


Liver Transplantation in Rescue Allocation: Comparison of the Donor Risk Index, Balance of Risk Score and Graft Function After Liver Transplantation

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ABSTRACT

Background: In the model for end-stage liver disease (MELD) system, the use of livers from rescue allocation (RA), those refused for the first five of the ranking, have conflicting results in the literature. **Objective:** Analysis of the characteristics of the different simulated patterns of allocation (pattern vs. rescue), using the donor risk index (DRI), the balance of risk score (BAR) and its impact on the graft function. **Method:** Cohort of 233 liver transplants in adults, performed between 2015 and 2022. **Results:** General characteristics, age 50.3 ± 11.8 years; 64.81% CHILD C; MELD in allocation 22.4 ± 7.6 . Initial graft dysfunction in 12.45% and primary nonfunction (PNF) in 8.15%; with DRI 1.41 ± 0.32 . Transplants in RA occurred in 18.03% ($n = 42$) of cases, in patients with significantly lower MELD (18.4 ± 4.8) and BAR (7.1 ± 3.2) compared to standard allocation (23.2 ± 7.9 ; 9.2 ± 4.2 respectively). The DRI was significantly higher ($p = 0.001$) in the RA (1.58 ± 0.37). Age ($p = 0.23$) and body mass index ($p = 0.85$) of the donor, cold ischemia time (CIT) ($p = 0.10$) showed no differences between the groups. RA organs came more often from out-of-state (50% vs. 2.62%) and less harvested by our surgical team (38.1% vs. 79.0%). Early graft dysfunction (EGD) in 16.67% ($n = 7$); 14.29% ($n = 6$) of primary nonfunctioning in the RA group, percentage higher than in the standard allocation group with 11.52% ($n = 22$) and 6.81% ($n = 13$) respectively; however, there was no difference with statistical significance ($p = 0.052$). There was no difference in survival (73.81% vs. 72.25%; $p = 0.83$). **Conclusion:** A strategy more frequently employed in patients with less severe conditions according to BAR score, liver grafts in a RA rescue allocation system had higher DRI scores and did not provide a difference in short-term survival.

Keywords: Primary graft dysfunction. Graft survival. Liver transplantation. Risk assessment.

Transplante Hepático na Alocação de Resgate: Comparação do Índice de Risco do Doador, Balanço de Risco e Função do Enxerto Após Transplante Hepático

RESUMO

Introdução: No modelo para doença hepática terminal (MELD), o uso de fígados de alocação de resgate (RA), aqueles recusados para os cinco primeiros do ranking, apresenta resultados conflitantes na literatura. **Objetivo:** Análise das características dos diferentes padrões simulados de alocação (padrão vs. resgate), utilizando o índice de risco do doador (DRI), o *balance of risk score* (BAR) e seu impacto na função do enxerto. **Método:** Coorte de 233 transplantes hepáticos em adultos, realizados entre 2015 e 2022. **Resultados:** Características gerais, idade $50,3 \pm 11,8$ anos; 64,81% CHILD C; MELD na alocação $22,4 \pm 7,6$. Disfunção inicial do enxerto em 12,45% e não função primária (PNF) em 8,15%; com DRI $1,41 \pm 0,32$. Transplantes na RA ocorreram em 18,03% ($n = 42$) dos casos, em pacientes com MELD ($18,4 \pm 4,8$) e BAR ($7,1 \pm 3,2$) significativamente menor em comparação à alocação padrão ($23,2 \pm 7,9$; $9,2 \pm 4,2$, respectivamente). O DRI foi significativamente maior ($p = 0,001$) na RA ($1,58 \pm 0,37$). Idade ($p = 0,23$) e índice de massa corporal ($p = 0,85$) do doador, tempo de isquemia fria (CIT) ($p = 0,10$) não apresentaram diferenças entre os grupos. Órgãos de RA vieram mais frequentemente de fora do estado (50% vs. 2,62%) e menos captados pela equipe cirúrgica local (38,1%

vs. 79,0%). Disfunção precoce do enxerto (EGD) em 16,67% (n = 7); 14,29% (n = 6) de não funcionamento primário no grupo RA, percentual maior do que no grupo de alocação padrão com 11,52% (n = 22) e 6,81% (n = 13) respectivamente; entretanto não houve diferença com significância estatística (p = 0,052). Não houve diferença na sobrevida em 90 dias (73,81% vs. 72,25%; p = 0,83). **Conclusão:** Uma estratégia mais frequentemente empregada em pacientes com condições menos graves de acordo com o escore BAR, os enxertos hepáticos em um sistema de alocação de resgate de RA tiveram escores DRI mais altos e não proporcionaram diferença na sobrevida em curto prazo.

Descritores: Disfunção primária do enxerto. Sobrevivência de enxerto. Transplante de fígado. Medição de risco.

INTRODUCTION

The successful and widespread use of liver transplantation (LT) requires optimizing the use of the donor organ. Organs may be rejected for the top-listed patients but used for other recipients in allocation systems based on the model for end-stage liver disease score (MELD), as in Brazil. These organs may be referred to as *rescue*, *orphans*, or *discarded*, and their definition in the literature varies.¹⁻⁶

Based on the successful use of grafts from expanded criteria donors,^{7,8} the French transplantation system defined a *rescue* allocation (RA) when a graft was refused for the five top-listed patients, allowing the transplantation center to freely choose a recipient from its own waiting list, with the goal of maximizing graft utilization.⁹ Members of Eurotransplant follow similar allocation principles.⁵

Although not a synonym for an extended criteria organ,⁶ these previously declined liver grafts may raise concerns about the utility of their use. The goal of this study was to analyze the characteristics of the organs and patients, and compare the functional outcomes of grafts in LT performed in a simulated rescue versus standard allocation.

METHODS

All consecutive patients who underwent deceased donor LT at Rocio Hospital between September 2015 and September 2022 were identified and retrospectively analyzed using our prospectively maintained database. All potential liver transplant candidates were placed on a separate waiting list based on their blood group and MELD score, as determined by Brazilian law.¹⁰

RA was defined as a liver that was declined for the top five patients on the list.^{9,11} In some cases, the top-ranked recipients can be youngsters, forcing them to reject the offered organ based more on anatomical than necessary functional criteria. The general policy for accepting these grafts included candidates with low MELD scores and clinical characteristics known to predict a poor outcome, such as difficult-to-control ascites or recurrent encephalopathy. Individual informed consent was obtained at the time of LT listing for the use of expanded criteria organ donors.¹²

The harvesting surgeon's macroscopic evaluation was used to evaluate the liver graft. Data on the donor and recipient were collected to calculate the liver donor risk index (DRI), balance of risk (BAR), donor's sequential organ failure assessment score (SOFA), and recipient survival outcomes following LT (SOFT). Death within 90 days of surgery was defined as postoperative mortality. If one or more of the following criteria were met, early graft dysfunction (EGD) was considered: bilirubin level ≥ 10 mg/dL on day 7; international normalized ratio ≥ 1.6 on day 7; ALT or AST level of $> 2,000$ units/L within the first 7 postoperative days.¹³ Primary nonfunction (PNF) was defined as either death or retransplantation occurring within the first post-transplantation week. An allograft with normal liver function or complete recovery was defined as having normal initial function.¹⁴

Cavocaval side to side anastomosis (Belghiti's modified piggy-back technique) without venovenous bypass is included in LT. Daily laboratory workups and Doppler ultrasonography were performed on the first and seventh postoperative days. All recipients were given an immunosuppressive regimen based on calcineurin inhibitors.¹²

All statistical analyses were performed with EpiInfo software.¹⁵ For continuous variables, the Kruskal-Wallis test for two groups was used. Qualitative variables were compared using the chi-square test. Linear regression was used to group comparison according to risk factors. The study protocol was designed according to the ethical guidelines of the 1975 Declaration of Helsinki. The present study complies with the guidelines endorsed by the STROBE initiative¹⁶ and has ethical approval through Plataforma Brasil under CAAE 65198822.6.0000.0020.

RESULTS

The studied population has 233 consecutive deceased donor liver transplants, either primary (97.42%, n = 227) or retransplant (2.58%; n = 6). Standard allocation offer was observed in 81.97% (n = 191) and RA in 18.03% (n = 42). The recipients were predominantly male (65.67%; n = 153), with 50.3 ± 11.8 years and disease severity characterized by CHILD C (64.81%); MELD 22.4 ± 7.6 ; BAR 8.9 ± 4.1 ; SOFT 11.5 ± 7.8 . The mean DRI was 1.41 ± 0.32 . Overall frequency of EGD was 12.45% (n = 29) and PNF 8.15% (n = 19).

Regarding donors' characteristics, depicted in Table 1, national offer ($p = 0.000$) and graft procurement by another surgical team ($p = 0.000$) were significantly more frequent in RA group than in SA group. Histidine-tryptophan-ketoglutarate (HTK) preservation solution was more used ($p = 0.001$) in SA group. Number of days in intensive care unit (ICU) before procurement ($p = 0.44$), cold ischemia time (CIT) in hours ($p = 0.100$); and SOFA ($p = 0.52$) score did not differ between the groups. DRI ($p = 0.0013$) was higher in the RA group.

Table 1. Donor characteristics.

	RA n = 42 (18.03%)	Standard allocation n = 191 (81.97%)	P
Gender (male)	66.7% (n = 28)	71.20% (n = 136)	0.15
Age (years)	43.16 ± 15.88	40.43 ± 15.17	0.23
National Organ Offering	50% (n = 21)	2.62% (n = 5)	0.000*
Harvesting by transplant team	38.10% (n = 16)	79.06% (n = 151)	0.000*
CIT (h)	7.71 ± 1.69	7.16 ± 1.53	0.100
HTK preservation solution	80.95% (n = 34)	95.19% (n = 178)	0.001*
DRI	1.58 ± 0.37	1.37 ± 0.30	0.0013*
SOFA Score	9.73 ± 2.18	9.59 ± 2.25	0.52
ICU stay (days)	4.6 ± 3.3	3.9 ± 2.5	0.44

CIT: cold ischemia time; HTK: Histidine-tryptophan-ketoglutarate; DRI: donor risk index; SOFA: sequential organ failure assessment score; ICU: intensive care uni.; * represents statistical significance.

Figures 1 and 2 respectively show how the mean DRI is clustered and fluctuates over donation location, in SA and RA groups, using the heat map data visualization technique.

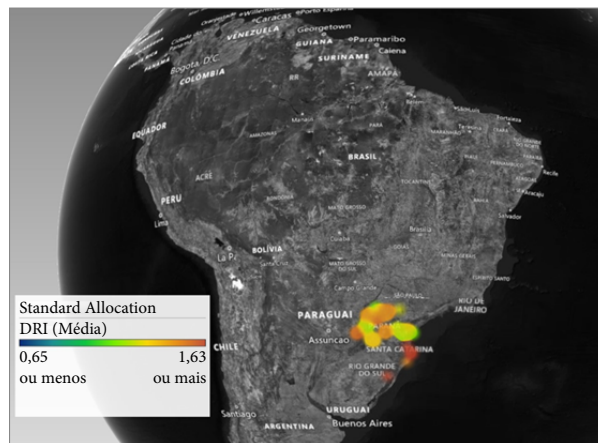


Figure 1. Heat map of donor's DRI and location in standard allocation.

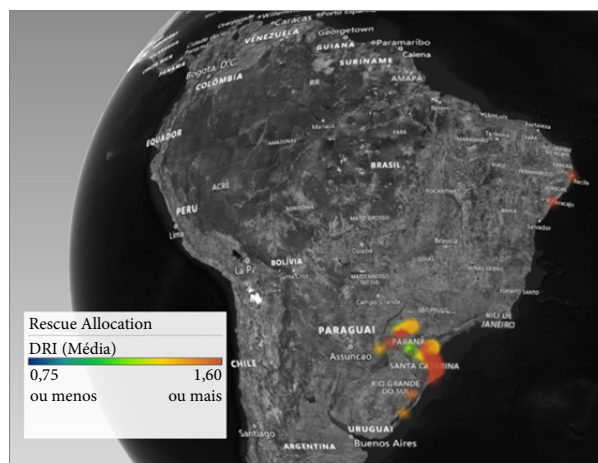


Figure 2. Heat map of donor's DRI and location in RA.

The frequency of each DRI of the cohort is displayed in a scatter plot (Fig. 3).

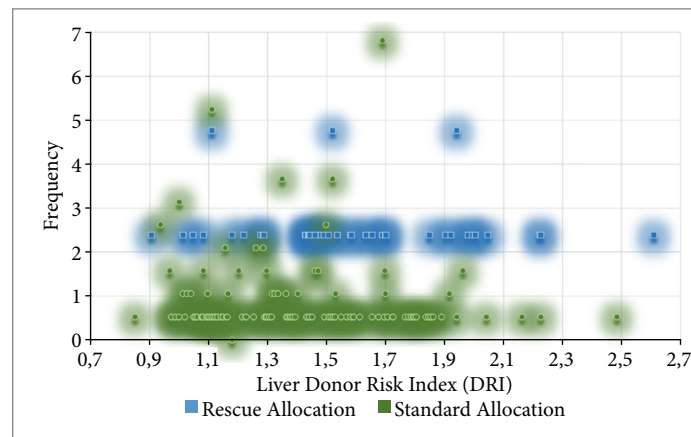


Figure 3. Scatter graph of the frequency of DRI.

As shown in Table 2, dedicated to recipient characteristics, the median position in the RA group was 15th. The majority (76.19%) of RA patients were at home before transplantation, insofar 49.74% of SA recipients were in the hospital, either in the ward or ICU (p = 0.0084). Time in the waiting list did not differ between groups (p = 0.06). MELD (p = 0.000) and BAR (p = 0.0028) were higher in the SA group than in the RA group. SOFT score was similar between groups (p = 0.0602).

Table 2. Recipient characteristics.

	RA n = 42 (18.03%)	Standard allocation n = 191 (81.97%)	P
Gender (male)	61.9% (n = 26)	66.49% (n = 127)	-
Median allocation position	15.5 (min 6; max 482)	1 (min 1; max 5)	-
Age (years)	53 ± 8.64	49.7 ± 12.39	0.1703
Medical condition			
Home	76.19% (n = 32)	50.26% (n = 96)	
Hospital	4.76% (n = 2)	16.23% (n = 31)	0.0084
ICU	19.05% (n = 8)	33.51% (n = 64)	
Waiting time to LT (days)	116.3 ± 157.2	83.58 ± 131	0.0665
CHILD-			
A	3 (7.14%)	10 (5.24%)	-
B	19 (45.24%)	50 (26.18%)	-
C	20 (47.62%)	131 (68.59%)	-
MELD Score	18.47 ± 4.86	23.27 ± 7.90	0.0000*
BAR Score	7.16 ± 3.29	9.29 ± 4.25	0.0028*
SOFT Score	9.35 ± 6.06	12.05 ± 8.17	0.0602

*Represents statistical significance.

In the RA group, the median position for grafts received within the state was 10 (IQR 7–15) and 25 (IQR 16–58) for received outside our state, with significant difference (p = 0.000).

Regarding surgical complications, the frequency of arterial thrombosis (p = 0.17), portal vein thrombosis (p = 0.45) and biliary complications (p = 0.70) were similar between the allocation groups. The rates of EGD and PNF were not different between the RA and SA groups (p = 0.052).

No difference was observed between the two groups regarding allograft function (p = 0.052), nor difference in survival between the two groups (p = 0.83) (Table 3).

Table 3. Postoperative evolution.

	RA n = 42 (18.03%)	Standard allocation n = 191 (81.97%)	P
Arterial thrombosis	0%	4.19% (n = 8)	p = 0.17
Portal vein thrombosis	2.78% (n = 1)	1.15% (n = 2)	p = 0.45
Biliary complications	11.90% (n = 5)	14.14% (n = 27)	p = 0.70
Normal initial function	69.05% (n = 29)	81.68% (n = 156)	
Early graft dysfunction (EGD)	16.67% (n = 7)	11.52% (n = 22)	p = 0.052
Primary nonfunction (PNF)	14.29% (n = 6)	6.81% (n = 13)	
90-day survival	73.81% (n = 31)	72.25% (n = 138)	p = 0.83

DISCUSSION

The current study found that the grafts used in the RA group were of lower quality (higher DRI score) and were assigned to less severe patients (lower BAR and MELD scores). When compared to those who received SA livers, this allocation pattern produced similar short-term results.

Given that RA livers have previously been denied for the top five waiting list patients, usually by more than one transplant team, graft quality is expected to be poor. The brush used here is to define graft quality because the definition of grafts from extended criteria donor is subjective and varies between centers and countries.³⁻⁵

Using the acknowledged DRI score as a graft quality indicator score, we observed a significant difference between RA and SA livers. DRI was idealized to determine the relative risk of a specific graft when compared to an ideal donor (whole organ from a donor less than 40 years of age with brain death secondary to trauma or anoxia). In Feng's seminal work, a mean DRI of 1.58—as found in the RA group—represented 86.3% of 3 months' graft survival.¹⁷

DRI score employs eight variables, among which etiology of brain death, height, and race were not independently examined. It should be considered that it is challenging to determine race in the Brazilian population because of racial miscegenation. Donor age did not differ between groups, and this cohort did not use split liver or donation after cardiac death. The score is completed by two variables: national offer and CIT.

Because of the higher frequency of national offers observed, it was reasonable to expect longer CITs between the groups, as previously reported in the RA framework.^{6,11,18,19} Nevertheless, CIT was not different between the groups, a finding not isolated in literature.⁵ One explanation for this finding stems from a corollary: the graft must be inside the hospital at least with 8 h of cold ischemia allowing portal reperfusion in less than 10 h according to the team's protocol. Of course, this was made possible by the state transplant agency's internal organization and logistical support. As a result, a graft offered in national allocation in which the logistics do not meet this corollary is refused.

The mean CIT of less than 8 h is well bellowing the usual 12 h cut-off, recognized as a risk factor in the BAR score²⁰ and when using the University of Wisconsin's gold standard solution.²¹ However, the observed CIT was above the protective effect of less than 6 h observed in SOFT score.²² Regarding the preservation solution, it remains to be determined whether any of the solutions currently used (HTK, IGL-1) are better or worse than UW when CIT is prolonged over 12 h.²³

The hot spots show the more frequent national offer (50%) and higher DRI in the RA group—higher DRI varies towards the orange and red colors—moving towards Santa Catarina state and some spots in Rio Grande do Sul and the northeastern region of Brazil (Figs. 1 and 2). Grafts obtained from outside the state (national allocation) less frequently (38.1%) had liver grafts harvested by the surgical team responsible for the transplant. In Brazil, a MELD-based allocation system is currently in use, and each state is in charge of organizing donor and graft procurement.²⁴ Grafts are primarily used within the state, except in emergency situations; as a result, grafts harvested under national allocation were already refused by local teams. This explains why national offers have a higher median allocation position than local offers.

Inferring that the number of organ dysfunctions in the donor could possibly influence graft function, we stratified it using the SOFA score²⁵ and didn't find difference between the groups, indicating a homogeneous selection of donors and correlating with a previous finding that SOFA did not preclude successful organ donation.²⁶ The progressive deterioration of physiologic homeostasis secondary to brain death may influence graft function, a factor that did not play a role in our study due to similar number of donors' ICU days between the groups.

We found no differences between the SA and RA groups using established definitions for EGD¹³ and PNF¹⁴ ($p = 0.052$). Although not statistically significant, EGD and PNF were more common in the RA group, a finding that merits consideration. Giretti et al.¹¹ demonstrated this type of impact in graft survival rather than patient survival, and long-term survival does not appear to be influenced by initial graft function.²⁷

The overall incidence of PNF in our study (8.15%) is consistent with previous findings in literature;^{28,29} however, the incidence of PNF (14.29%) in the RA group deserves some discussion. *Death or retransplantation within the first post-transplantation week* is included in the methodological definition of PNF, as used in University of California Los Angeles.¹⁴ This definition may overestimate the incidence of PNF because some deaths during this early period could be attributed to multiorgan failure, sepsis, neurological injury or even a combination of graft and recipient characteristics. This broader definition is advocated by beacons of LT.¹⁴ We prefer to use this broader definition because our ultimate goal is to improve donor-recipient matching, thereby reducing early negative outcomes.

The literature brings the notion that livers from expanded criteria donors may be directed to candidates with low MELD scores^{4,27,30} and in this cohort lower quality organs (RA group – higher DRI) were allocated to patients with lower MELD scores, finding already reported in literature.^{3-6,11}

MELD is well known for its inability to predict post-operative mortality,³¹ owing to a lack of fine tuning regarding the graft-recipient match, such as clinical conditions or operative factors. “Even the best organ may fail when transplanted in a severely ill environment with marginal perfusion”,^{14(p.960)} SOFT and BAR scores better predict graft-recipient interaction and post-operative mortality.³¹ Given that, our findings demonstrated that the RA group was constituted by less severe patients stratified by BAR score ($p = 0.0028$), reassuring the notion of *high risk organs to fewer sick patients*. There was no difference in SOFT score ($p = 0.0602$), possibly because SOFT score includes recipients’ characteristics (ascites, portal vein thrombosis, previous surgeries) that may raise the final score in the RA group. These details are frequently regarded as *mortality enhancers* in recipients with lower MELD scores.

Despite the fact that the analyzed data was obtained from a prospectively maintained database, the study is retrospective, which has its limitations. We cannot rule out selection bias related to patients and accepted RA grafts. Indeed, the authors arbitrarily chose the definition of RA, among others reported,¹⁻⁶ based on the French definition and legal pattern of their allocation system. This definition is problematic because it is based solely on the number of declines rather than some scheme that incorporates clinical criteria.

Some grafts may have been rejected due to a variety of factors such as size, donor characteristics that were not considered in the scores, risk of disease transmission, medical history,³ transplantation center factors,³² *domino effect*,⁴ organizational,¹⁸ or unclear reasons.⁵ This uncertainty is evident in the presented data because grafts with DRI scores lower than the median were transplanted in the RA group (Fig. 3), demonstrating that factors not included in DRI play a significant role. These findings suggest that donor evaluation varies significantly between transplant surgeons, and that accepting and then allocating RA organs according to institutional guidelines is justified, as demonstrated by other studies.^{5,18}

A fruitful question would be to ask if this kind of strategy could be expanded. Our study used 18% of grafts in the RA group, whilst the strategy frequency was 22.7% in UK,³ Argentina 50.9%,⁴ Germany (33, 47.2, and 34%),^{1,5,6} and France (33.9%).¹¹

One strength of the present study was to compare objective functional endpoints (EGD, PNF) with an objective, reproducible, and comparable DRI, and using a better score (BAR) to analyze donor-recipient match. To the best of our knowledge, this combination has never been used in previous studies that compared standard versus rescued allocated organs. Either did not use DRI^{3,4,6,18} or did not report graft function, only patient or graft survival.^{1,2,5} Increasing patient overall survival is crucial but it is a difficult topic to discuss because it takes into account variables like allocation, the characteristics of the donor-recipient pair, postoperative care, and socioeconomic progress in society.^{31,33}

The donor-recipient match area is still a study field,³ possibly a myth,³⁴ and the future will tell whether it is still important or will be crushed by the advent of cold or normothermic perfusion technology. This type of outcome analysis is critical to ensure the best possible standard of care in this area of LT, improve transplant benefit⁴ and assess the actual degree of risk to the recipient using world in development data.

CONCLUSION

A strategy more frequently employed in patients with less severe conditions according to BAR score, liver grafts in a RA system had higher DRI scores and did not provide a difference in short-term survival.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHORS’ CONTRIBUTION

Substantive scientific and intellectual contributions to the study: Silveira F, Silveira FP and Silveira CRS; **Conception and design:** Silveira F and Silveira FP; **Data analysis and interpretation:** Silveira F and Silveira FP; **Article writing:** Silveira F and Silveira FP; **Critical revision:** Silveira F, Silveira FP and Schulz RT; **Final approval:** Silveira F, Silveira FP, Silveira CRS, Montero AS, Higa HC, Ruzzon A and Schulz RT.

DATA AVAILABILITY STATEMENT

Data will be available upon request.

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Not applicable.

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