Modelling Kidney Outcomes Based On MELD Eras - Impact of MELD Score In Renal Endpoints After Liver Transplantation

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Abstract

Background: Acute kidney injury is a common complication in solid organ transplants, notably liver transplantation. The MELD is a score validated to predict mortality of cirrhotic patients, which is also used for organ allocation, however the influence of this allocation criteria on AKI incidence and mortality after liver transplantation is still uncertain.

Methods: This is a retrospective single center study of a cohort of patients submitted to liver transplant in a tertiary Brazilian hospital: Jan/2002 to Dec/2013, divided in two groups, before and after MELD implementation (pre MELD and post MELD). We evaluate the differences in AKI based on KDIGO stages and mortality rates between the two groups.

Results: 874 patients were included, 408 in pre-MELD and 466 in the post MELD era. The proportion of patients that developed AKI was lower in the post MELD era ($p = 0.04$), although renal replacement therapy requirement was more frequent in this group ($p < 0.01$). Overall mortality rate at 28, 90 and 365 days was respectively 7%, 11% and 15%. The 1-year mortality rate was lower in the post MELD era (20% vs. 11%, $p < 0.01$). AKI incidence was 50% lower in the post MELD era even when adjusted for clinically relevant covariates ($p < 0.01$).

Conclusion: Liver transplants performed in the post MELD era had a lower incidence of AKI, although there were more cases requiring dialysis. 1-year mortality was lower in the post MELD era, suggesting that patient care was improved during this period.

Background

Liver transplantation (LT) is preferred therapy for individuals with advanced chronic liver disease and those with acute liver failure¹. Disparities among grafts distribution and patient selection force transplant policies to draw a specific liver allocation criterion that include MELD score²⁻⁵. From the past 10 years, this score has been used by the UNOS, Eurotransplant for prioritizing allocation of liver transplants and Brazilian liver allocation policy instead of the previous CPT score^{2,6,7}.

MELD score based liver allocation policy continues under discussion, especially because some authors criticize that patients with remarkably high scores are too sick to undergoing liver transplantation⁷. Other studies call attention to the increasing prevalence of hepatocellular carcinoma that could lead patients without this condition to receive a liver transplant late – because hepatocellular carcinoma diagnosis supplements MELD scores irrespective to laboratorial data⁸. On the other hand, this allocation policy can reduce the time on the waiting list for LT and mortality from all causes of the patient with end-stage liver disease^{9,10}.

Patients undergoing LT frequently experience some degree of AKI through the perioperative period of LT¹¹. This AKI could be explained by liver transplantation by itself plus additional insults to the kidney, such

as hemorrhage¹², administration of nephrotoxic drugs^{12,13}, post reperfusion syndrome¹⁴, hypotension¹⁵ and often substantial blood transfusion¹⁶. Although kidney injury is usually reversible, it implies some complications, such as increased length of hospitalization, longer mechanical ventilation time, sepsis, and progression to chronic renal failure, directly contributing to lower liver graft and patient survival^{16,17}.

Serum creatinine is a cornerstone of AKI diagnosis in general population¹¹. Despite interferences in end-stage liver disease and post LT, this test is still consistent for AKI diagnosis in these setting¹⁸. Also, MELD score employs serum creatinine as a variable, and it's known that end stage liver disease patient with AKI is more likely to receive a higher priority in transplantation list based on MELD score¹⁹.

Few studies report time disparities in kidney disfunction after LT based on MELD score-based liver allocation policy implementation. Lee et al. failed to demonstrate differences between three ages (1996–2000 / 2001–2005 / 2006–2008) in identifying chronic kidney disease in a cohort of 431 patients after 6 months of LT²⁰. Leithead et al. shows increase in incidence of AKI over 3 study periods (2000–2003, 2004–2007 and 2008–2011) even after adjusted for confounding variables²¹. However, this United Kingdom cohort adopts LT allocation policy with a different model – the UKELD score-based model for LT, a slightly different score compared with MELD score⁵.

Considering the high incidence of AKI in LT recipients, we proposed this observational study to evaluate the impact of MELD score-based liver allocation policy implementation on AKI diagnosis, classification, RRT requirement, and mortality.

Methods

This study was approved by local ethics committee of the Hospital Israelita Albert Einstein and informed consent were waived by the same committee - (number 00737118.6.0000.0071), São Paulo, Brazil. The study protocol agrees with the good clinical practices guideline of the Declaration of Helsinki.

Data collection

Data were collected from a series of liver transplants performed at the Hospital Israelita Albert Einstein, São Paulo, Brazil from January 2002 to December 2014 from living and deceased donors. Patients extracted until December 2006 were labelled as pre-MELD ERA, while patients after January 2007 as post MELD ERA. All transplantation recipients were admitted to the ICU in the immediate postoperative period. Before January 2007, the allocation of organs for liver transplantation was done by waiting time on the list, and subsequently started to be based on the MELD score.²² This study adheres to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines for the reporting of cohort studies – STROBE²³

Medical records for patients undergoing LT from 2002 to 2014 were retrospectively reviewed to reclaim hospitalization clinical data, including baseline demographic characteristics and comorbidities,

preoperative clinical and laboratory records, main indication of LT, liver disease stage according to the CPT and MELD score, and intraoperative variables including liver graft donor type, surgical time, total ischemia period, vasopressor and transfusion requirement. Admission eGFR was calculated by MDRD equation as formerly recommended for cirrhotic patients ¹¹.

A single surgical team, all particularly trained in LT, performed all procedures. The immunosuppressive routine lay on a calcineurin inhibitor (cyclosporine predominantly until 2005 and tacrolimus later), an antiproliferative drug (mycophenolate) and a corticosteroid. Whole blood levels of calcineurin inhibitor were measured by fluorescence polarization immunoassay.

Postoperative variables included the development of sepsis, need for vasopressor drugs, use of well-recognized nephrotoxic agents, including radiocontrast agents, nonsteroidal anti-inflammatory drugs, and antimicrobials (vancomycin, aminoglycosides, polymyxin B and amphotericin B). APACHE II score or SAPS3 were determined at the time of admission to the ICU ^{24,25}. MELD score was calculated according to the equation described by Kamath and coworkers ^{3,4}. Sepsis was defined consistent with the international consensus definition ²⁶. Severe liver graft dysfunction included primary nonfunction and graft dysfunctions according to a former described criterion for liver failure ^{27,28}.

AKI was defined according to the AKI KDIGO recommendations ²⁹. Exact dates of AKI event and stage reached in seven days were obtained by computerized scanning of the results of daily laboratory tests for serum creatinine and 24-h urinary output from the electronic record system for each LT as the index event. RRT was initiated at the discretion of the nephrology team, based on common clinical indications such as hypervolemia, hyperkalemia, refractory acidosis, uremic sign or symptoms, and/or anuria. All attending nephrologists were part of the same group. Patients who developed AKI before LT or required RRT prior to LT were excluded from this analysis, as well as those receiving simultaneous kidney and liver transplant or who underwent liver re-transplantation. The main predictor variable of interest for the primary outcome was the period which LT were performed (Before or after MELD score-based liver allocation policy implementation, Pre-MELD and Post MELD, respectively).

The primary outcome in this analysis was AKI development after LT. Secondary outcomes were death for any cause, RRT requirement, AKI stages and RRT duration.

Statistical analysis

Numerical variables were labelled by median and interquartile range, and categorical variables by absolute and relative frequencies. For appraisal of baseline characteristics regarding the main predictor variable and primary outcome, univariable analysis was performed with the chi-squared test and Mann-Whitney U test for categorical and continuous variables, respectively. A multiple imputation approach was used to create homogeneity among APACHE 2 and SAPS 3 scores – the first were ICU elected score until December 2011, while SAPS 3 surpass this one after January 2012.

Univariable analysis was performed to identify additional variables associated with primary outcome as potential confounders, with each variable in the database entered a logistic regression as a single covariate with AKI diagnosis as dependent variable. Those variables with a p value <0.1 in univariable analysis or with undoubtedly clinical relevance were subsequently entered into a multivariable logistic model. A Cox proportional hazard model were performed within the main predictor (MELD era), clinical variables and AKI classification as covariates and one-year survival as independent variable. All tests were performed using SPSS version 26.0 (SPSS, Chicago, IL).

Results

Among 991 patients, 874 were included in final analysis, 408 (41.7%) patients were labelled as pre-MELD group while 466 (58.3%) as post-MELD group (Fig. 1). Baseline characteristics of patients are provided in Table 1 according to MELD era. Our results show no differences between age, gender, albumin level and admission eGFR between groups. Post MELD era shows a higher prevalence of hypertension, diabetes, hepatocellular carcinoma, and non-hepatitis virus and/or alcoholic liver disease as etiology of liver disease (Fig. 1). Also, post MELD era patients have a higher BMI and calculated MELD score. Pre-MELD era shows a higher proportion in living donor transplantation, lower total ischemia times and higher total procedure time. During in-hospital post-transplant care, there were no differences in sepsis diagnosis. Post MELD patients experimented lower first week tacrolimus concentration and lower nephrotoxic drugs exposure. A higher proportion of post MELD patients were needed vasopressors drugs, during and in the first week after liver transplantation (Table 1).

Table 1

Basal patient characteristics according to MELD era. Data are expressed as median [IQR] or percentage. BMI: body mass index, APACHE 2: Acute Physiology and Chronic Health Evaluation II, SAPS 3: Simplified Acute Physiology Score III, eGFR: estimated Glomerular filtration rate, MELD: Model for End-Stage Liver Disease, CPT: Child-Pugh-Turcote, ICU: Intensive Care Unit

	PRE-MELD ERA	POST MELD ERA	P value
	N = 408	N = 466	
Age, years	52.5 [45.25; 60]	54 [45; 61]	0.11
Gender, male (%)	266 (65)	328 (70)	0.18
BMI (Kg/m ²)	25.2 [22.6; 28]	25.95 [23.1; 29.8]	0.02
Hypertension (%)	31 (8)	139 (30)	< 0.01
Diabetes (%)	79 (8)	139 (30)	0.02
APACHE 2	16 [13; 20]	17 [15; 18]	0.01
SAPS 3	39 [36; 42]	39 [28; 53]	0.83
Admission eGFR (mL/min/1.73m ²)	91.5 [72; 110]	88 [57; 125]	0.46
Cause of liver disease			
Hepatitis C (%)	190 (47)	209 (45)	0.63
Hepatitis B (%)	40 (10)	30 (6)	0.08
Alcoholic liver cirrhosis (%)	83 (20)	92 (20)	0.87
Others (%)	75(18)	122 (26)	0.01
Hepatocellular carcinoma (%)	94 (23)	180 (39)	< 0.01
Familial amyloid polyneuropathy (%)	17 (4)	22 (5)	0.74
Pre-Transplant Albumin level (g/dL)	3.1 [2.7; 3.4]	3 [2.6; 3.4]	0.14
CPT Score			< 0.01
A or non-cirrhotic (%)	70 (17)	54 (12)	
B (%)	203 (50)	209 (45)	
C (%)	135 (33)	203 (44)	
MELD score	14 [10; 18]	18 [11; 25]	< 0.01
Preoperative Creatinine (mg/dL)	0.9 [0.7; 1.07]	0.92 [0.7; 1.32]	0.01
Preoperative Total bilirubin (mg/dL)	2.6 [1.7; 4.6]	3 [1.8; 7;5]	< 0.01
Preoperative prothrombin time, INR	1.6 [1.4; 1.96]	1.7 [1.35; 2.22]	0.14

	PRE-MELD ERA	POST MELD ERA	P value
Surgical aspects			
Deceased donor (%)	252 (62)	466 (100)	< 0.01
Piggyback technique (%)	389 (95.3)	464 (99.6)	< 0.01
Operation time (h)	7.55 [6.67; 8.5]	6 [5.17; 6.94]	< 0.01
Total ischemia time (h)	6.77 (2.70; 10.15]	9.08 [7.87; 10.67]	< 0.01
Vasopressor (%)	40 (9.8)	315 (67.6)	< 0.01
Number of blood packs	4 [2; 8]	3 [2; 7]	0.18
Post-transplant care			
Sepsis during hospitalization (%)	157 (39)	158 (34)	0.18
Vasopressor after transplant (%)	70 (17)	264 (30)	< 0.01
Tacrolimus based immunosuppression (%)	299 (73)	459 (98.5)	< 0.01
First week Tacrolimus peak level (ng/mL)	12.6 [9.9; 15.9]	5.7 [3.9; 7.5]	< 0.01
Acute liver rejection (%)	123 (30)	69 (15)	< 0.01
Nephrotoxic exposure (%)	285 (70)	152 (30)	< 0,01
Urinary output (ml/Kg/H)	0.25 [0.15; 0.37]	0.55 [0.35; 0.83]	< 0.01

As primary outcome analysis, 706 patients (81%) fulfill KDIGO AKI criteria after liver transplant procedure, 297 (34%) KDIGO stage 1, 186 (21.3%) 2, and 223 (25.5%) 3. Among study periods, AKI were present in 342 (84%) and 364 (78%) in pre and post-MELD periods, respectively (p 0.04). Pre-MELD patients KDIGO AKI classification proportion were 171 (41.9%) stage 1, 113 (27.7%) 2 and 58 (14.2%) 3, while post-MELD patients were 126 (27%) stage 1, 73 (15.7%) 2 and 165 (35.4%) 3, with a higher proportion of KDIGO 2 and 3 (severe AKI) in post-MELD group (p < 0.01, Table 3).

Table 3

Secondary outcomes according to AKI diagnosis. Data are expressed as median [IQR] or percentage. ICU: Intensive care unit, AKI: Acute Kidney Injury, RRT: Renal replacement therapy.

	PRE-MELD ERA	POST MELD ERA	P value
	N = 408	N = 466	
Hospital length (days)	15 [11; 23]	13 [8; 22]	< 0.01
ICU length (days)	3 [2; 8]	2 [1; 4]	< 0.01
Retransplant during index hospitalization (%)	36 (8.8)	36 (7.7)	0.62
Acute liver rejection (%)	123 (30)	69 (15)	< 0.01
Acute Kidney Injury (%)	342 (84)	364 (78)	0.04
KDIGO 1	171 (41.9)	126 (27)	< 0.01
KDIGO 2	113 (27.7)	73 (15.7)	< 0.01
KDIGO 3	58 (14.2)	165 (35.4)	< 0.01
Duration of AKI (days)	16 [10; 23]	6 [2; 23]	< 0.01
Peak creatinine during AKI episode (mg/dL)	1.6 [1.1; 2.1]	1.9 [1.32; 2.69]	< 0.01
Dialysis (%)	68 (17)	131 (28)	< 0.01
Continuous therapies (%)	39 (10)	68 (15)	0.03
Intermittent therapies (%)	50 (12)	115 (28)	< 0.01
Time of RRT dependence (days)	11.5 [3; 26.75]	17.5 [6; 43.75]	< 0.01
Hospital mortality (%)	33 (8)	36 (8)	0.90
28 days mortality (%)	25 (6)	45 (10)	0.36
90 days mortality (%)	51 (13)	45 (10)	0.19
1-year mortality (%)	81 (20)	50 (11)	< 0.01

AKI diagnosis following liver transplantation remained more frequent in patients with lower pre-transplant albumin levels, lower estimated glomerular filtration rate and higher MELD values. Otherwise, patients with hepatocellular carcinoma diagnosis shows lower AKI proportion. Higher procedure time, wider total ischemic times, sepsis diagnosis after transplantation, vasopressor exposure and nephrotoxic drug prescription were statistically more likely in patients with AKI (Table 2).

Table 2

Basal patient characteristics according to AKI occurrence. Data are expressed as median [IQR] or percentage. BMI: body mass index, APACHE 2: Acute Physiology and Chronic Health Evaluation II, SAPS 3: Simplified Acute Physiology Score III, eGFR: estimated glomerular filtration rate

	NON-AKI	AKI	P value
	N = 168	N = 706	
Age, years	55 [44; 63]	53 [45; 60]	0.06
Gender, male (%)	114 (67.9)	480 (68)	0.97
BMI (Kg/m ²)	25.7 [22.6; 28.5]	25.6 [22.9; 29.1]	0.38
Hypertension (%)	37 (22)	133 (18.8)	0.35
Diabetes (%)	41 (24.4)	25.6 [22.9; 29.1]	0.66
APACHE 2	17 [14; 19]	16 [14; 19]	0.90
SAPS 3	38 [30.25; 43]	39 [32; 44,25]	< 0.01
Admission eGFR (mL/min/1.73m ²)	95.5 [76.2; 118]	90 [63; 121]	0.01
Pathogenesis of liver disease			
Hepatitis C (%)	75 (44.6)	324 (45.9)	0.77
Hepatitis B (%)	17 (10.1)	53 (7.5)	0.26
Alcoholic liver cirrhosis (%)	27 (16.1)	148 (21)	0.15
Others (%)	35 (20.8)	162 (22.9)	0.56
Hepatocellular carcinoma (%)	75 (44.6)	199 (28.2)	< 0.01
Familial amyloid polyneuropathy (%)	11 (6.5)	28 (4)	0.15
Pre-Transplant Albumin level (g/dL)	3.1 [2.9; 3.6]	3 [2.7; 3.3]	< 0.01
CPT Score			< 0.01
A or non-cirrhotic (%)	35 (20.8)	89 (12.6)	
B (%)	83 (49.4)	329 (46.6)	
C (%)	50 (29.8)	288 (40.8)	
MELD score	13 [8; 18]	16 [11; 23]	< 0.01
Preoperative Creatinine (mg/dL)	0.8 [0.7; 1.0]	0.9 [0.7; 1.2]	0.01
Preoperative Total bilirubin (mg/dL)	2.15 [1.4; 4.45]	3 [1.8; 5.9]	< 0.01
Preoperative prothrombin time, INR	1.5 [1.23; 1.9]	1.7 [1.4; 2.15]	< 0.01

	NON-AKI	AKI	P value
Surgical aspects			
Deceased donor (%)	150 (89.3)	568 (80.5)	< 0.01
Piggyback technique (%)	161 (95.8)	692 (98)	0.09
Operation time (h)	6 [5.1; 7.31]	7 [5.67; 8]	< 0.01
Total ischemia time (h)	8.6 [6.8; 10.6]	8.3 [6.4; 10.4]	0.19
Vasopressor (%)	64 (38.1)	291 (41.2)	0.49
Number of blood packs	3 [1; 9]	4 [2; 8]	0.31
Post-transplant care			
Sepsis during hospitalization (%)	24 (14.3)	291 (41.2)	< 0.01
Vasopressor after transplant (%)	41 (24.4)	293 (41.5)	< 0.01
Tacrolimus based immunosuppression (%)	153 (91.1)	605 (85.7)	0.08
First week Tacrolimus peak level (ng/mL)	7.7 [5.7; 11.8]	8.1 [4.9; 12.5]	0.77
Acute liver rejection (%)	18 (10.7)	174 (24.6)	< 0.01
Nephrotoxic exposure (%)	56 (33.3)	381 (54)	< 0.01
Urinary output (ml/Kg/H)	0.68 [0.43; 0.97]	0.36 [0.21; 0.56]	< 0.01

Renal replacement therapy was more frequent in post-MELD group, and even continuous as intermittent therapies were more prevalent in this group (p 0.03 and < 0.01, respectively) (Table 3). Despite that, mortality rates during hospital stay, 28 and 90 days were similar among two groups. Surprisingly, one-year mortality rates were lower in post-MELD group, even with higher MELD, SAPS3, KDIGO 2 and 3 AKI diagnosis as RRT needs in that group (p < 0.01). AKI diagnosis did not impact in mortality rates (in-hospital, 28, 90 and 365 days), but the length of stay in the ICU and hospital has increased. (Table 4).

Table 4

Primary and secondary outcomes according to MELD era. Data are expressed as median [IQR] or percentage. ICU: Intensive care unit KDIGO: Kidney disease – Improving Global Outcomes AKI: Acute Kidney Injury RRT: Renal Replacement Therapy

	NON-AKI	AKI	P value
	N = 168	N = 706	
Hospital length (days)	9 [7; 12]	16 [11; 25]	< 0.01
ICU length (days)	2 [1; 3]	3 [2; 6]	< 0.01
Retransplant during index hospitalization (%)	10 (6)	62 (8.8)	0.23
Acute liver rejection (%)	18 (10.7)	174 (24.6)	< 0.01
Hospital mortality (%)	13 (7.7)	56 (7.9)	0.93
28 days mortality (%)	14 (8.3)	48 (6.8)	0.50
90 days mortality (%)	15 (8.9)	81 (11.5)	0.41
1-year mortality (%)	17 (10.1)	114 (16.1)	0.05

Table 5 shows logistic regression panels for AKI, RRT and mortality. We constructed 5 models using covariates that shows clinical relevance and/or statistical significance at univariate analysis. Our models support that post-MELD era reduces AKI diagnosis, mainly sinking AKI KDIGO 1 and 2 insults. Otherwise, these period augment RRT needs, even corrected by many covariates but shows a signal for mortality decline after logistic regression modelling – model 4 and 5 for 90 days mortality. For illustration porpoise, Fig. 2 shows each KDIGO stratum AKI risk according to MELD era group, showing that post MELD era shrinks AKI risk predominantly by KDIGO 1 and 2 reduction effect.

Table 5

Logistic regression showing unadjusted and 5 distinctive adjusting models for AKI, RRT and 28 days mortality risk between MELD eras. BMI: Body mass index MELD: Model for end-stage liver disease, eGFR: estimated glomerular filtration rate, SAPS 3: Simplified Acute Physiology Score III.

<i>Predictor</i>	<i>HR</i>	<i>95% CI</i>	<i>P- value</i>
AKI risk by performing transplantation in Post MELD era			
Unadjusted	0.68	0.48, 0.97	0.03
Model 1 - Adjusted for age and gender	0.69	0.49, 0.97	0.03
Model 2 - Adjusted for age, gender, diabetes, hypertension, BMI and MELD	0.59	0.41, 0.86	< 0.01
Model 3 - Adjusted for age, gender, diabetes, hypertension, BMI, MELD and eGFR	0.60	0.41, 0.87	< 0.01
Model 4 - Adjusted for age, gender, diabetes, hypertension, BMI, MELD, eGFR, Vasopressor (During and after transplant), Transfusion, First week Tacrolimus peak level and Nephrotoxic drug exposure	0.46	0.24, 0.85	0.01
Model 5 - Adjusted for age, gender, diabetes, hypertension, BMI, MELD, eGFR, Vasopressor (During and after transplant), Transfusion, First week Tacrolimus peak level, Nephrotoxic drug exposure, Acute liver rejection, Sepsis and SAPS 3	0.49	0.26, 0.92	0.02
RRT risk by performing transplantation in Post MELD era			
Unadjusted	1.95	1.40, 2.71	< 0.01
Model 1 - Adjusted for age and gender	1.99	1.43, 2.78	< 0.01
Model 2 - Adjusted for age, gender, diabetes, hypertension, BMI and MELD	1.61	1.12, 2.32	< 0.01
Model 3 - Adjusted for age, gender, diabetes, hypertension, BMI, MELD and eGFR	1.73	1.20, 2.50	< 0.01
Model 4 - Adjusted for age, gender, diabetes, hypertension, BMI, MELD, eGFR, Vasopressor (During and after transplant), Transfusion, First week Tacrolimus peak level and Nephrotoxic drug exposure	1.89	0.94, 3.80	0.07
Model 5 - Adjusted for age, gender, diabetes, hypertension, BMI, MELD, eGFR, Vasopressor (During and after transplant), Transfusion, First week Tacrolimus peak level, Nephrotoxic drug exposure, Acute liver rejection, Sepsis and SAPS 3	2.11	1.01, 4.43	0.04
30 days mortality risk by performing transplantation in Post MELD era			
Unadjusted	1.32	0.78, 2.23	0.29

<i>Predictor</i>	<i>HR</i>	<i>95% CI</i>	<i>P-value</i>
Model 1 - Adjusted for age and gender	1.35	0.79, 2.29	0.26
Model 2 - Adjusted for age, gender, diabetes, hypertension, BMI and MELD	1.37	0.78, 2.40	0.26
Model 3 - Adjusted for age, gender, diabetes, hypertension, BMI, MELD and eGFR	1.31	0.79, 2.44	0.25
Model 4 - Adjusted for age, gender, diabetes, hypertension, BMI, MELD, eGFR, Vasopressor (During and after transplant), Transfusion, First week Tacrolimus peak level and Nephrotoxic drug exposure	0.11	0.02, 0.52	< 0.01
Model 5 - Adjusted for age, gender, diabetes, hypertension, BMI, MELD, eGFR, Vasopressor (During and after transplant), Transfusion, First week Tacrolimus peak level, Nephrotoxic drug exposure, Acute liver rejection, Sepsis and SAPS 3	0.13	0.02, 0.60	< 0.01

Figure 3 shows a cox proportional hazard analysis for 365 days mortality risk analysis. Liver transplantation after MELD policies implementation shows as protection factor, furthermore AKI KDIGO 3 classification impact negatively on patient survival, as MELD score and hepatocellular carcinoma diagnosis.

Discussion

As far as we know, this is the first time series that exclusively compares before and after MELD liver transplantation policy implementation influence on kidney outcomes. Our data shows that post-MELD period impact in fewer AKI diagnosis, however there were more severe AKI and these patients require more dialysis. Despite that, post-MELD era shows a decline in mortality rates after 1-year period.

Our data show a noticeable high incidence in AKI after liver transplantation which corroborate with previous studies that adopt KDIGO diagnostic criterion as surrogate of AKI ¹⁶. We hypothesized that higher KDIGO sensitivity for AKI diagnosis ³⁰, more burden of comorbidities like hypertension and diabetes, and sicker patients, denoted by higher MELD scores ^{13,21}, could explain these numbers.

Surprisingly, post MELD period shows a lesser proportion in AKI diagnosis even after adjustments with 5 proposed models of logistic regression. This result could be explained by a complex interaction between dampening previous known AKI risk factors and by adopting new strategies that could mitigate kidney damage. A well-known AKI associated risk factor is surgical time, it's recognized that reducing these periods of insults could mitigate kidney insult, both in general as liver transplant surgery ¹⁶. Reduced nephrotoxic agent prescription could also support our results, summarized by protocolized sepsis treatment sparing potential nephrotoxic agents or postpone/switch radiocontrast exams by another kind of radiologic propaedeutic ³¹. Adopting tacrolimus as standard post-transplant immunosuppression agent is also a previous known strategy to amend kidney injury. In addition, better tacrolimus monitoring

policies could also attenuate kidney injury occurrence³². However, in our analysis, the first week peak tacrolimus trough concentration was not found to be significantly associated with development of AKI, possibly because recipients who are suspected to occurrence AKI receive a low dose and/or late introduction of calcineurin inhibitor. None of these covariates individually shows impact in AKI diagnosis, but we could hypothesize that all of those together could impact in our primary endpoint.

Higher MELD and SAPS3 could impact in more severe AKI diagnosis, as previous described³³, also higher liver ischemic times^{14,32,34} and more vasopressor requirement^{35,36} preclude AKI progression after liver transplantation. Briefly, sicker patients with higher vasoactive requirement and worse liver draft quality is going to experience more period and higher grade of post reperfusion syndrome³⁷, denoting higher risk for AKI development and progression^{14,38}.

As previously shown, when AKI develop in post MELD patients, these diagnosis incline to worse classification categories and carries more risk for renal replacement therapy requirement, even with lower AKI diagnosis proportion in this group and lower mortality. This singularities, higher dialysis requirement with lower associated mortality, had also seen in another scenarios³⁹⁻⁴¹ and could be explained by protocolized watchfulness for kidney injury patterns reducing transient AKI episodes resulting in proportional higher persistent and severe AKI episodes³⁹. Also, changing dialysis treatment patterns over the time period of the study may account for reduced mortality ratios. That is, despite lack of randomized controlled data to funding this argument, perhaps earlier and higher dose and more frequent dialysis may be beneficial^{42,43}. Previous data from our group also shows that lower AKI exposure time could reduce mortality in post liver transplant patients⁴⁴.

Liver transplant mortality rate is decreasing, which is encouraging, but it is important to recognize that all transformations had been made in care over the last decade resulted in this improvement^{8,37,45,46}. It is remarkable to note that mortality in other conditions, like acute kidney injury dialysis patients has also declined over the last decade despite the paucity of randomized trials which have shown a benefit of any specific intervention^{39,42,43}; so, it is possible that multiple changes/bundles/improvements over period have combined to improve outcomes^{47,48}.

This study has several limitations. The retrospective design of this study has its inherent shortcomings. First, we could not determine AKI etiology in part of absence of routine urinalysis after liver transplantation. Second, liver donor characteristics to calculate donor risk index, post-reperfusion syndrome temporal data and associated variables were unavailable. Third, because retrospective design itself, we couldn't assert that liver allocation policies change was exclusively responsible for our results in AKI and one-year mortality rates reduction (about 50% in logistic and cox proportional hazards regression models, respectively). These results help to strengthen that liver transplant MELD allocation policies positively impact in non-direct correlated endpoints, like acute kidney injury.

In conclusion, MELD adoption as standard liver allocation policies reduce AKI diagnosis after liver transplantation, resulting in lower mortality rates even with higher renal replacement therapy requirement

in these population.

Abbreviations

AKI	Acute Kidney Injury
APACHE 2	Acute Physiology and Chronic Health Evaluation II
BMI	Body mass index
CMV	Cytomegalovirus
CPT	Child-Pugh-Turcote score
CRRT	Continuous Renal Replacement Therapy
eGFR	Estimated glomerular filtration rate
HDi	Intermittent hemodialysis
ICU	Intensive Care Unit
IQR	Interquartile Range
KDIGO	Kidney Disease – Improving Global Outcomes – Acute Kidney Injury Guidelines
LT	Liver Transplantation
MDRD	Modification of Diet in Renal Disease
MELD	Model for End Stage Liver Disease
RRT	Renal Replacement Therapy
SAPS 3	Simplified Acute Physiology Score III
TAC	Tacrolimus
UKELD	United Kingdom – End Stage Liver Disease Score
UNOS	United Network for Organ Sharing

Declarations

1. ETHICS APPROVAL AND CONSENT TO PARTICIPATE: This study was approved by the Ethics in Research Committee of the Hospital Israelita Albert Einstein and informed consent were waived by the same committee - (number 00737118.6.0000.0071).

2. CONSENT TO PUBLISH: Not applicable.

3. AVAILABILITY OF DATA AND MATERIALS: The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

4. Numbers

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5. AUTHOR`S CONTRIBUTIONS:

Paulo Ricardo Gessolo Lins: participated in study design, data acquisition, data analysis and interpretation, written manuscript drafting, critical revision of manuscript drafts, and final approval of manuscript for publication. Accountability for all aspects of the work, including resolution of all questions related to the accuracy or integrity of all aspects of the work.

Roberto Camargo Narciso: participated in data acquisition, data analysis and interpretation, critical revision of manuscript drafts, and final approval of manuscript for publication. Accountability for all aspects of the work, including resolution of all questions related to the accuracy or integrity of all aspects of the work.

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Tables

Table 1 - Basal patient characteristics according to MELD era. Data are expressed as median [IQR] or percentage. BMI: body mass index, APACHE 2: Acute Physiology and Chronic Health Evaluation II, SAPS 3: Simplified Acute Physiology Score III, eGFR: estimated Glomerular filtration rate, MELD: Model for End-Stage Liver Disease, CPT: Child-Pugh-Turcote, ICU: Intensive Care Unit

	PRE-MELD ERA	POST MELD ERA	P value
	N= 408	N=466	
Age, years	52.5 [45.25; 60]	54 [45; 61]	0.11
Gender, male (%)	266 (65)	328 (70)	0.18
BMI (Kg/m ²)	25.2 [22.6; 28]	25.95 [23.1; 29.8]	0.02
Hypertension (%)	31 (8)	139 (30)	<0.01
Diabetes (%)	79 (8)	139 (30)	0.02
APACHE 2	16 [13; 20]	17 [15; 18]	0.01
SAPS 3	39 [36; 42]	39 [28; 53]	0.83
Admission eGFR (mL/min/1.73m ²)	91.5 [72; 110]	88 [57; 125]	0.46
Cause of liver disease			
Hepatitis C (%)	190 (47)	209 (45)	0.63
Hepatitis B (%)	40 (10)	30 (6)	0.08
Alcoholic liver cirrhosis (%)	83 (20)	92 (20)	0.87
Others (%)	75(18)	122 (26)	0.01
Hepatocellular carcinoma (%)	94 (23)	180 (39)	<0.01
Familial amyloid polyneuropathy (%)	17 (4)	22 (5)	0.74
Pre-Transplant Albumin level (g/dL)	3.1 [2.7; 3.4]	3 [2.6; 3.4]	0.14
CPT Score			<0.01
A or non-cirrhotic (%)	70 (17)	54 (12)	
B (%)	203 (50)	209 (45)	
C (%)	135 (33)	203 (44)	
MELD score	14 [10; 18]	18 [11; 25]	<0.01
Preoperative Creatinine (mg/dL)	0.9 [0.7; 1.07]	0.92 [0.7; 1.32]	0.01
Preoperative Total bilirubin (mg/dL)	2.6 [1.7; 4.6]	3 [1.8; 7;5]	<0.01
Preoperative prothrombin time, INR	1.6 [1.4; 1.96]	1.7 [1.35; 2.22]	0.14
Surgical aspects			
Deceased donor (%)	252 (62)	466 (100)	<0.01
Piggyback technique (%)	389 (95.3)	464 (99.6)	<0.01

Operation time (h)	7.55 [6.67; 8.5]	6 [5.17; 6.94]	<0.01
Total ischemia time (h)	6.77 (2.70; 10.15]	9.08 [7.87; 10.67]	<0.01
Vasopressor (%)	40 (9.8)	315 (67.6)	<0.01
Number of blood packs	4 [2; 8]	3 [2; 7]	0.18
Post-transplant care			
Sepsis during hospitalization (%)	157 (39)	158 (34)	0.18
Vasopressor after transplant (%)	70 (17)	264 (30)	<0.01
Tacrolimus based immunosuppression (%)	299 (73)	459 (98.5)	<0.01
First week Tacrolimus peak level (ng/mL)	12.6 [9.9; 15.9]	5.7 [3.9; 7.5]	<0.01
Acute liver rejection (%)	123 (30)	69 (15)	<0.01
Nephrotoxic exposure (%)	285 (70)	152 (30)	<0,01
Urinary output (ml/Kg/H)	0.25 [0.15; 0.37]	0.55 [0.35; 0.83]	<0.01

Table 2 - Basal patient characteristics according to AKI occurrence. Data are expressed as median [IQR] or percentage. BMI: body mass index, APACHE 2: Acute Physiology and Chronic Health Evaluation II, SAPS 3: Simplified Acute Physiology Score III, eGFR: estimated glomerular filtration rate

	NON-AKI	AKI	P value
	N= 168	N= 706	
Age, years	55 [44; 63]	53 [45; 60]	0.06
Gender, male (%)	114 (67.9)	480 (68)	0.97
BMI (Kg/m ²)	25.7 [22.6; 28.5]	25.6 [22.9; 29.1]	0.38
Hypertension (%)	37 (22)	133 (18.8)	0.35
Diabetes (%)	41 (24.4)	25.6 [22.9; 29.1]	0.66
APACHE 2	17 [14; 19]	16 [14; 19]	0.90
SAPS 3	38 [30.25; 43]	39 [32; 44,25]	<0.01
Admission eGFR (mL/min/1.73m ²)	95.5 [76.2; 118]	90 [63; 121]	0.01
Pathogenesis of liver disease			
Hepatitis C (%)	75 (44.6)	324 (45.9)	0.77
Hepatitis B (%)	17 (10.1)	53 (7.5)	0.26
Alcoholic liver cirrhosis (%)	27 (16.1)	148 (21)	0.15
Others (%)	35 (20.8)	162 (22.9)	0.56
Hepatocellular carcinoma (%)	75 (44.6)	199 (28.2)	<0.01
Familial amyloid polyneuropathy (%)	11 (6.5)	28 (4)	0.15
Pre-Transplant Albumin level (g/dL)	3.1 [2.9; 3.6]	3 [2.7; 3.3]	<0.01
CPT Score			<0.01
A or non-cirrhotic (%)	35 (20.8)	89 (12.6)	
B (%)	83 (49.4)	329 (46.6)	
C (%)	50 (29.8)	288 (40.8)	
MELD score	13 [8; 18]	16 [11; 23]	<0.01
Preoperative Creatinine (mg/dL)	0.8 [0.7; 1.0]	0.9 [0.7; 1.2]	0.01
Preoperative Total bilirubin (mg/dL)	2.15 [1.4; 4.45]	3 [1.8; 5.9]	<0.01
Preoperative prothrombin time, INR	1.5 [1.23; 1.9]	1.7 [1.4; 2.15]	<0.01
Surgical aspects			
Deceased donor (%)	150 (89.3)	568 (80.5)	<0.01
Piggyback technique (%)	161 (95.8)	692 (98)	0.09

Operation time (h)	6 [5.1; 7.31]	7 [5.67; 8]	<0.01
Total ischemia time (h)	8.6 [6.8; 10.6]	8.3 [6.4; 10.4]	0.19
Vasopressor (%)	64 (38.1)	291 (41.2)	0.49
Number of blood packs	3 [1; 9]	4 [2; 8]	0.31
Post-transplant care			
Sepsis during hospitalization (%)	24 (14.3)	291 (41.2)	<0.01
Vasopressor after transplant (%)	41 (24.4)	293 (41.5)	<0.01
Tacrolimus based immunosuppression (%)	153 (91.1)	605 (85.7)	0.08
First week Tacrolimus peak level (ng/mL)	7.7 [5.7; 11.8]	8.1 [4.9; 12.5]	0.77
Acute liver rejection (%)	18 (10.7)	174 (24.6)	<0.01
Nephrotoxic exposure (%)	56 (33.3)	381 (54)	<0.01
Urinary output (ml/Kg/H)	0.68 [0.43; 0.97]	0.36 [0.21; 0.56]	<0.01

Table 3 - Secondary outcomes according to AKI diagnosis. Data are expressed as median [IQR] or percentage. ICU: Intensive care unit, AKI: Acute Kidney Injury, RRT: Renal replacement therapy.

	PRE-MELD ERA	POST MELD ERA	P value
	N= 408	N=466	
Hospital length (days)	15 [11; 23]	13 [8; 22]	<0.01
ICU length (days)	3 [2; 8]	2 [1; 4]	<0.01
Retransplant during index hospitalization (%)	36 (8.8)	36 (7.7)	0.62
Acute liver rejection (%)	123 (30)	69 (15)	<0.01
Acute Kidney Injury (%)	342 (84)	364 (78)	0.04
KDIGO 1	171 (41.9)	126 (27)	<0.01
KDIGO 2	113 (27.7)	73 (15.7)	<0.01
KDIGO 3	58 (14.2)	165 (35.4)	<0.01
Duration of AKI (days)	16 [10; 23]	6 [2; 23]	<0.01
Peak creatinine during AKI episode (mg/dL)	1.6 [1.1; 2.1]	1.9 [1.32; 2.69]	<0.01
Dialysis (%)	68 (17)	131 (28)	<0.01
Continuous therapies (%)	39 (10)	68 (15)	0.03
Intermittent therapies (%)	50 (12)	115 (28)	<0.01
Time of RRT dependence (days)	11.5 [3; 26.75]	17.5 [6; 43.75]	<0.01
Hospital mortality (%)	33 (8)	36 (8)	0.90
28 days mortality (%)	25 (6)	45 (10)	0.36
90 days mortality (%)	51 (13)	45 (10)	0.19
1-year mortality (%)	81 (20)	50 (11)	<0.01

Table 4 - Primary and secondary outcomes according to MELD era. Data are expressed as median [IQR] or percentage. ICU: Intensive care unit KDIGO: Kidney disease – Improving Global Outcomes AKI: Acute Kidney Injury RRT: Renal Replacement Therapy

	NON-AKI	AKI	P value
	N= 168	N= 706	
Hospital length (days)	9 [7; 12]	16 [11; 25]	<0.01
ICU length (days)	2 [1; 3]	3 [2; 6]	<0.01
Retransplant during index hospitalization (%)	10 (6)	62 (8.8)	0.23
Acute liver rejection (%)	18 (10.7)	174 (24.6)	<0.01
Hospital mortality (%)	13 (7.7)	56 (7.9)	0.93
28 days mortality (%)	14 (8.3)	48 (6.8)	0.50
90 days mortality (%)	15 (8.9)	81 (11.5)	0.41
1-year mortality (%)	17 (10.1)	114 (16.1)	0.05

Table 5 - Logistic regression showing unadjusted and 5 distinctive adjusting models for AKI, RRT and 28 days mortality risk between MELD eras. BMI: Body mass index MELD: Model for end-stage liver disease, eGFR: estimated glomerular filtration rate, SAPS 3: Simplified Acute Physiology Score III.

<i>Predictor</i>	<i>HR</i>	<i>95% CI</i>	<i>P- value</i>
AKI risk by performing transplantation in Post MELD era			
Unadjusted	0.68	0.48, 0.97	0.03
Model 1 - Adjusted for age and gender	0.69	0.49, 0.97	0.03
Model 2 - Adjusted for age, gender, diabetes, hypertension, BMI and MELD	0.59	0.41, 0.86	<0.01
Model 3 - Adjusted for age, gender, diabetes, hypertension, BMI, MELD and eGFR	0.60	0.41, 0.87	<0.01
Model 4 - Adjusted for age, gender, diabetes, hypertension, BMI, MELD, eGFR, Vasopressor (During and after transplant), Transfusion, First week Tacrolimus peak level and Nephrotoxic drug exposure	0.46	0.24, 0.85	0.01
Model 5 - Adjusted for age, gender, diabetes, hypertension, BMI, MELD, eGFR, Vasopressor (During and after transplant), Transfusion, First week Tacrolimus peak level, Nephrotoxic drug exposure, Acute liver rejection, Sepsis and SAPS 3	0.49	0.26, 0.92	0.02
RRT risk by performing transplantation in Post MELD era			
Unadjusted	1.95	1.40, 2.71	<0.01
Model 1 - Adjusted for age and gender	1.99	1.43, 2.78	<0.01
Model 2 - Adjusted for age, gender, diabetes, hypertension, BMI and MELD	1.61	1.12, 2.32	<0.01
Model 3 - Adjusted for age, gender, diabetes, hypertension, BMI, MELD and eGFR	1.73	1.20, 2.50	<0.01
Model 4 - Adjusted for age, gender, diabetes, hypertension, BMI, MELD, eGFR, Vasopressor (During and after transplant), Transfusion, First week Tacrolimus peak level and Nephrotoxic drug exposure	1.89	0.94, 3.80	0.07
Model 5 - Adjusted for age, gender, diabetes, hypertension, BMI, MELD, eGFR, Vasopressor (During and after transplant), Transfusion, First week Tacrolimus peak level, Nephrotoxic drug exposure, Acute liver rejection, Sepsis and SAPS 3	2.11	1.01, 4.43	0.04
30 days mortality risk by performing transplantation in Post MELD era			
Unadjusted	1.32	0.78, 2.23	0.29

Model 1 - Adjusted for age and gender	1.35	0.79, 2.29	0.26
Model 2 - Adjusted for age, gender, diabetes, hypertension, BMI and MELD	1.37	0.78, 2.40	0.26
Model 3 - Adjusted for age, gender, diabetes, hypertension, BMI, MELD and eGFR	1.31	0.79, 2.44	0.25
Model 4 - Adjusted for age, gender, diabetes, hypertension, BMI, MELD, eGFR, Vasopressor (During and after transplant), Transfusion, First week Tacrolimus peak level and Nephrotoxic drug exposure	0.11	0.02, 0.52	<0.01
Model 5 - Adjusted for age, gender, diabetes, hypertension, BMI, MELD, eGFR, Vasopressor (During and after transplant), Transfusion, First week Tacrolimus peak level, Nephrotoxic drug exposure, Acute liver rejection, Sepsis and SAPS 3	0.13	0.02, 0.60	<0.01

Figures

Figure 1

Overview of the study cohort. Flow chart shows patients screened, included and excluded from analysis. ESRD: End-stage renal disease

AKI risk prediction by MELD era and stratification by KDIGO stages

Figure 2

AKI risk prediction using 2 periods of me (Pre-MELD and Post MELD) and grouped by KDIGO AKI classification. AKI: Acute Kidney Injury, MELD: Model of End-Stage Liver Disease, KDIGO: Kidney disease improving global outcomes.

Figure 3

Cox proportional hazard analysis for 1-year mortality. SAPS3: Simplified Acute Physiology Score III, BMI: Body mass index, KDIGO: Kidney disease – Improving Global Outcomes, AKI: Acute Kidney Injury