Impact of Italian Score for Organ Allocation System on Deceased Donor Liver Transplantation: A Monocentric Competing Risk Time-to-Event Analysis

Simone Khouzam[a], Duilio Pagano[b], Marco Barbàra[b], Davide Cintorino[b], Sergio Li Petri[b], Fabrizio di Francesco[b], Calogero Ricotta[b], Pasquale Bonsignore[b], Aurelio Seidita[b], Sergio Calamia[b], Marco Canzonieri[b], Alessandro Tropea[b], and Salvatore Gruttadauria[b,c,*]

[a]Sidney Kimmel Medical College, Thomas Jefferson University, Philadelphia, PA, USA; [b]Department for the Treatment and Study of Abdominal Diseases and Abdominal Transplantation, IRCCS-ISMETT (Istituto di Ricovero e Cura a Carattere Scientifico - Istituto Mediterraneo per i Trapianti e Terapie ad alta specializzazione), UPMC (University of Pittsburgh Medical Center) Italy, Palermo, Italy; and [c]University of Catania, Catania, Italy

ABSTRACT

Background. Liver transplantation (LT) is the only definitive and curative treatment for patients with end-stage liver disease and hepatocellular carcinoma. We aimed to evaluate the impact of the Italian score for organ allocation (ISO) in terms of the waiting-list mortality, probability of LT, and patient survival after LT.

Patient and methods. All of the adult patients on the waiting list for LT at our institute from January 2014 to December 2017 were included in the study. The probabilities of death while on the waiting list, dropout from the list, and LT were compared by means of cumulative incidence functions, in a competing risk time-to-event analysis setting. Uni- and multivariable logistic regression models were used to estimate and compare the probability of death and to find potential risk factors for waiting-list death.

Results. There were 286 patients on the waiting list for LT during the study period, 122 of whom entered the waiting list prior to the implementation of ISO (Group A) and 164 afterward (Group B). Group A had 62 transplants, and Group B had 116 transplants. Group B showed a lesser probability of death ($P = .005$) and a greater probability of transplant ($P < .001$) compared to Group A. In the 2 groups, post-transplant survival was similar.

Conclusion. Based on preliminary clinical experience from a single transplant center, the ISO allocation system demonstrated an overall reduced probability of patient death while on the waiting list without impairing post-LT survival, suggesting that the ISO system might represent an improved method of organ allocation, with a more beneficial distribution of livers.

LIVER transplantation (LT) is the definitive treatment of choice for most end-stage liver diseases (ESLD) and hepatocellular carcinoma (HCC). Limited organ supply necessitates that allocation for orthotopic LT must be optimized for effective allocation, requiring the use of a priority-based allocation system. From November 2002 to January 2016, the Model for End-Stage Liver Disease (MELD) scoring system and MELD correction were used throughout Italy, prioritizing the sickest patients awaiting LT [1,2].

Transplant centers in Europe and Brazil have published retrospective analyses showing an 8% to 10% reduction in

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*Address correspondence to Salvatore Gruttadauria, IRCCS-ISMETT, Via E. Tricomi 5, 90127 Palermo, Italy. Tel: +39 091 21 92 111; Fax: +39 091 21 92 400. E-mail: sgruttadauria@ismett.edu

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Table 1. Characteristics of 286 Patients Who Entered the Waiting List for Liver Transplantation From 2014 to 2017

	Before ISO Adoption	After ISO Adoption	*P* Value
N	122	164	
Male Gender, no. (%)	79 (64.8)	120 (73.2)	.153
ABO, no. (%)			.994
0	55 (45.1)	77 (47.0)	
A	42 (34.4)	54 (32.9)	
B	20 (16.4)	27 (16.5)	
AB	5 (4.1)	6 (3.7)	
Age at WL insertion, mean ± SD	54.5 (9.4)	55.7 (8.8)	.276
BMI at WL insertion, mean ± SD	26.1 (4.3)	26.3 (4.3)	.668
Main Diagnosis, no. (%)			.005
HCC	41 (33.6)	91 (55.5)	
HCV	32 (26.2)	20 (12.2)	
HBV	11 (9.0)	7 (4.3)	
Alcohol	8 (6.6)	16 (9.8)	
Biliary cirrhosis	11 (9.0)	7 (4.3)	
NASH	4 (3.3)	6 (3.7)	
Autoimmune cirrhosis	3 (2.5)	4 (2.4)	
Cryptogenic cirrhosis	7 (5.7)	8 (4.9)	
Metabolic disease	1 (0.8)	4 (2.4)	
Other tumor	1 (0.8)	0 (0.0)	
Miscellaneous	3 (2.5)	1 (0.6)	
Primary liver disease			
HBV infection	14 (11.5)	20 (12.2)	1.000
HCV infection	61 (50.0)	75 (45.7)	.550
HDV infection	4 (3.3)	5 (3.0)	1.000
HIV infection	4 (3.3)	2 (1.2)	.407
NASH	7 (5.7)	22 (13.4)	.046
cryptogenic cirrhosis	9 (7.4)	8 (4.9)	.451
Alcohol	18 (14.8)	31 (18.9)	.428
autoimmune	4 (3.3)	5 (3.0)	1.000
Biliary cirrhosis	12 (9.8)	5 (3.0)	.022
HCC	41 (33.6)	91 (55.5)	< .001
MELD at WL insertion, median [IQR]	21.0 [16.0, 22.0]	16.0 [12.0, 19.0]	< .001

BMI, body mass index; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; MELD, Model for End-Stage Liver Disease; NASH, nonalcoholic steatohepatitis; SD, standard deviation; WL, waiting list.

waiting-list mortality after the implementation of the MELD system for liver allocation, as well as similar post-LT survival [3–5]. While MELD can predict pretransplant mortality, accounting for the urgency criteria, it fails to predict post-transplant outcomes and does not fulfill equitable allocation [6,7]. MELD requires a system of exception points in which diseases are subdivided into standardized and nonstandardized exceptions. Standardized exceptions consist of diseases such as HCC within Milan criteria, hepatopulmonary syndrome, and cholangiocarcinoma, while nonstandardized exceptions include HCC beyond Milan criteria, cholangitis, and hyponatremia [8,9]. The lack of standardization for the exception criteria has created further challenges for achieving fairness in organ allocation [8].

Italy's organ transplantation network is managed by the National Transplantation Center. It is comprised of 21 LT centers, based in 13 regions, and since its founding, there have been several changes in liver allocation rules. Following a multistep consensus-based approach, the Italian Board of Experts in the Field of Liver Transplantation determined that a "blended principle model" of organ allocation principles was the best solution [9,10]. This consensus led to the development of the Italian Score for Organ allocation (ISO) system, a transparent and precise method for organ allocation, incorporating a priority criterion for MELD exception conditions. Thus, in January 2016, Italy adopted the standardized point method of ISO in LT [2]. The aim of this study was to evaluate and determine the impact of adopting the ISO system on waiting-list mortality and post-transplant outcomes.

PATIENTS AND METHODS

Our retrospective analysis studied 286 adult LT candidates for a liver from a deceased donor and who entered the waiting list at our institute from January 2014 until December 2017. The ISO system was implemented in January 2016, and candidates were categorized into 2 cohorts based on when they entered the waiting list for LT. We investigated all adult candidates (18 years of age or older), excluding patients who were listed for fulminant or acute hepatic failure, were awaiting any type of combined transplant, were awaiting a living donor transplant, or had already received an organ transplant.

The primary outcome of this study was the probability of waiting-list mortality before and after the implementation of the ISO system; a secondary outcome of interest was the probability of transplant. Accordingly, 3 different waiting-list exit statuses were defined as death, transplant, or dropout because of a deteriorating condition or medical unsuitability. In order to achieve a complete separation of the 2 groups and to harmonize waiting-list follow-up lengths, all candidates in Group A still awaiting LT were administratively censored on December 31, 2015, i.e. the day before the beginning of the ISO system period; candidates in Group B were similarly censored on December 31, 2017.

Statistical Analysis

Quantitative variables are represented in tabular form as mean ± standard deviation, or as a median and interquartile range when variable distribution was not approximately normal; categorical variables are represented as frequency and percentage. Differences between variable distributions of the 2 groups were tested for statistical significance utilizing the Student *t* test and the ANOVA test or, when not approximately normal, the Kruskal-Wallis and the Mann-Whitney U tests, as appropriate.

The probabilities of death while on the waiting list, dropout from the list, and LT were compared utilizing the Allen-Johansen estimator of cumulative cause-specific hazard, in a competing risk time-to-event analysis setting and tested for differences between groups using Gray's test. Uni- and multivariable logistic regression models were also used to estimate and compare the probability of death while on the waiting list of the 2 groups and to find potential risk factors for death. The final multivariable model was selected by a forward stepwise procedure, using Akaike information criterion as a stopping rule. All analyses and graphics were done with the R statistical computing environment.

Table 2. Waiting List Outcome Measures

	Group A	Group B	*P* Value
N	122	164	
Time on waiting list, months			< .001
Median [IQR]	3.0 [0.7, 7.4]	1.3 [0.4, 3.7]	
Mean ± SD	4.9 ± 5.1	2.9 ± 4.0	
Exit status at the end of follow-up, n (%)			< .001
Transplant	62 (50.8)	116 (70.7)	
Death	27 (22.1)	15 (9.1)	
Dropout	4 (3.3)	3 (1.8)	
Still in list	29 (23.8)	30 (18.3)	
Cumulative probabilities of death*			
Overall			.005†
At 3 months	12.8 [7.8-20.3]%	3.2 [1.3-7.5]%	
At 6 months	15.8 [10.2-23.9]%	6.2 [3.2-1.2]%	
At 1 year	25.1 [17.7-34.8]%	10.5 [6.2-17.4]%	
HCC patients			.143†
At 3 months	4.9 [1.2-18.1]%	2.2 [0.6-8.7]%	
At 6 months	7.6 [2.5-21.8]%	4.7 [1.8-12.0]%	
At 1 year	16.4 [7.7-33.0]%	4.7 [1.8-12.0]%	
HCV patients (w/ or w/o HCC)			.018†
At 3 months	15.2 [8.2-27.2]%	4.2 [1.3-12.5]%	
At 6 months	17.2 [9.6-29.7]%	6.0 [2.3-15.2]%	
At 1 year	27.4 [16.9-42.6]%	6.0 [2.3-15.2]%	
Cumulative probabilities of transplantation*			
Overall			< .001†
At 3 months	27.4 [20.2-36.5]%	61.3 [53.8-68.9]%	
At 6 months	41.3 [32.7-51.1]%	71.6 [64.0-78.7]%	
At 1 year	56.9 [47.4-66.8]%	77.6 [69.9-84.5]%	
HCC patients			< .001†
At 3 months	29.7 [18.1-46.4]%	69.9 [60.1-79.1]%	
At 6 months	48.9 [34.5-65.6]%	80.2 [70.7-88.3]%	
At 1 year	65.3 [50.6-79.8]%	85.8 [75.7-93.2]%	
HCV patients (w/ or w/o HCC)			< .001†
At 3 months	20.5 [12.2-33.3]%	66.3 [55.3-77.0]%	
At 6 months	38.2 [26.8-52.4]%	77.1 [66.1-86.5]%	
At 1 year	60.1 [46.8-73.8]%	80.3[68.9-89.5]%	

HCC, hepatocellular carcinoma; HCV, hepatitis C virus; IQR, interquartile range; SD, standard deviation.
*Aalen-Johansen estimators of cause-specific hazard.
†Gray's test for equality of cause-specific hazard.

RESULTS

Study Population

Of the 286 LT candidates considered for this study, 122 entered the waiting-list before the adoption of the ISO system (Group A), from January 2014 until December 2015, while Group B consisted of 164 patients who entered the waiting list after the implementation of the ISO system, from January 2016 to December 2017. Patients in Group B were prevalently male (74% vs 65% in Group A, $P = .153$), slightly older (56 ± 9 vs 55 ± 9 years old, $P = .276$), with very similar distributions in respect to BMI (26 ± 4 kg/m^2 in both cohorts, $P = .546$) and ABO (Table 1). The most frequent indication for LT was HCC for both Group A and B, with a much higher prevalence in Group B (55% vs 31%, $P < .001$). Distribution of primary liver disease was similar between the 2 groups, with the remarkable exceptions of nonalcoholic steatohepatitis (13% Group B vs 6% Group A, $P = .046$) and biliary cirrhosis (3% Group B vs 10% Group A, $P = .022$).

Waiting-List Outcomes

Patients remained on the waiting list for a median time of 1.3 months in Group B and 3.0 months in Group A ($P < .001$). Of the 286 patients, 178 (62%) underwent LT, 42 (15%) died while waiting for an LT, 7 (2%) were removed from the list because of their deteriorating condition or medical unsuitability, and 59 (21%) were alive and still on the waiting list at the end of their respective observation periods (December, 31, 2015, for Group A and December, 31, 2017, for Group B). Looking at differences between groups, Group B showed a much higher transplantation rate with respect to Group A (116 [71%] vs 62 [51%]), a much lower death rate (15 [9%] vs 27 [22%]), and a slightly lower dropout rate (3 [2%] vs 4 [3%], $P < .001$) (Table 2).

In a competing risk time-to-event setting, the mortality rate after 1 year from waiting-list insertion was estimated to be 10% (95% CI: [6%=17%]) for patients in Group B and 25% (95% CI: [18%-35%]) for patients in Group A (Gray's

Table 3. Uni- and Multivariable Logistic Regression Models for the Probability of Death

	Univariable Models		Multivariable Model	
	OR [95% CI]	*P*	OR [95% CI]	*P*
Group B	0.35 [0.18, 0.69]	.003	0.46 [0.22, 0.93]	.033
Male sex	0.37 [0.19, 0.72]	.004	0.37 [0.18, 0.73]	.005
Age	0.99 [0.96, 1.03]	.570		
BMI	0.99 [0.91, 1.07]	.759		
HBV [co-]infection	0.75 [0.21, 2.04]	.609		
HCV [co-]infection	0.90 [0.46, 1.73]	.745		
NASH	0.64 [0.15, 1.95]	.489		
Cryptogenic cirrhosis	1.87 [0.51, 5.61]	.295		
Alcohol	0.61 [0.20, 1.52]	.334		
Autoimmune cirrhosis	1.69 [0.25, 7.31]	.521		
Biliary cirrhosis	2.61 [0.79, 7.50]	.087		
HCC	0.41 [0.20, 0.83]	.015		
MELD	1.06 [1.02, 1.11]	.005	1.05 [1.01, 1.10]	.026

BMI, body mass index; CI, confidence interval; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; MELD, Model for End-Stage Liver Disease; NASH, nonalcoholic steatohepatitis.

test, P value = .005), while the transplantation rate was estimated to be 78% (95% CI: [70%-85%]) for patients in Group B and 57% (95% CI: [47%-67%]) for patients in Group A (Gray's test, P value < .001) (Table 2). Lower death rates and higher transplant rates in Group B with respect to Group A were also estimated by looking at both the subsets of patients diagnosed with HCC for any etiology (1-year death rate 5% [2%-12%] in Group B vs 16% [8%-33%] in Group A, P = .143; 1-year transplant rate 86% [76%-93%] in Group B vs 65% [50%-80%] in Group A, P < .001) and the subsets of patients with hepatitis C virus (HCV) infection (1-year death rate 6% [2%-15%] in Group B vs 27% [17%-42%] in Group A, P = .018; 1-year transplant rate 80% [69%-89%] in Group B vs 60% [47%-74%] in Group A, P < .001) (Table 2).

Univariable logistic models for the probability of death while on the waiting list showed a mortality-reducing effect of the new ISO allocation system (OR 0.35, 95% CI: [0.18, 0.69], P = .003), male sex (OR 0.37, 95% CI: [0.19, 0.72] P = .004), and HCC (OR 0.41, 95% CI: [0.20, 0.83] P = .015) and confirmed the MELD score as predictor of mortality (OR 1.06, 95% CI: [1.02, 1.11] P = .005) (Table 3). The selected multivariable logistic regression model confirmed the new ISO allocation system, male sex, and MELD as independent factors affecting mortality but not HCC.

Post-transplant survival Kaplan-Meier curves show a slightly better survival for patients in Group B with respect to Group A, although the difference was not statistically significant (1-year survival from transplant 91%, 95% CI: [86%-97%] for Group B vs 87% [79%-96%] for Group A, log-rank P value = .090 [Fig 1A]). Considering overall survival starting from waiting-list insertion, Group B showed a much better survival rate (84.3% [79%-90%]) than Group A (58% [59%-77%], log-rank P value = .002) (Fig 1B).

DISCUSSION

Transitioning from the MELD system to the implementation of the ISO system for liver allocation resulted in great

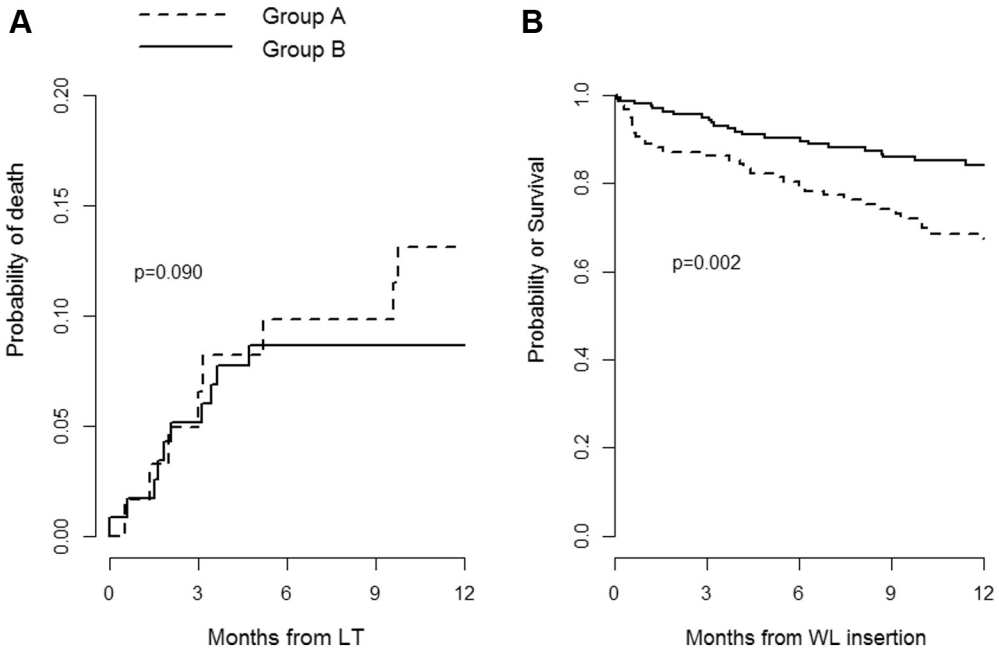

Fig 1. Cumulative incidence functions for the probability of patient death during waiting-list time (A) and liver transplantation occurrence (B).

improvement in the waiting-list mortality rates, without impairing survival of transplanted patients. Data confirms that there was an increased number of LTs, as well as an increased number of new waiting-list insertions. The various etiologies necessitating an LT was different between Group A and Group B, with proportionately more patients diagnosed with HCC in Group B but relatively fewer patients diagnosed with viral infections (HCV ESLD, hepatitis B ESLD). Potentially, the decreased percentage of non-HCC HCV ESLD as a primary diagnosis was due to the novel direct-acting antiviral (DAA) therapy for HCV infection. DAA therapy has proven extremely effective, with a cure rate above 90% and a reduction in recurrence of the virus [11,12]. Despite decreased HCV ESLD, Group B patients maintained a significantly higher rate of HCC. Several studies have noted that despite effective DAA therapy, the occurrence of liver cancer is not reduced in HCV-related cirrhotic patients, suggesting close monitoring and follow-up during and after DAA therapy [13,14].

Nonetheless, the probability of waiting-list mortality significantly decreased, and the probability of transplant significantly increased, suggesting that ISO is a better model for allocating livers and that MELD overprioritized advanced disease statuses (decompensated liver cirrhosis). In this series, the ISO system provided an organ allocation distribution that better benefited all recipients. It is necessary to widen the analysis of the ISO system, as well as prospectively collect data to quantify the true overall impact of the ISO system compared to MELD.

CONCLUSION

Patient survival and reducing waiting-list mortality is the gold standard for assessing a new allocation system such as ISO compared to MELD. The goal of the ISO system is to optimize organ allocation, considering not only urgency but also utility and benefit. Regarding the new waiting-list insertions and LTs performed at ISMETT, there was clearly a significant reduction in deaths while waiting for a liver and an increase in the percentage of LT recipients. Finally, patient survival and graft survival were significantly lengthened for all patients, irrespective of their diagnosis.

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