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ABSTRACT

Background & Aims: In Italy, since August 2014, LT candidates with MELD≥30 receive a national allocation priority. This multi-center cohort study aims to evaluate waiting time in the list, dropout rate, and graft survival before and after introducing the macroarea sharing policy.

Methods: 4,238 patients registered from 2010 to 2018 have been enrolled and categorized in an ERA-1 Group (n=2,013; before August 2014) and an ERA-2 Group (n=2,225; during and after August 2014). Cox proportional hazard model was used to estimate the HR of receiving LT or death between the two ERAs. The Fine-Gray model was used to estimate the HR for dropout from the waiting list and graft loss, considering death as a competing risk event. A Fine-Gray model was also used to estimate risk factors of graft loss.

Results: MELD≥30 patients had a lower median waiting time in the list for LT (4vs.12 days, p<0.001) and a higher probability to be transplanted (HR=2.27, 95%CI 1.78-2.90; p=0.001) in the ERA-2 when compared to ERA-1. The subgroup analysis on 3,515 LTs confirmed ERA-2 (odds ratio=0.56, 95%CI=0.46-0.68; p=0.001) as a protective factor for better graft survival rate. The protective variables for lower dropouts on the waiting list were: ERA-2, high volume centers, no competition centers, male recipients, and hepatocellular carcinoma. The protective variables for graft loss were high volume center and ERA-2, while MELD≥30 remained related to a higher risk of graft loss.

Conclusions: The national MELD≥30 priority allocation was associated with improved patient outcomes, although MELD≥30 had a higher risk of graft loss. The transplant centers volume and competition among centers may have a role in the recipient prioritization and outcome.

LAY SUMMARY:

After introducing the Italian national MELD≥30 priority, more LT, fewer dropouts, and shorter waiting times were observed in patients with MELD≥30. However, a higher risk of graft loss still burdens these cases compared to MELD<30. The volume of transplant centers and competitions among centers may have a role in the recipient prioritization and outcome.

INTRODUCTION

Liver transplantation (LT) is the only effective therapy for patients with end-stage liver disease, but donor shortage limits its applicability. Most allocation policies are based on the model for end-stage liver disease (MELD) score, developed in 2002, and aim at prioritizing the sickest patients at higher risk of death or dropout from the waiting list[1-2]. In many countries, patients with MELD score above a pre-defined cut-off (30, 35, or 40, depending on the allocation system) are granted a preferential allocation for LT within a determined geographical area[3-4]. The rationale for transplanting the sickest patients is to shorten the delay with the final goal of avoiding renal and infectious complications that may negatively affect post-transplant outcomes and/or preclude LT. This allocation strategy is nonetheless exposed to criticism as it may lead to reduced overall survival after LT[5-6], limiting access to LT for low-MELD patients, particularly those suffering from hepatocellular carcinoma (HCC). Additionally, another critique that has been raised is related to increased costs of postoperative care of globally sicker recipients[7-8].

However, for the criticisms mentioned above, variability has been observed among centers having a different experience, a different volume of liver transplantation performed yearly[9], and extended criteria donors (ECD), which were described to have a substantial impact on LT outcome in high-MELD patients. Therefore, when comparing clinical outcomes between allocation policies, such factors should be considered in statistical analysis.

In Italy, since August 2014, LT candidates with MELD $\geq$ 30 have the benefit of being allocated even outside the geographical area of the transplant center where they are waitlisted. In particular, two extended areas (so-called "macroareas") were established: Center-North and Center-South. Currently, patients with MELD$\geq$30 are allocated the first available liver from an adult donor in their macroarea if there is no concomitant higher-degree emergency (e.g., fulminant hepatic failure) having priority allocation on a national basis. If more patients with MELD$\geq$30 are waitlisted in the same macroarea, the first available liver is allocated to the one that has been signalled first. This

new allocation scheme was introduced to reduce waiting list time and perform LT in better clinical conditions while preserving the allocation algorithm's equity.

Whether the introduction of MELD≥30 scheme has effectively reduced waiting list time in these patients without negatively affecting waiting list time in patients with MELD<30 has not been evaluated so far. Moreover, the effects of this new rule on patient and graft survival have not been investigated.

Thus, this multicentre national study aimed to evaluate the effects of introducing MELD≥30 allocation scheme on waiting list time, dropout rate, and patient and graft survival in Italy.

PATIENTS AND METHODS

Study design

This study was designed as a multi-center cohort study involving six Italian transplant centers. A total of 4,330 LT candidates were initially considered for the study. Exclusion criteria for the study were: candidates aged <18 years (n=0), combined transplantation (n=21), living donor liver transplantation (n=6), and deceased cardiac donation (n=65). In the end, 4,238 LT candidates were enrolled for the present study. The patients included in the study were adult (≥18 years) candidates for isolated liver transplantation. All the indications for LT, also comprehending the cases of re-transplantation and acute liver failure, were considered. Only donors after brain death were considered in the study. Prospectively collected data from each participating center were retrospectively analyzed.

Study cohorts

According to their waiting list entry date, patients were divided into ERA-1 Group (August 2010 - July 2014) and ERA-2 Group (August 2014 - July 2018).

All the patients were categorized in high- or low-MELD (≥30 or <30) according to the MELD score calculated at the time of entering the waiting list. The rationale for this choice was to preserve the intention-to-treat design of the study. Therefore, cases with an initial MELD<30 presenting a progressive worsening of the liver function during the waiting period overpassing the threshold value of 30 were maintained in the initial low-MELD group.

Italy is characterized by heterogeneity in terms of geographical distribution and volume of LT centers. Some regions have a single transplant center, while other regions have multiple transplant centres with patients inscribed into a common regional list and access to the same donor pool. Moreover, organ availability is highly variable among regions, with some regions presenting more than 40 donors per million inhabitants per year and others less than 10. Consequently, we classified the centres participating in this study as SCR (single center per region; non-competitive allocation) or MCR (multiple centers per region; presence of allocation competition). Additionally, as

previously reported,[10] centers performing≥70 cases per year were defined as high-volume (HV), whereas centers performing<70 cases per year were defines as low volume (LV).

Data collection

Collected data for donors and recipients included age, sex, height, weight, medical history of hepatocellular carcinoma (HCC), anti-HCV and HBV-anticore positivity, the dropout from the waiting list, overall and graft survival, and the MELD score. The MELD score was calculated at the time of listing using serum creatinine, serum total bilirubin and INR according to the following formula: 9.57∗logecreatinine (mg/dL) + 3.78 ∗ logebilirubin (mg/dL) + 11.20∗logeINR + 6.43[1,11,12]. Definition of ECD was based on the presence of one of the following: hemodynamic instability, age>65 years, BMI>30 kg/m2, bilirubin>3 mg/dL, aspartate aminotransferase (AST) o alanine aminotransferase (ALT)≥three times the reference level, sodium>165 mmol/l, days on intensive care unit (ICU)>7, macrovesicular steatosis≥40%.[13]

Study endpoints

The study's primary endpoint was the time on the waiting list, a surrogate of physical and functional decline in LT candidates.[14] The waiting time was calculated from the time of waiting list inscription to the time of LT, dropout, or last follow-up in the patients still waiting in the list at the time of censoring. The waiting time calculated for the entire enlisted population was adopted in the analyses without excluding delisted cases. This approach was used for maintaining the initial intention-to-treat design of the study.

Secondary endpoints were death within 365 days after LT, the cumulative hazard of death, graft loss within 365 days after LT, the cumulative hazard of graft loss, prognostic factors related to waitlist dropout, and graft loss.

Follow-up period

Patients were followed up from the waiting list entry date and censored at the occurrence of LT, end of the follow-up period, or end of data coverage. Patients receiving LT were followed from the day

of LT to the date of the occurrence of the study outcome, end of the follow-up period, or end of data coverage.

Ethics

Local institutional review boards of the six Italian transplant centers approved the study. The study has been registered as an observational study on ClinicalTrials.gov (NCT04530240).

The Italian allocation system for liver transplantation

Before August 2014, each region in Italy had a different MELD-based allocation scheme. Super-urgent cases (i.e., acute liver failures and early retransplants) were granted national priority allocation, whereas all other candidates had access exclusively to the regional donor pool. The minimum MELD score to access the waiting list was 15, except for patients HCC who can enter the list with lower MELD values.

Internal Regional rules for prioritization were based on the principle of "urgency" for which the sickest patients had priority for allocation. Patients with HCC were even more prioritized for allocation based on their cancer stage and the MELD score.

Since August 2014, the allocation process changed with the introduction of macroareas to allocate organs for LT candidates with MELD score ≥ 30 (http://www.trapianti.salute.gov.it/).[15] When a patient entered the waiting list of a macroarea, there were no additional prioritization principles for LT.

Statistical analysis

Socio-demographic and clinical characteristics of patients in ERA-1 and ERA2 were compared at the time of entrance in the waiting list and at the time of LT using the analysis of variance (ANOVA) F test, Student T-test, and Fisher's exact test.

The propensity score of being in ERA-2 rather than ERA-1 was computed using a logistic regression model based on covariates (**Table 1**) at the time of entrance on the waiting list and at the time of LT[16-18]. In particular, the propensity score at the time of entrance on the waiting list was computed using the following variables: age (years), sex, height (cm), weight (kg), blood group

(AB-B), HCC, HCV positivity, MELD, high-volume center, and regional competitive status. The propensity score at the time of LT was computed using the following variables: recipient age, recipient sex, recipient height (cm), recipient weight (kg), recipient HCC, recipient HCV positivity, MELD, high-volume center, regional competitive status, donor age, donor sex, donor height (cm), donor weight (kg), donor HCV positivity, donor HBcAb positivity.

To inspect the exchangeability between the two ERAs given socio-demographic and clinical characteristics, we plotted the kernel density estimates of the propensity score at the time of entrance in the waiting list. We computed the area of overlap between the two density functions. To assess exchangeability between ERAs in terms of patients' socio-demographic and clinical characteristics, we tested if half of the propensity score distributions was between 0.3 and 0.7. Additionally, we tested if the overlap of the propensity score was greater than 75%. Density functions of MELD between the two ERAs among centers with different volumes and regional allocation were plotted.

Cause-specific Cox proportional hazard model was used to estimate the HR of receiving LT or death between the two ERAs. Cumulative hazards were then derived and used to estimate median waiting list time. This model was considered advisable over the Fine-Gray regression for this specific analysis because the cause-specific Cox regression presents the advantage of giving detailed insights into the relationship between a risk factor and each separate outcome, which was the purpose of this analysis[19].

The Fine-Gray model was used to estimate the hazard ratio for patient death and graft loss, considering dropout from the waiting list as a competing risk event. In this model, sub-distribution hazards are computed that are interpreted as the hazard of dropout from the waiting list and patient death / graft loss, given that a subject has survived. Otherwise noted, the term hazard for these two outcomes refers to sub-distribution hazards. Fine-Gray model was used to estimate risk factors of graft loss.

Graft loss was defined as patient death or documented graft failure requiring relisting for second transplantation.

In the adjusted analyses, the propensity score was added to the statistical models. In particular, for the outcomes LT, dropout from the waiting list, and death, we used the propensity score computed at the time of entrance in the waiting list. For graft loss, we used the propensity score computed at the time of LT. We decided to adjust the models with the propensity score instead of creating a pseudo-population using a propensity score or an inverse probability weighting. The decision to use this approach should be controversial. For survival data analyses with proportional hazards models, adjustment on the propensity score should entail a, although minimal, bias in estimating the marginal treatment effect,[20] and optimal full matching, mainly using an inverse probability of treatment weighting,[21] may be preferable. However, some simulations comparing the effect of using the different models showed significant overlaps in the confidence interval estimates, which did not conclude the statistical superiority of one method versus the other.[22] Therefore, we decided to use the adjustment with the propensity score, although it should not appear as the best approach to use, because it was the most reader-friendly approach, considering that the differences of the different approaches to use may be smaller in practice than the uncertainty of estimates.

The cumulative hazards for LT, graft loss, and death were plotted, and the cumulative hazard functions were compared using the Gray test.

A P value<0.05 was considered statistically significant. The statistical analysis was carried out using R (R Development Core Team, Austria, Vienna).

RESULTS

Study population

4,238 LT candidates waitlisted from August 2010 to July 2018 were enrolled. The last date of follow-up was December 2018. The median follow-up period of the entire population from the time of waiting list inscription was 29 months (interquartile ranges: 9-56). None of the patients was lost to follow up. A total of 3,515/4,238 (82.9%) patients were transplanted, with 529/3,515 (15.0%) cases of post-LT death reported. As for the post-LT graft losses, 511/3,515 (14.5%) cases were reported.

In detail, patients were recruited from LT centres located in Bologna (n=961), Pisa (n=980), Turin (n=897), Milan Niguarda (n=859), Rome Sapienza (n=268), and Rome Cattolica (n=273). The transplant volume of study centers represented close to half of the entire Italian liver transplant activity in the same period. Two centers (Pisa and Turin) were SCR, whereas the others (Bologna, Milan Niguarda, Rome Sapienza, and Rome Cattolica) were MCR. Pisa, Turin, Bologna, and Milan Niguarda were defined as HV centers, whereas Rome Sapienza and Rome Cattolica were defined as LV (**Supplementary Table 1)**.

A total of 2,013 patients were waitlisted in ERA-1 and 2,225 in ERA-2. A total of 1,725 and 1,790 patients were transplanted in ERA-1 and ERA-2, respectively, with 324 and 205 cases of post-LT graft losses reported. As for the post-LT death, 329 and 182 cases were reported, respectively. A total of 414 cases (319 LT, 88 dropouts) initially enlisted in ERA-1 were transplanted or dropped out during the ERA-2 period. However, only the limited number of 18/4,238 (0.4%) with MELD ≥30 presented a potential allocative benefit passing from an era without macroarea allocation to another one with this opportunity.

Socio-demographic and clinical characteristics of the study population are reported in **Table 1**. The median recipient age was 56 years, with 77% of male recipients. At the time of waiting list inscription, patients with MELD≥30 were 327/4,238 (7.7%), and they were equally distributed between the two eras (ERA-1=155/2,013 cases [7.7%] vs. ERA-2=172/2,225 cases [7.7%]). During

the waiting time period, 66/4,238 (1.6%) patients initially presenting a MELD<30 overpassed the threshold of MELD 30. They were similar between the two eras (ERA-1=31/2,013 cases [1.5%] vs. ERA-2=35/2,225 cases [1.6%]).

The median waiting time of MELD≥30 patients was significantly shorter in ERA-2 (4 vs. 12 days; p<0.001), and the percentage of MELD≥30 was different according to the transplant volume and the presence of single or multiple transplant centers per region, and it did not change between the two ERAs (**Figure 1A and 1B**).

With the intent to exclude the possibility that the shorter waiting time observed in ERA 2 resulted from a more significant number of patients dropping out more often and quicker in this ERA, we performed a separate analysis in only transplanted cases. Also, in this case, the median waiting time in the sub-group of patients with MELD≥30 who underwent LT was significantly shorter in ERA-2 when compared to ERA-1 (3 vs. 9 days; p<0.001).

Single transplant center per region with high volume had 4% MELD≥30 in ERA 2 vs. 2% in ERA-1 (P<0.001). Multiple transplant centers per region with high volume had 11% MELD≥30 in ERA 2 vs. 10% in ERA-1 (P=0.75), and multiple transplant centers per region with low volume had 13% MELD≥30 in ERA 2 vs. 12% in ERA-1 (P=0.81).

Density functions of the propensity score of patients in ERA-1 and ERA-2 are provided in **Supplementary Figure 1**. The overlap of propensity score was 77%, with more than 90% of density functions included in the range 0.3 and 0.7 of the propensity score, confirming comparable socio-demographic and clinical patient characteristics between two ERAs.

Liver transplantation & time on the waiting list

The cumulative hazard of LT within 365 days from the first day in the waiting list among patients with MELD<30 and MELD≥30 in ERA-1 and -2 is provided in **Figure 2A**. Patients with MELD≥30 in ERA-2 had the highest cumulative hazard for LT (3.29, 95%CI 2.35-4.23) if

compared to patients with MELD≥30 in ERA-1 (cumulative hazard 2.64, 95%CI 1.93-3.35), and MELD<30 in ERA-2 (cumulative hazard 1.49, 95%CI 1.47-1.51) and ERA-1 (cumulative hazard 1.40, 95%CI 1.39-1.41). Analogously, patients with MELD≥30 in ERA-2 had the lowest median time in the waiting list (4 days, 95% 3-5 days) if compared to patients with MELD≥30 in ERA-1 (median 12, 95%CI 9-20), and MELD<30 in ERA-2 (median 87, 95%CI 77-100) and ERA-1 (median 126, 95%CI 116-135) (**Figure 3**). The hazard ratio of LT of patients in ERA2 with MELD≥30 was 2.27 (95%CI 1.78-2.90) compared to patients with MELD≥30 in ERA-1 (**Table 2**).

Risk factors of dropout from the waiting list

Six different variables were identified as statistically significant factors of dropout from the waiting list (**Figure 4**). In detail, patient age at the time of enlisting was a hazard factor for dropout, with a 1% increase in the hazard of dropping out for each one-year increase of age (hazard ratio=1.01, 95%CI=1.01-1.02). HCC as main indication of LT (hazard ratio=0.57, 95%CI=0.47-0.69), SCR status (hazard ratio=0.31, 95%CI=0.25-0.39), ERA-2 (hazard ratio=0.79, 95%CI=0.67-0.94), high-volume center (hazard ratio=0.69, 95%CI=0.56-0.84), and male gender (hazard ratio=0.73, 95%CI=0.57-0.93) were all protective factors for the hazard of drop-out (**Figure 4**).

Overall survival and graft loss

The cumulative hazard of death within 365 days from LT among patients with MELD<30 and MELD≥30 in ERA-1 and 2 is provided in **Figure 2B**. Patients with MELD≥30 in ERA-2 had a similar cumulative hazard for death (0.32, 95%CI 0.21-0.43) than patients with MELD≥30 in ERA-1 (cumulative hazard 0.37, 95%CI 0.26-0.49). Similarly, patients with MELD<30 in ERA-2 (cumulative hazard 0.08, 95%CI 0.06-0.09) and ERA-1 (cumulative hazard 0.10, 95%CI 0.08-0.11) had similar cumulative hazards for death within 365 days from LT.

In both crude and adjusted analyses, being in ERA-2 and having a MELD≥30 was not associated with an increased hazard of death compared to patients receiving LT in ERA-1 among those having MELD≥30 (**Table 2**). In both crude and adjusted analyses, being in ERA-2 and having a MELD≥30

was not associated with an increased hazard of graft loss than patients receiving LT in ERA-1 among those having MELD≥30 (**Table 2**).

MELD≥30 (HR=2.98, 95%CI=2.20-4.03) was identified as a statistically significant factor of graft loss following LT (**Figure 5**). Vice versa, age at the time of LT (HR=0.98, 95%CI=0.97-0.99), and high volume centers (HR=0.61, 95%CI=0.43-0.86) were associated with a lower probability of undergoing graft loss (**Figure 5**).

DISCUSSION

This multi-center study shows improved LT outcomes after introducing a prioritization scheme for candidates with MELD≥30 in a European series.

The introduction of the MELD score as a criterion for the prioritization of LT candidates was associated with an improvement of their intention-to-treat survival[1,2]. Subsequently, implementing national sharing models aimed at favoring high-MELD patients has represented a further step to improve outcomes in sickest patients[3,4].

Different priority cut-offs have been applied worldwide[11,23]. The MELD≥30 cut-off has been chosen in Italy. Our study results show that the new allocation policy was associated with a reduction of the median waiting time of these patients, also showing a global protective effect on the risk of dropout.

In this European study, differently from other U.S. series[3,12,24], the MELD≥30 sharing scheme introduction did not improve graft and patient survival rates of high-MELD patients after LT. In our series, MELD≥30 was an independent risk factor of poor graft survival.

This last observation is open to multiple potential explanations. For example, the ECD rate reported in the present series was high (approximately 40% of the cases), and it was related in most cases to advanced donor age. Typically, optimal grafts are allocated to a high-MELD patient, whereas ECD to low-MELD cases (i.e., HCC patients)[25]. This strategy might not be applicable, at least consistently, in the Italian setting, where roughly 40% of donors are ECD. These results are in keeping with the results from studies reporting improved outcomes in high-MELD patients after introducing the MELD sharing schemes due to improved donor-recipient matching, in which use of ECD donors in recipients with severe liver failure was minimized[7,12].

MELD≥30 patients received grafts from significantly younger donors in our series compared to the MELD<30, but the median donor age was still high (approximately 60 vs. 55 years in MELD<30 vs. ≥30). The impossibility of obtaining a better donor-recipient allocation process due to the great

number of ECD observed on the national territory may explain the lack of an evident outcome improvement in MELD≥30 patients, despite faster allocation.

Another factor with a possible detrimental effect on graft survival is the high rate of HCV-positive patients among LT candidates[26], in a country like Italy, in which HCV has been endemic for a long time. Longer follow-up will probably be needed to appreciate the statistical effect of the introduction of new antivirals. Undoubtedly, the improvement achieved in HCV treatment may have accounted for part of the positive effect observed for ERA-2.

It should be highlighted that the observed 5-year patient survival rates observed in patients with MELD≥30 are well above the proposed futile threshold of 50%[5,15], showing similarities with the results of a recent series of LTs performed for acute-on-chronic liver failure[27].

Similarly, the equity principle[16,28,29] was maintained because recipients with MELD<30, including those with HCC, improved their overall outcomes, showing similarities with previous experiences using a MELD-35 sharing scheme[15].

As for the other risk factors for dropout observed in our study, we noted that HCC as the main indication for transplantation was associated with a lower risk of dropout. HCC patients represented more than 40% of the entire investigated population. The high percentage of HCC cases justifies the different MELD≥30 rates on the waiting list observed in our study compared to the US series (10-15% vs. 30%)[8,11]. The protective effect of HCC for the risk of the dropout was probably due to different factors, like specific peculiarities of the regional allocation systems and a propensity of the Italian centers to allocate grafts from ECD to this category of patients[15,25]. The strategy to favor equity among HCC and non-HCC is still debated,[30] and it was not the aim of our study. We can only report that in the HCC patients, representing more than 40% of the entire investigated population, no disadvantage in terms of dropout risk was observed after introducing the MELD≥30 scheme.

Other variables connected with a lower risk of dropout were the waiting list inscription in a high-volume center and the absence of a regional competition.

The positive effect of the center volume was expected, having been already demonstrated in previous studies[31,32]. The presence of a single center able to perform a high number of LTs seems to be the ideal condition for minimizing the risk of death or the deterioration of the LT candidate clinical conditions in the waiting list.

The role of the regional competition is more complex to explain. In this scenario, we can argue that patient selection before wait listing may play a role. Indeed, centers competing in the same region may have an attitude to select more severe cases to implement their activity, whereas the same pressure is likely not an issue for mono-regional centers. Accordingly, we observed a significantly higher rate of MELD≥30 in centers with a regional competition. It has been observed that competition among transplant centers favors the attitude to" push the limits" and reduce risk avoidance policy[9], and the introduction of the national share for MELD≥30 allocation policy may further favor this trend.

Interestingly, the national share MELD≥30 allocation policy seemed to favor the waiting list inscription of the sickest patients in centers without regional competition. An increased rate of more severe patients on the waiting list was reported in these centers in the second era.

However, as confirmed in our series, the tendency to transplant more clinically advanced cases should be carefully analyzed, taking into account the worse results observed in these patients after transplantation. A balancing between costs and benefits in transplanting severely sick patients should be considered[8].

Our study clearly shows how difficult it is to maintain a balance among risk avoidance, prevalence of high MELD patients, dropout rate, and satisfactory postoperative outcomes. Furthermore, our analysis confirms the importance of continuous monitoring of any MELD-based prioritization scheme. Policymakers should weigh the benefit of shortening waiting list time in sickest patients against the decreased graft survival observed in this subset.

This study presents some limitations. This study did not include all the transplant centers of Italy due to the difficulty to meet the approval and to recruit all the data, even if the study was discussed

during the annual Italian meeting of the S.I.T.O. (Italian Organ Transplantation Society) and the total number of cases represent half of the transplant series in Italy. Furthermore, our analyses did not account for improvements in medical practices from ERA-1 to ERA-2 that may have accounted for the clinical and therapeutic improvements observed in the transplant centers during this latter ERA. We explored if the shorter waiting time observed in the ERA-2 patients should be artificially caused by the shorter follow-up observed in these patients. However, only 62/4,238 (1.5%) ERA-2 cases were still on the waiting list at the time of the study enrolment interruption (i.e., July 2018), and only 24 (0.6%) of them were enlisted within the year 2018. So, we can say that 4,214 (99.4%) of the cases enrolled in our study were followed up for at least one year from the time of their enlisting. Consequently, we considered minimal the impact on our results of the shorter waiting time in ERA-2 patients. Another unexplored aspect of the study is the unexplored impact of the direct-acting antivirals in the present series. Given the consideration that HCV represents a common indication for LT in Italy, unfortunately, the study's retrospective nature impaired us to investigate this important aspect in the present analysis. We did not adjust the models present in our analyses using exception MELD points but using only the laboratory MELD values. Such a decision should impact the results, mainly considering a large number of HCC patients present in our analysis. However, considering that the study explored the impact of the MELD-30 rule, the MELD progression in all the exception-point cases was stopped when a value of MELD 29 was reached,[15] therefore not impacting the obtained results. Only Exception P1 patients (i.e., Rendu-Osler-Weber disease, young adult hepatoblastoma, Kasabach-Merritt disease, and retransplant >10 days but ≤30 days from the first transplant) were able to reach the macroarea allocation no matter on their MELD value. Only 34 “late” reLT were enrolled in this series, thus minimally impacting the observed results.

Another limit is that all the patients initially showing a MELD value<30 and showing a MELD worsening during the waiting time remained categorized in the MELD<30 group. Such a decision derived from the necessity to maintain the study's initial intention-to-treat design and avoid placing

a "mobile" starting time point for calculating the waiting time. Understanding the potential bias of such a decision, we considered it the best way to capture a complex dynamic process in which the waiting-list patients present continuous oscillations of their MELD score. As a partial limitation of the potential bias, the cases involved in this process only represented 1.6% of the entire population.

We should also report that we used two different propensity scores for adjusting our analyses. In detail, the propensity score computed at the time of entrance in the waiting list was used for adjusting the models with the outcomes LT, dropout from the waiting list, and death. For graft loss, we used the propensity score computed at the time of LT. With the intent to observe if a significant effect derived from this methodological decision, we performed a sub-analysis in which we used the propensity score measured at the time of waiting list inscription for adjusting the model for graft loss. As reported in **Supplementary Table 2**, no relevant differences were observable using the adjustment of the two different propensity scores, therefore showing a minimal impact on the reported results. However, it should be highlighted that due to the observational nature of this study, we will never be able to claim the complete absence of residual confounding.

Lastly, as for the causes of dropout, in a small percentage of cases (i.e., 62/658 cases), they were composed of patients showing improved clinical conditions (i.e., HCC complete response or MELD decline), poor compliance, or the decision to move to other LT centers. The retrospective nature of the study limited our capacity to clarify these patients further. However, considering their small number, we decided to consider them as "dropouts" in the competing risk models due to their only marginal impact on the observed results.

In conclusion, after adopting the Italian national MELD≥30 priority allocation, we observed more LT for patients with MELD≥30, a shortening of their time on the waiting list, and improved graft survival. Transplant centers volume and competition between different centers in the same region may impact on recipient prioritization and outcome and should be considered in future studies on the subject.

ABBREVIATIONS

LT Liver Transplantation

MELD Model for End-stage Liver Disease

HCC Hepatocellular Carcinoma

ECD Extended Criteria Donors

SCR Single Centre per Region

MCR Multiple Centres per Region

HV High-Volume

LV Low-Volume

HCV hepatitis C virus

HBcAb hepatitis B core antibody

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REFERENCES

[1] Ravaioli M, Grazi GL, Ballardini G, Cavrini G, Ercolani G, Cescon M, et al. Liver transplantation with the Meld system: a prospective study from a single European center. Am J Transplant 2006;6:1572-7. DOI: 10.1111/j.1600-6143.2006.01354.x.

[2] Kamath PS, Wiesner RH, Malinchoc M, Kremers W, Therneau TM, Kosberg CL, et al. A model to predict survival in patients with end-stage liver disease. Hepatology 2001;33:464-470. DOI: 10.1053/jhep.2001.22172.

[3] Nekrasov V, Matsuoka L, Rauf M, Kaur N, Cao S, Groshen S, et al. National Outcomes of Liver Transplantation for Model for End-Stage Liver Disease Score ≥40: The Impact of Share 35. Am J Transplant 2016;16:2912-2924. DOI: 10.1111/ajt.13823.

[4] Goldberg DS, Levine M, Karp S, Gilroy R, Abt PL. Share 35 changes in center-level liver acceptance practices. Liver Transpl 2017;23:604-613. DOI: 10.1002/lt.24749.

[5] Weismüller TJ, Fikatas P, Schmidt J, Barreiros AP, Otto G, Beckebaum S, et al. Multicentric evaluation of model for end-stage liver disease-based allocation and survival after liver transplantation in Germany - limitations of the 'sickest first'-concept. Transpl Int 2011;24:91-9. DOI: 10.1111/j.1432-2277.2010.01161.x.

[6] Habib S, Berk B, Chang CC, Demetris AJ, Fontes P, Dvorchik I, et al. MELD and prediction of post-liver transplantation survival. Liver Transpl 2006;12:440. DOI: 10.1002/lt.20721.

[7] Croome KP, Lee DD, Harnois D, Taner CB. Effects of the Share 35 Rule on Waitlist and Liver Transplantation Outcomes for Patients with Hepatocellular Carcinoma. PLoS One 2017 25;12:e0170673. DOI: 10.1371/journal.pone.0170673.

[8] Nicolas CT, Nyberg SL, Heimbach JK, Watt K, Chen HS, Hathcock MA, et al. Liver transplantation after share 35: Impact on pretransplant and posttransplant costs and mortality. Liver Transpl 2017;23:11-18. DOI: 10.1002/lt.24641.

[9] Ravaioli M, Grande G, Di Gioia P, Cucchetti A, Cescon M, Ercolani G, et al. Risk Avoidance and Liver Transplantation: A Single-center Experience in a National Network. Ann Surg 2016;264:778-786. DOI: 10.1097/SLA.0000000000001887.

[10] Avolio AW, Franco A, Schlegel A, Lai Q, Meli S, Burra P, et al. Development and Validation of a Comprehensive Model to Estimate Early Allograft Failure Among Patients Requiring Early Liver Retransplant. JAMA Surg. 2020;1;155(12):e204095. DOI: 1001/jamasurg.2020.4095. Erratum in: doi: 0.1001/jamasurg.2020.5513.

[11] Nagai S, Chau LC, Schilke RE, Safwan M, Rizzari M, Collins K, et al. Effects of Allocating Livers for Transplantation Based on Model for End-Stage Liver Disease-Sodium Scores on Patient Outcomes. Gastroenterology 2018;155:1451-1462.e3. DOI: 10.1053/j.gastro.2018.07.025.

[12] Kwong AJ, Goel A, Mannalithara A, Kim WR. Improved posttransplant mortality after share 35 for liver transplantation. Hepatology 2018;67:273-281.

[13] European Association for the Study of the Liver. Electronic address: easloffice@easloffice.eu. EASL Clinical Practice Guidelines: Liver transplantation. J Hepatol. 2016 Feb;64(2):433-485. doi: 10.1016/j.jhep.2015.10.006. Epub 2015 Nov 17. PMID: 26597456.

[14] Lai JC, Dodge JL, Sen S, Covinsky K, Feng S. Functional decline in patients with cirrhosis awaiting liver transplantation: Results from the functional assessment in liver transplantation (FrAILT) study. Hepatology 2016;63:574-80.

[15] Cillo U, Burra P, Mazzaferro V, Belli L, Pinna AD, Spada M, et al. A Multistep, Consensus-Based Approach to Organ Allocation in Liver Transplantation: Toward a "Blended Principle Model". Am J Transplant 2015;15:2552-61. DOI: 10.1111/ajt.13408.

[16] Kang S, Little RJ, Kaciroti N. Missing not at random models for masked clinical trials with dropouts. Clin Trials 2015,12:139–148. DOI: 10.1002/hep.29301.

[17] Caliendo M, Kopeinig S. Some practical guidance for the implementation of propensity score matching. J Econ Surv 2008;22:31–72. https://doi.org/10.1111/j.1467-6419.2007.00527.x.

[18] Austin PC, Lee DS, Fine JP. Introduction to the analysis of survival data in the presence of competing risks. Circulation 2016;133:601-609. DOI: 10.1161/CIRCULATIONAHA.115.017719.

[19] Ozenne B, Soerensen AL, Scheike TH, Torp-Pedersen CT, Gerds TA. Risk regression: Predicting the risk of an event using Cox regression models. R Journal 2017;9:440-460.

[20] Gayat E, Resche-Rigon M, Mary JY, Porcher R. Propensity score applied to survival data analysis through proportional hazards models: a Monte Carlo study. Pharm Stat 2012;11:222-229.

[21] Austin PC, Stuart EA. The performance of inverse probability of treatment weighting and full matching on the propensity score in the presence of model misspecification when estimating the effect of treatment on survival outcomes. Stat Methods Med Res 2017;26:1654-1670.

[22] Zhu K. Comparing Propensity Score And Inverse Weighting Methods In A Longitudinal Time-To-Event Study. Public Health Theses 2012;1348.

[23] Nekrasov V, Matsuoka L, Kaur N, Pita A, Whang G, Cao S, et al. Improvement in the Outcomes of MELD ≥ 40 Liver Transplantation: An Analysis of 207 Consecutive Transplants in a Highly Competitive DSA. Transplantation 2017;101:2360-2367. DOI: 10.1097/TP.0000000000001738.

[24] Luo X, Leanza J, Massie AB, Garonzik-Wang JM, Haugen CE, Gentry SE, et al. MELD as a metric for survival benefit of liver transplantation. Am J Transplant 2018;18:1231-1237. DOI: 10.1111/ajt.14660.

[25] Ravaioli M, Grazi GL, Ercolani G, Cescon M, Del Gaudio M, Zanello M, et al. Liver allocation for hepatocellular carcinoma: a European Center policy in the pre-MELD era. Transplantation 2006 27;81:525-30. DOI: 10.1097/01.tp.0000198741.39637.44.

[26] Ghinolfi D, Lai Q, Pezzati D, De Simone P, Rreka E, Filipponi F. Use of Elderly Donors in Liver Transplantation: A Paired-match Analysis at a Single Center. Ann Surg 2018;268:325-331. DOI: 10.1097/SLA.0000000000002305.

[27] Sundaram V, Kogachi S, Wong RJ, Karvellas CJ, Fortune BE, Mahmud N, et al. Effect of the clinical course of acute-on-chronic liver failure prior to liver transplantation on post-transplant survival. J Hepatol 2020;72:481-488. DOI: 10.1016/j.jhep.2019.10.013.

[28] Jasseron C, Francoz C, Antoine C, Legeai C, Durand F, Dharancy S, et al. Impact of the new MELD-based allocation system on waiting list and post-transplant survival - a cohort analysis using the French national CRISTAL database. Transpl Int 2019;10.1111/tri.13448. doi:10.1111/tri.13448.

[29] Tschuor C, Ferrarese A, Kuemmerli C, Dutkowski P, Burra P, Clavien PA, et al. Liver Allocation Study Group. Allocation of liver grafts worldwide - Is there a best system? J Hepatol 2019;71:707-718. DOI: 10.1016/j.jhep.2019.05.025.

[30] Ishaque T, Massie AB, Bowring MG, Haugen CE, Ruck JM, Halpern SE, et al. Liver transplantation and waitlist mortality for HCC and non-HCC candidates following the 2015 HCC exception policy change. Am J Transplant 2019;19:564-572. DOI: 10.1111/ajt.15144.

[31] Beal EW, Black SM, Mumtaz K, Hayes D Jr, El-Hinnawi A, Washburn K, et al. High Center Volume Does Not Mitigate Risk Associated with Using High Donor Risk Organs in Liver Transplantation. Dig Dis Sci 2017;62:2578–2585. DOI: 10.1007/s10620-017-4639-2.

[32] Yoo S, Jang EJ, Yi NJ, Kim GH, Kim DH, Lee H, et al. Effect of Institutional Case Volume on In-hospital Mortality After Living Donor Liver Transplantation: Analysis of 7073 Cases Between 2007 and 2016 in Korea. Transplantation 2019;103:952–958. DOI: 10.1097/TP.0000000000002394.

Table 1. Recipient- and donor-related characteristics in the two ERAS. Level of significance: p <0.05 (ANOVA test, Student T-test, and Fisher's exact test).

Variables	**Data at waiting list**		**P**
	ERA-1 (n=2,013)	**ERA-2 (n=2,225)**	
	Median (IQR) or N (%)		
Age (years)	56 (51-62)	55 (49-61)	<0.001
Male gender	1,544 (76.7)	1,673 (75.2)	0.27
Height (cm)	170 (165-176)	170 (165-176)	0.25
Weight (kg)	74 (65-83)	73 (65-80)	<0.001
Blood group (AB-B)	369 (18.3)	392 (17.6)	0.55
HCC	954 (47.4)	871 (39.1)	<0.001
HCV positivity	790 (39.2)	973 (43.7)	0.003
MELD	13 (8-18)	14 (10-20)	<0.001
High-volume center	1,729 (85.9)	1,968 (88.4)	0.01
Regional competitive status	1,069 (53.1)	1,292 (58.1)	0.001
Variables	**Data at transplant**		**P**
	ERA-1 (n=1,725)	**ERA-2 (n=1,790)**	
Recipient age	56 (50.61)	55 (49-61)	<0.001
Recipient male gender	1,341 (77.7)	1,361 (76.0)	0.25
Recipient height (cm)	170 (165-176)	170 (165-176)	0.59
Recipient weight (kg)	74 (65-83)	73 (65-80)	0.001
Recipient HCC	844 (48.9)	762 (42.6)	<0.001
Recipient HCV positivity	677 (39.2)	783 (43.7)	0.007

MELD	13 (9-20)	15 (10-21)	0.001
High-volume center	1,503 (87.1)	1,617 (90.3)	0.02
Regional competitive status	807 (46.8)	893 (49.9)	0.07
Donor age	65 (51-76)	63 (49-74)	0.001
Donor male gender	948 (55.0)	958 (53.5)	0.40
Donor height (cm)	170 (162-175)	170 (162-175)	0.60
Donor weight (kg)	73 (65-80)	73 (65-80)	0.93
Donor HCV positivity	28 (1.6)	32 (1.8)	0.80
Donor HBcAb positivity	317 (18.4)	356 (19.9)	0.27

Abbreviations: n, number; IQR, interquartile ranges; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; MELD, Model for End-stage Liver Disease; HBcAb=hepatitis B core antibody.

Table 2. Hazard ratio estimates from head-to-head comparisons. Level of significance: p <0.05 (cause-specific Cox proportional hazard analysis).

Outcome	**Group**	**Hazard ratio (95% Confidence Interval)**	**Reference group**	**Type**
LT	ERA 2 - MELD≥30	2.27 (1.78-2.90)	ERA 1 - MELD≥30	Adjusted
	ERA 2 - MELD<30	0.36 (0.30-0.44)	ERA 1 - MELD≥30	Adjusted
	ERA 1 - MELD<30	0.29 (0.24-0.35)	ERA 1 - MELD≥30	Adjusted
	ERA 2 - MELD≥30	2.07 (1.62-2.63)	ERA 1 - MELD≥30	Crude
	ERA 2 - MELD<30	0.42 (0.35-0.51)	ERA 1 - MELD≥30	Crude
	ERA 1 - MELD<30	0.36 (0.29-0.43)	ERA 1 - MELD≥30	Crude
All-cause mortality	ERA 2 - MELD≥30	0.86 (0.54-1.36)	ERA 1 - MELD≥30	Adjusted
	ERA 2 - MELD<30	0.31 (0.21-0.46)	ERA 1 - MELD≥30	Adjusted
	ERA 1 - MELD<30	0.34 (0.23-0.49)	ERA 1 - MELD≥30	Adjusted
	ERA 2 - MELD≥30	0.89 (0.57-1.41)	ERA 1 - MELD≥30	Crude
	ERA 2 - MELD<30	0.24 (0.17-0.35)	ERA 1 - MELD≥30	Crude
	ERA 1 - MELD<30	0.27 (0.18-0.38)	ERA 1 - MELD≥30	Crude
Graft loss	ERA 2 - MELD≥30	0.83 (0.53-1.31)	ERA 1 - MELD≥30	Adjusted
	ERA 2 - MELD<30	0.34 (0.23-0.49)	ERA 1 - MELD≥30	Adjusted
	ERA 1 - MELD<30	0.37 (0.25-0.53)	ERA 1 - MELD≥30	Adjusted
	ERA 2 - MELD≥30	0.84 (0.53-1.32)	ERA 1 - MELD≥30	Crude
	ERA 2 - MELD<30	0.28 (0.19-0.40)	ERA 1 - MELD≥30	Crude
	ERA 1 - MELD<30	0.30 (0.21-0.43)	ERA 1 - MELD≥30	Crude

FIGURE LEGENDS

Figure 1. Density functions of the MELD-score. (A) Patients in the list for LT between the two ERAs. (B) Patients in the list for LT between the two ERAs and divided according to the center volume and centers in the same region. Level of significance: overlap of the curves >75% (Kernel density estimates of the propensity scores). Abbreviations: V70, high-volume; MCR, multiple centers in the same region; SCR, single center in the region; V, low-volume. MELD scores were calculated according to the laboratory values, without considering the exception additive points.

Figure 2. Level of significance: overlap of the curves >75% (Kernel density estimates of the propensity scores). Abbreviations: V70, high-volume; MCR, multiple centers in the same region; SCR, single center in the region; V, low-volume. MELD scores were calculated according to the laboratory values, without considering the exception additive points.

Figure 3. Boxplot of the waiting time in the list for liver transplantation. Box plots represent the 25%-75% values; dashed lines are the largest or the smallest values within 1.5 times the interquartile ranges above the 75% or beyond the 25% percentiles; black circles are the median waiting times; the blue circles are the outside values. Levels of significance: $p < 0.05$ (Mann-Whitney U-test).

Figure 4. Risk factors of dropout from the waiting list. Level of significance: $p < 0.05$ (Cause-specific Cox proportional hazard model).

Figure 5. Risk factors of graft-loss. Level of significance: $p < 0.05$ (Fine-Gray test).

Figure 1A

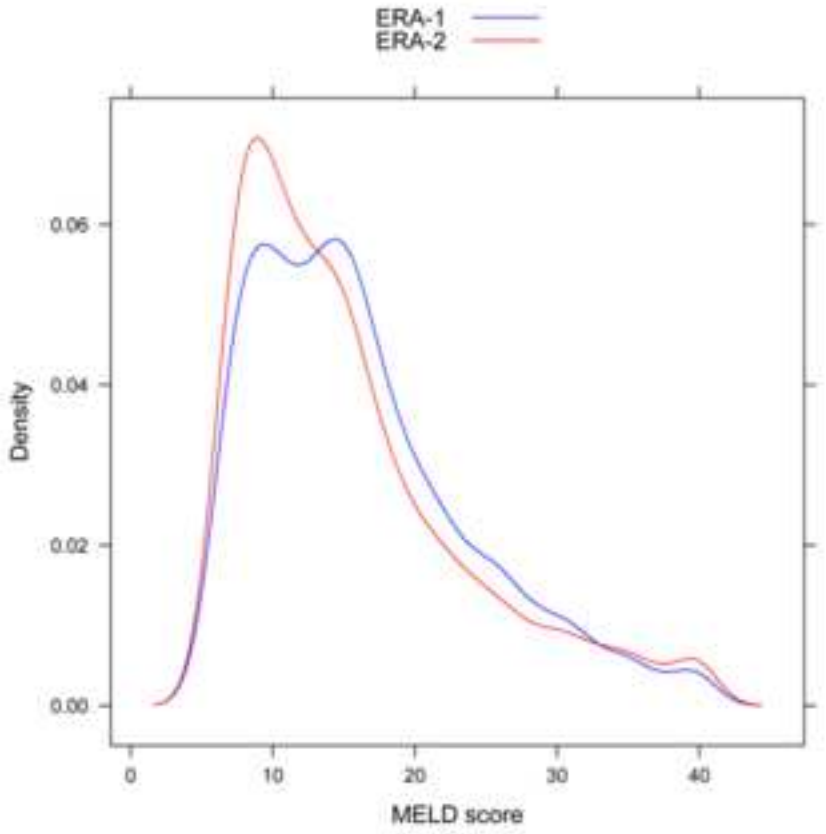

Figure 1B

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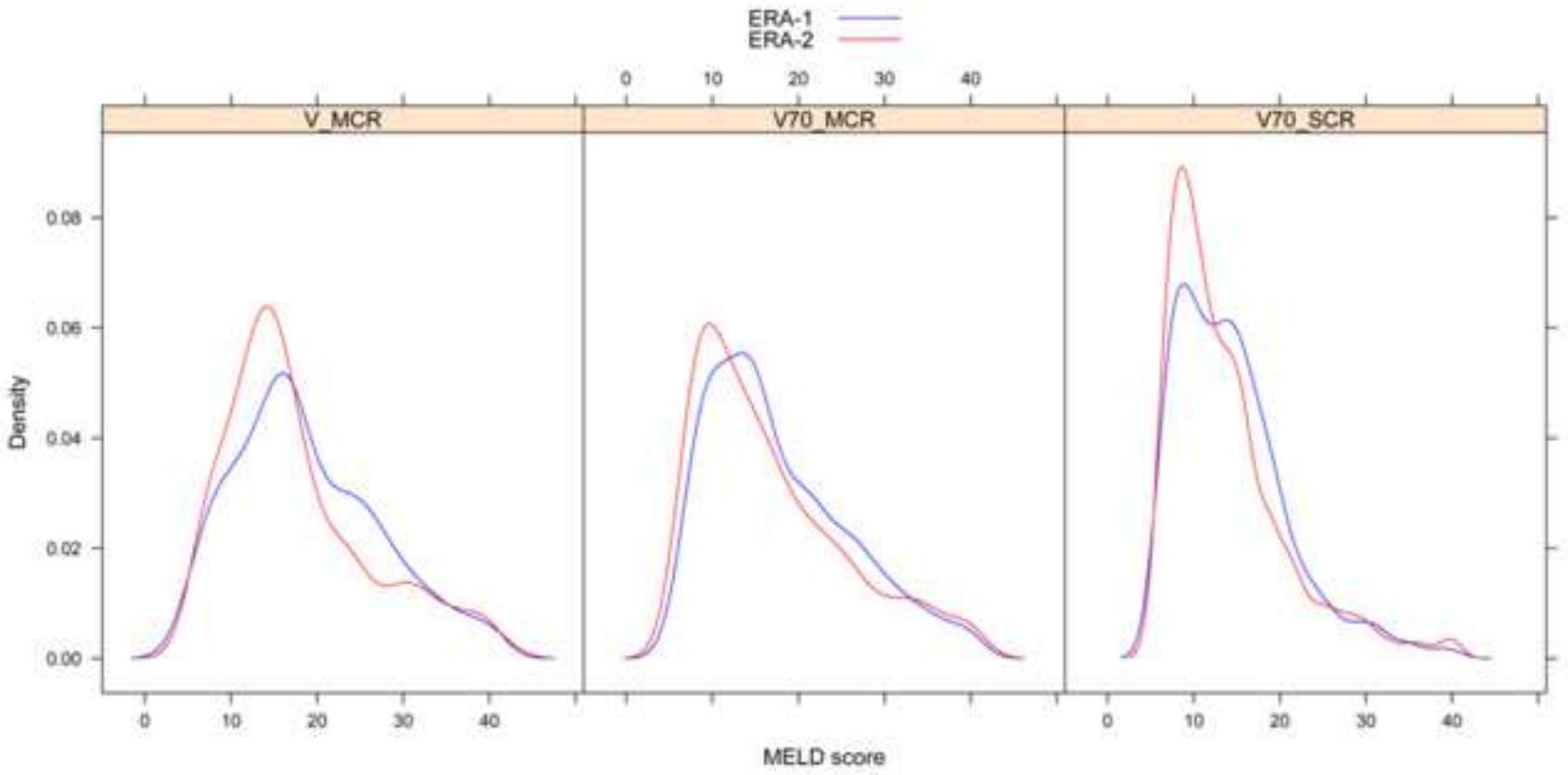

Figure 2

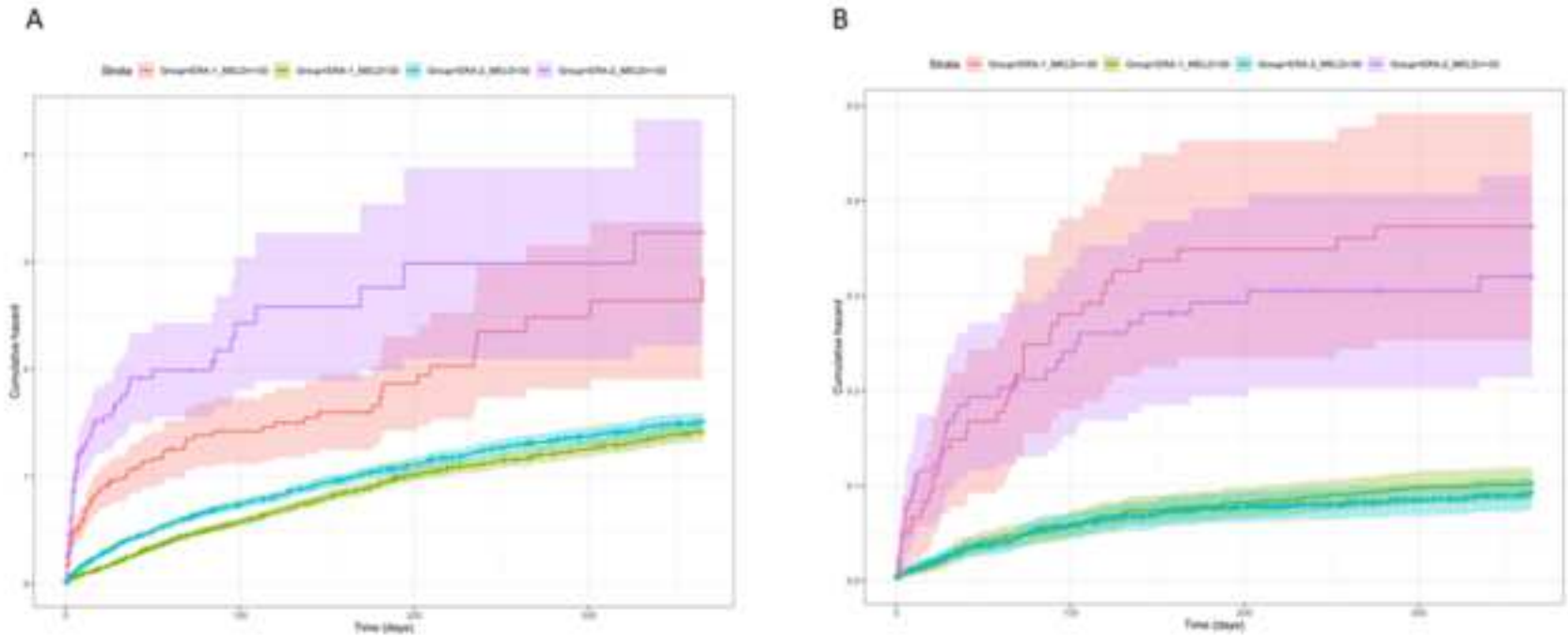

Figure 3

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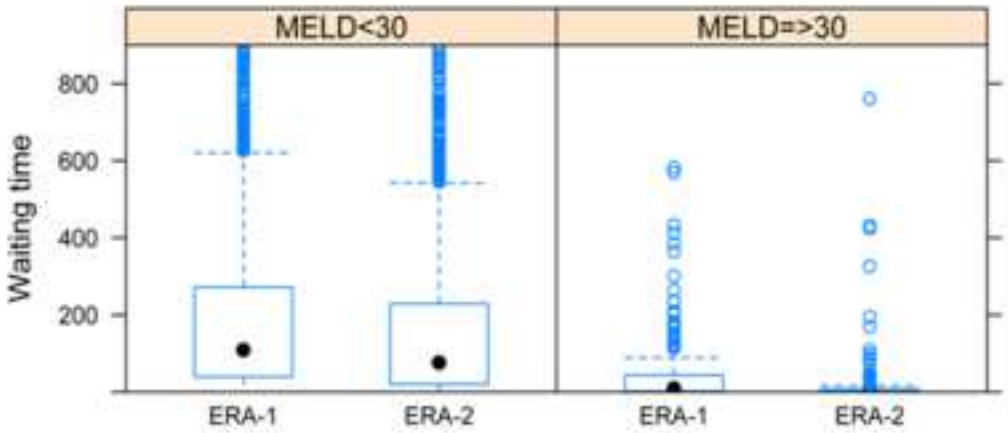


Figure 4

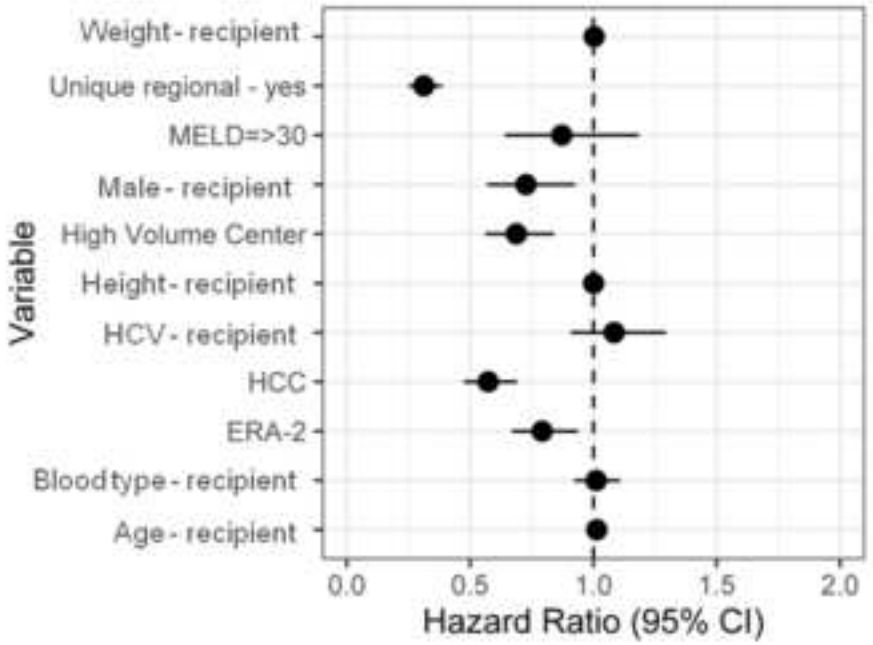
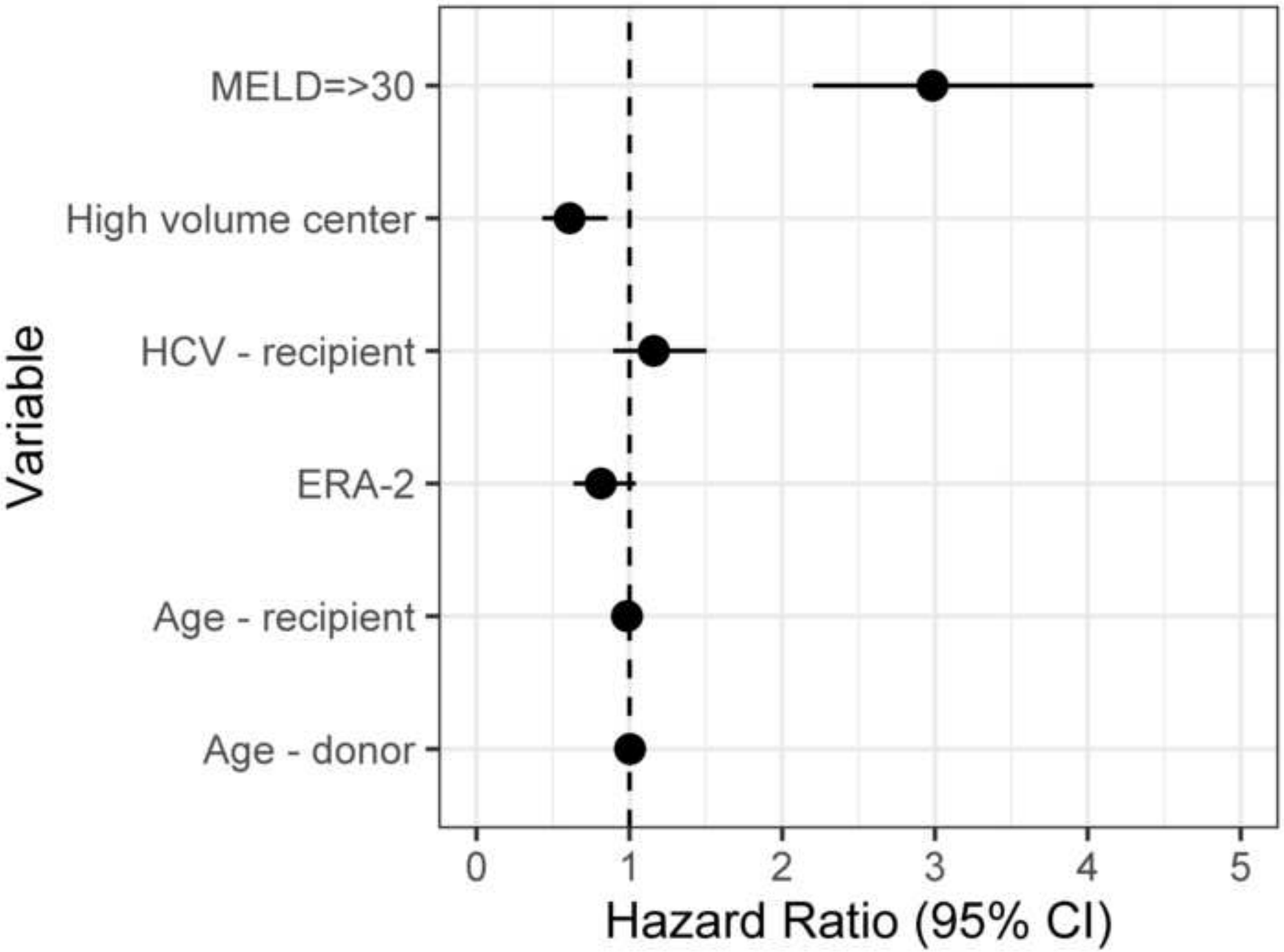
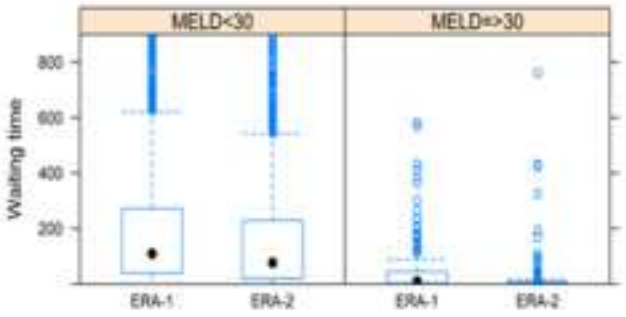


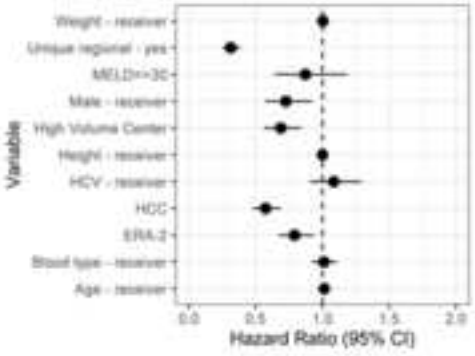
Figure 5



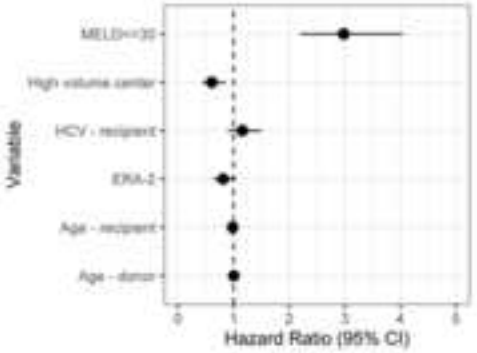
Graphical Abstract



Boxplot of the waiting time in list for liver transplantation



Risk factor of dropout from the waiting list.



Risk factor of graft-loss.

HIGHLIGHTS:

- Priority allocation for MELD ≥30 candidates for liver transplantation
- Donor age, MELD ≥ 30 and ERA-1 were independent predictors of worst graft survival
- MELD ≥ 30 patients had lower median waiting time in the list in the ERA-2
- Low-volume and multiple regional transplant centres were independent predictors of higher dropout rate