5% [33.5% – 66.9%] |
| Number of patients at risk* | | 23 | 20 | 17 |

[1] *sepsis = septicemia, ascitic fluid infection, or pneumonia*

**Figure 4** (a) One-year survival after liver transplantation according to model for end-stage liver disease (MELD) score in patients transplanted for cirrhosis without hepatocellular carcinoma (HCC; 2007–2012/*N* = 2207). (b) One-year survival after liver transplantation according to MELD score and risk factors in patients transplanted for cirrhosis without HCC (2007–2012/*N* = 2207). (c) One-year survival after liver transplantation according to MELD score and risk factors in patients transplanted for cirrhosis without HCC (2007–2012/*N* = 2207).
*Number of patients not censored who are event free




| MELD score and prognosis | N | 1-month survival | 3-month survival | 1-year survival |
|---|---|---|---|---|
| -1 MELD < 35 | 1929 | 95.1% [94.0% – 96.0%] | 91.6% [90.3% – 92.8%] | 86.3% [84.7% – 87.8%] |
| Number of patients at risk* | | 1798 | 1724 | 1587 |
| 0 MELD ≥ 35 good prognosis[1] | 162 | 92.4% [87.1% – 95.6%] | 89.3% [83.3% – 93.2%] | 84.8% [78.1% – 89.5%] |
| Number of patients at risk* | | 146 | 140 | 127 |
| 1 MELD ≥ 35 bad prognosis[2] | 116 | 79.3% [70.7% – 85.6%] | 69.0% [59.7% – 76.5%] | 61.2% [51.7% – 69.4%] |
| Number of patients at risk* | | 92 | 80 | 69 |

[1] *Good prognosis: no or one risk factor (intubation, dialysis, or infection)*

[2] *Poor prognosis: two or three risk factors (intubation, dialysis, or infection)*

**Figure 4** Continued.
*Number of patients not censored who are event free

isolated cirrhosis and MELD ≥35: intubation in 31%, dialysis in 35%, sepsis in 32% (septicemia, ascites or pneumonia), and intensive care unit admission in 63% (Table 3). Patients with MELD ≥35 at LT also had a MELD ≥35 at registration in 61.5% of cases.

Using univariate Cox survival model, factors associated with 1-year post-LT mortality in patients with isolated cirrhosis without HCC and MELD ≥35 were as follows: intubation, sepsis (septicemia, ascites or pneumonia), dialysis, gastrointestinal bleeding, hepatorenal syndrome, pulmonary hypertension, intensive care unit admission, waiting time longer than 7 months, MELD >40, and HCV-related cirrhosis (Table 3).

In a multivariate Cox model, factors associated with 1-year post-liver transplant mortality in patients with isolated cirrhosis without HCC and MELD ≥35 were as

**Table 2.** Cox regression analysis for 1-year mortality after liver transplantation (univariate and multivariate) in patients transplanted for cirrhosis without hepatocellular carcinoma (2007–2012/*N* = 2207)

| | | | Univariate analysis | | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|---|---|---|
| Variables | *N* | % | % 1-year death | HR | 95% CI | *P* | HRa | 95% CI | *P*-value |
| MELD score at transplantation | | | | | | | | | |
| <35 | 1929 | 87.4 | 13.4 | 1 | – | <0.01 | 1 | – | 0.5 |
| ≥35 | 278 | 12.6 | 24.8 | 2.0 | 1.6–2.6 | | 1.1 | 0.8–1.7 | |
| Intubation | | | | | | | | | |
| No | 2052 | 93.0 | 13.5 | 1 | | <0.01 | 1 | | <0.01 |
| Yes | 155 | 7.0 | 32.3 | 2.7 | 2.1–3.7 | | 2.0 | 1.4–2.8 | |
| GFR (glomerular filtration rate) | | | | | | | | | |
| >90 | 1079 | 48.9 | 11.4 | 1 | – | <0.01 | 1 | – | <0.01 |
| 60–89 | 591 | 26.8 | 14.7 | 1.3 | 1.0–1.7 | | 1.3 | 1.0–1.7 | |
| 30–59 | 357 | 16.2 | 18.2 | 1.7 | 1.2–2.2 | | 1.6 | 1.2–2.2 | |
| 15–29 | 66 | 3.0 | 18.2 | 1.7 | 0.9–3.0 | | 1.3 | 0.7–2.4 | |
| <15 or dialysis | 114 | 5.2 | 35.1 | 3.7 | 2.6–5.2 | | 2.3 | 1.4–3.8 | |

**Table 3.** Cox regression for 1-year mortality after liver transplantation (univariate and multivariate) in patients transplanted for cirrhosis without hepatocellular carcinoma and MELD ≥35 (2007–2012/*N* = 278)

| | | | Univariate analysis | | | | Multivariate analysis *N* = 230 | | |
|---|---|---|---|---|---|---|---|---|---|
| Variables | *N* | % | % 1-year death | HR | 95% CI | *P*-value | HR | 95% CI | *P*-value |
| Intubation/ventilation | 81 | 30.9 | 37.0 | 2.4 | 1.4–3.9 | <0.01 | 2.3 | 1.3–4.1 | <0.01 |
| Infection[†] | 77 | 32.4 | 35.1 | 2.2 | 1.3–3.8 | <0.01 | 2.8 | 1.3–6.3 | 0.01 |
| Dialysis | 93 | 34.6 | 35.5 | 2.1 | 1.3–3.3 | <0.01 | 2.3 | 1.0–5.1 | 0.049 |
| One complication[‡] | 161 | 57.9 | 30.4 | 1.9 | 1.1–3.2 | 0.02 | | | |
| Gastrointestinal bleeding | 25 | 10.6 | 36.0 | 1.9 | 0.9–3.9 | 0.08 | | | |
| Hepatorenal syndrome | 108 | 46.0 | 30.6 | 1.9 | 1.1–3.4 | 0.02 | | | |
| Pulmonary hypertension | 14 | 6.3 | 42.9 | 2.6 | 1.1–6.1 | 0.03 | | | |
| Intensive care unit | 170 | 63.2 | 29.4 | 1.9 | 1.1–3.4 | 0.02 | | | |
| Waiting time >7 months | 18 | 6.5 | 38.9 | 1.9 | 0.9–4.2 | 0.1 | | | |
| MELD >40 | 119 | 42.8 | 30.3 | 1.5 | 0.9–2.5 | 0.09 | | | |
| HCV-related cirrhosis | 37 | 13.3 | 35.1 | 1.7 | 0.9–3.0 | 0.1 | | | |
| Age ≥65 | 25 | 9.0 | 36.0 | 1.6 | 0.8–3.1 | 0.22 | | | |
| Male | 78 | 28.1 | 25.0 | 1.1 | 0.6–1.8 | 0.8 | | | |
| BMI ≥26 | 157 | 56.5 | 26.8 | 1.2 | 0.8–2.0 | 0.4 | | | |
| Hydrothorax | 24 | 10.6 | 35.1 | 1.3 | 0.6–3.0 | 0.5 | | | |
| MELD at registration ≥35 | 171 | 61.5 | 26.9 | 1.3 | 0.8–2.1 | 0.3 | | | |

[*]Infection = septicemia, ascitic fluid infection, or pneumonia.

[†]At least one complication among the following: gastrointestinal bleeding, hepatorenal syndrome, pulmonary hypertension, septicemia, ascitic fluid infection or pneumonia, and hydrothorax.

follows: intubation (HR = 2.3; 95% CI: 1.3–4.1; $P < 0.01$), sepsis (septicemia, ascites, or pneumonia; HR = 2.8; 95% CI: 1.3–6.3; $P = 0.01$), and dialysis (HR = 2.3; 95% CI: 1.0–5.1; $P = 0.05$; Table 3). The discriminative capacity of this model determined by the CPE was 0.67. Interestingly, cirrhotic patients with MELD score ≥35 without renal or respiratory failure or infection had a 1-year post-LT survival of 91.8% (95% CI: 83.6–96.0%; Fig. 4b). Cirrhotic patients with a MELD score ≥35 and good prognosis (no or only one risk factor) had a fairly similar 1-year post-LT survival rate to that observed in patients with a MELD score <35

[84.8% (78.1–89.5%) vs. 86.3% (84.7–87.8%)], whereas patients with a MELD score ≥35 presenting 2 or 3 risk factors (dialysis, intubation or infection) had a lower 1-year survival of 61.2% (51.7–69.4%) ($P < 0.01$; Fig. 4c).

## Discussion

This is the first French national survey designed to objectively analyze the impact of our new MELD-based allocation system on waitlist and post-LT survivals. Two large-scale cohorts of patients registered and transplanted before and after inclusion of the MELD score in a "liver score" were compared, and the main findings can be summarized as follows: (i) Candidates on the waiting list had higher MELD scores at the time of listing; (ii) overall survival on the waiting list was similar between the two periods and, after adjustment for MELD score, the risk of waitlist mortality was reduced during the second period; (iii) patients transplanted since 2007 were older, more severely ill, and had higher MELD scores; (iv) 1-year post-transplant overall survival was nevertheless similar between the two LT periods; (v) in cirrhotic recipients, patients transplanted with MELD score ≥35 had lower 1-year post-LT compared to those with MELD <35, but the MELD score at LT presented a low discriminative capacity to predict post-transplant survival; (vi) the lower survival observed in the MELD 35–40 subgroup can be explained by higher intubation and renal failure rates; (vii) intubation, sepsis (septicemia, ascites, or pneumonia), and dialysis were associated with a higher risk of 1-year post-transplant mortality in cirrhotic patients with MELD ≥35; and (viii) cirrhotic patients with a MELD score ≥35 and good prognosis (no or only one risk factor) had a fairly similar 1-year post-LT survival rate to that observed in patients with a MELD score <35, whereas patients with a MELD score ≥35 presenting 2 or 3 risk factors (dialysis, intubation, or infection) had a lower 1-year survival of 61%.

Not surprisingly, the introduction of MELD as the pivotal allocation criterion resulted in transplantation of more severely ill patients due to facilitated access to liver transplants and an expected short waiting time for those more severely ill patients according to the "sickest first policy" [13] and subsequent reduced access to transplantation for HCC patients. The new system induced a change of listing policies with registration of candidates with higher MELD scores. Nevertheless, waitlist survival was not decreased and was even increased when adjusting for MELD score, demonstrating the benefit of the "sickest first policy." Furthermore, despite reduced access to transplantation in the subgroups of HCC candidates, no significant difference in terms of waitlist survival was observed.

Interestingly, in our nationwide experience, this change in the allocation criteria had no sustained impact on post-transplant overall survival. Although the MELD score has been clearly associated with the risk of mortality in different chronic liver disease settings [4,5] and remains an accurate tool to predict waiting list mortality [6], the use of the MELD to stratify the risk of post-LT mortality remains controversial. In a recent study, all of the models investigated (MELD score and 8 MELD score variants) failed to reach relevant areas under the ROC curve greater than 0.7 for the prediction of post-LT mortality [14], which is not surprising, as many other validated factors are involved in the outcome of LT candidates, such as general fitness, recipient and donor ages, liver graft features, and hospitalization status (ICU), which are not integrated in the MELD score. Conflicting results have therefore been reported in the literature. In 2009, Weismüller *et al.* [9] demonstrated 10% increase in 3-month mortality at their transplant center in the Eurotransplant zone after the adoption of MELD-based allocation as a result of pretransplant factors. These conflicting results, compared to the results of the present study, could be explained by differences in pretransplant patient selection and clinical management, especially for patients with high MELD scores and complex morbidity. Another retrospective longitudinal analysis of United Network for Organ Sharing (UNOS) data on all liver transplantations performed between February 2002 and June 2011, including 33 398 transplant recipients, showed that overall post-transplant patient survival was inversely correlated with increasing MELD score, but LT in recipients with MELD scores ≥40 achieved acceptable long-term survival outcomes [15]. Moreover, another recent analysis of UNOS data from 2002 to 2013, based on 50 838 transplant recipients, showed a significant interaction between MELD score and hospitalization status on post-LT survival. Compared to hospitalized patients with a MELD score of 30–34, ICU patients with a MELD score ≥35 had significantly higher 3-, 6-, and 12-month post-transplant mortality rates. In this study, pretransplant ICU status modified the risk of early post-transplant mortality, independently of MELD score [16].

In our study, although patients transplanted with a MELD score ≥35 had a lower 1-year post-transplant survival, MELD *per se* was not a predictive factor of post-transplant survival in cirrhotic patients without HCC, as the CPE of the MELD score at LT presented a low discriminative capacity in terms of survival, close to

a random value. The lower survival in supposedly high-risk candidates can mainly be explained by higher rates of intubated and dialyzed patients in this group. Intubation and dialysis, related to intensive care management, were independently associated with post-transplant survival in the study by Bitterman *et al.* [16]. The combination of intensive care unit hospitalization before LT, mechanical ventilation, and renal failure must be investigated as potential future futility predictors of LT in future dedicated studies.

This study highlights that the presence of renal and respiratory failure as well as sepsis (septicemia, ascites, or pneumonia) was more predictive of post-LT survival than the severity of liver disease. The collective benefit of transplanting high-MELD patients presenting at least 2 risk factors among renal failure, respiratory failure, and infection (ascites, septicemia, or pneumonia) is questionable, as the 1-year post-transplant survival rate of these patients is only 61% compared to 92% for patients with none of these risk factors. In the age of severe organ shortage, LT should not be contraindicated in patients with a high MELD score, but LT may not be formally indicated in patients who are intubated, infected, or dialyzed at the time of transplantation. Another warning signal demonstrated by this study is the poorer survival trend in patients registered and transplanted with MELD $\geq$35, suggesting that these patients may not have undergone extensive screening before LT comprising cardiopulmonary exercise tests and/or management of renal failure because of their compromised general status. The Liver Transplant Survival Index LTSI-35, which identifies risk factors for graft loss in a high-MELD population (MELD $\geq$35) including ventilator support and portal vein thrombosis, could also be useful to guide the selection of high-MELD patients [17].

Finally, the introduction of MELD as an allocation criterion has led to registration and transplantation of more severely ill patients. However, this trend had no sustained impact on 1-year waitlist and post-transplant survivals. In this age of organ shortage, transplantation in "acute cirrhotic ICU patients," presenting at least 2 risk factors from among renal failure, respiratory failure, and sepsis (ascites, septicemia, or pneumonia), should be discussed case by case due to the expected lower post-LT survival of these patients.

One step toward optimizing the liver allocation system could consist of including in the system a survival benefit score such as the LivAS [18] developed in order to balance urgency versus efficacy. Luo *et al.* [19] demonstrated that "candidates with higher MELD scores benefit more from liver transplantation, so [...] directing livers to the sickest patients maximizes survival benefit." An alternative option would be to develop a national score such as the optimized prediction of mortality (OPOM) score developed by using machine learning optimal classification tree models [20].

## Authorship

CJ: conceived and designed the study, performed statistical analysis, interpreted the results, and wrote the manuscript. CF: conceived and designed the study, interpreted the results, critically revised the manuscript, and wrote the manuscript. CA: conceived and designed the study, interpreted the results, supervised the study, and wrote the manuscript. CL: conceived and designed the study, interpreted the results, and critically revised the manuscript. FD: conceived and designed the study, interpreted the results, and critically revised the manuscript. SD: conceived and designed the study, wrote the manuscript, interpreted the results, critically revised the manuscript, and supervised the study.

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## Conflicts of interest

Sebastien Dharancy reports receiving consulting fees from Novartis and lecture fees from MSD, Gilead, Astellas, and BMS, and serving as a board member of Novartis and Astellas. None of these activities present a conflict of interest concerning this work. Claire Francoz reports receiving consulting fees. François Durand reports receiving consulting fees. Carine Jasseron and the other co-authors have no conflict of interest in regard to this study.

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