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Early View

Research letter

Outcome of liver transplantation for hepatopulmonary syndrome: a Eurotransplant experience

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Title page

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Outcome of liver transplantation for hepatopulmonary syndrome: a Eurotransplant experience

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Abbreviations

HPS, hepatopulmonary syndrome; LT, liver transplantation; MELD, Model for End-Stage Liver Disease; SE, standard exception; HR, hazard ratio; CI, confidence interval; DRI, donor risk index.

Summary – Take home message

Equal overall survival among liver transplantation candidates supports current prioritization policy for severe hepatopulmonary syndrome

To the Editor:

Hepatopulmonary syndrome (HPS) is a pulmonary vascular complication of liver disease that affects up to 30% of patients with cirrhosis [1]. Intrapulmonary vascular dilatations and shunts result in gas exchange abnormalities, ranging from elevated alveolar-arterial oxygen gradients with no hypoxemia to very severe hypoxemia [1,2]. Currently, liver transplantation (LT) is the only treatment option [3]. The Model for End-Stage Liver Disease (MELD) is a scoring system for assessing liver disease severity that has been validated to predict the 3-months waitlist mortality, and is used by Eurotransplant for prioritizing allocation of liver transplants [4]. However, this score poorly predicts overall and post-transplant survival and does not take into account complications that affect outcomes independent of liver disease severity [5]. Hypoxemia in HPS is generally progressive and mortality is highest in advanced stages [6,7]. In this sense, a standard exception (SE) policy has been established to prioritize patients with severe HPS (PaO_2<60 mmHg), as their severity of illness is not properly reflected by the MELD score. In the pre-SE MELD era, Fallon *et al.* reported that HPS is associated with a doubled risk of mortality compared to patients without HPS [1]. In 2014, Goldberg *et al.* reviewed SE LT outcomes in HPS patients in the USA and found that LT candidates with SE for HPS had decreased pre-transplantation mortality and superior overall survival compared to non-HPS patients [5]. The European outcomes for patients with SE for HPS have never been explored. In this retrospective study, we analyzed overall, pre-transplant and post-transplant survival in LT candidates with SE for HPS within Eurotransplant and determined whether the intent of the exception policy is being met.

All analyses used anonymized data available through the Eurotransplant registry from January 1, 2006 until December 31, 2013, comprising patients from Germany, Belgium, Austria, The Netherlands, Croatia, Hungary and Slovenia. The HPS cohort included all waitlist candidates aged 18 years or older, registered for their first LT with SE approved by Eurotransplant, according to disease- and country-specific criteria [8]. The exceptional

MELD is expressed in percent 3-month probability of death on the waitlist. Patients with approved SE for HPS are granted an initial SE MELD compatible with a 3-month probability of death of 15% (a score of 22) in Austria, Belgium, Luxemburg, Germany, Slovenia and Croatia, and 10% (a score of 20) in the Netherlands. This exceptional MELD is reconfirmed every 90 days, and an update of +10% MELD equivalent applies in all Eurotransplant countries. The non-HPS group consisted of waitlist candidates without any exception, who were matched to the HPS cases (propensity score matching, 5:1 ratio) based on age, sex, etiology of liver disease and MELD score at the time of listing. Statistical analyses were performed using SPSS 25 (SPSS, Inc., Chicago, IL, USA) and R3.4.1 software packages (R Foundation for Statistical Computing, Vienna, Austria). The Eurotransplant Liver and Intestine Advisory Committee (ELIAC) and the ethical committee of the Faculty of Medicine and Health Sciences, Ghent University, approved the study protocol (2014/0927).

The study population consisted of 88 patients with SE for severe HPS and 442 non-HPS patients. Cox regression showed that overall mortality was not statistically different in HPS (HR 1.32; 95%CI: 0.93-1.88, P=0.13) vs non-HPS patients. Fine and Gray regression models were used to evaluate pre-transplantation outcome, considering transplantation as a competing risk [10]. Pre-transplant mortality risk was similar in HPS and non-HPS waitlist candidates (HR 0.88; 95%CI: 0.52-1.47, P=0.62). A total of 128 patients (24%) died on the waitlist: 17/88 (19%) HPS and 111/442 (25%) non-HPS patients. Causes of death did not differ between groups and mainly included infections (11/17 HPS, 58/111 non-HPS) and progression of liver disease (2/17 HPS, 13/111 non-HPS). Patients with HPS were prioritized for transplantation relative to patients without HPS due to the SE policy (HR 1.37; 95%CI 1.04-1.80, P=0.026). 69% of HPS patients received a transplant vs 54% of the non-HPS patients in the study period. 3% of patients in both groups were removed from the waiting list because they were too sick to be transplanted (3/88 HPS, 14/442 non-HPS), and one HPS patient (1%) and 45 non-HPS patients (10%) were removed because their clinical status had improved.

Overall, 80/298 (27%) transplanted patients had died at the time of data analysis (24/61 or 39% HPS vs 56/237 or 24% non-HPS; P=0.014). The median post-LT follow-up for HPS patients was 2 years. Survival analysis demonstrated 1- and 3-months post-LT survival rates of respectively 91% (95% CI: 83-99) and 84% (95% CI: 74-96) in HPS vs 96% (95% CI: 93-98) and 89% (95% CI: 85-94) in non-HPS patients. Death in the early postoperative period was primarily caused by infections (57% HPS and 50% non-HPS deaths). One HPS patient died because of respiratory insufficiency. Post-LT survival rates were 77% (95% CI: 66-91) in HPS and 85% (95% CI: 81-90) in non-HPS at 6 months, 70% (95% CI: 57-85) in HPS and 81% (95% CI: 75-86) in non-HPS at 1 year, and 64% (95% CI: 51-80) in HPS and 77% (95% CI: 71-83) in non-HPS patients at 2 years after LT. Drop-out at later time points post-transplant was more frequent in the HPS group (17/61 vs 36/237 in non-HPS), although causes of death did not differ between groups (mainly infections, P=0.275).

We present the first international analysis of the outcome of LT candidates with SE for HPS in Europe. Two observations have direct clinical importance. First, although cases with HPS had a greater chance of receiving a transplant, overall mortality, which is the most important measure of equity between patient groups, did not differ between LT candidates with HPS and those without. These data indicate that since the implementation of a SE policy for HPS, the outcome has improved in this specific patient population compared to the pre-SE era [1], which concurs with the conclusion from the most recent and largest analysis in the USA [5]. However, in contrast, observations in the USA even indicated an overall survival benefit for HPS compared to non-HPS patients [5]. This was due to decreased pre-transplantation mortality in patients with HPS, and suggested that current exception policy may overprioritize HPS patients. Pre-transplant mortality risk was equal in both groups in our study, which, combined with similar overall survival advocates against modification of current HPS exception policy. Defining a lower limit of PaO_2 for granting SE would result in increased waiting time, during which HPS may aggravate, and which ultimately may result in worse overall outcome.

Second, statistical analysis demonstrated that post-transplantation survival in patients with HPS is acceptable, but less favorable relative to patients without HPS. These data should however be interpreted with caution. Median follow-up time in the HPS cohort was rather short (2 years), resulted in a significant amount of censored cases beyond this time point, and as such limits drawing conclusions with regard to long-term post-transplant survival. Nonetheless, up to 2 years post-transplant, survival was comparable in both groups, and in agreement with results from previous studies [7;10-12]. Moreover, even beyond this period, causes of death did not differ.

Our observations are different from those reported by the UNOS zone [5], although decision-making with regard to transplant and the SE policy for HPS are similar in Eurotransplant [8] and UNOS [13]. In general, survival rates are lower in the Eurotransplant region compared to UNOS, which has been recognized before, and is explained by lower donor quality. The mean donor risk index (DRI), a metric of donor quality, is significantly higher in Eurotransplant, where more than 50% of organs are considered 'suboptimal', versus UNOS [14,15]. Only <6% of donor livers in the USA were reported to have a DRI>2, where organs of marginal quality are more frequently discarded, versus 23% in Eurotransplant [15].

Lastly, although SE criteria for HPS within Eurotransplant are limited to cases with severe HPS, and as such only patients with PaO_2<60 mmHg were included in this study, the exact values were not available through the registry. Consequently, the relationship between pre-transplantation oxygenation and post-LT survival could not be evaluated in this HPS cohort, which we acknowledge as a limitation to this study.

In conclusion, our results indicate that waitlist mortality and post-transplant survival in patients with severe HPS are fairly balanced under current SE policy, without disadvantaging the general transplant population.

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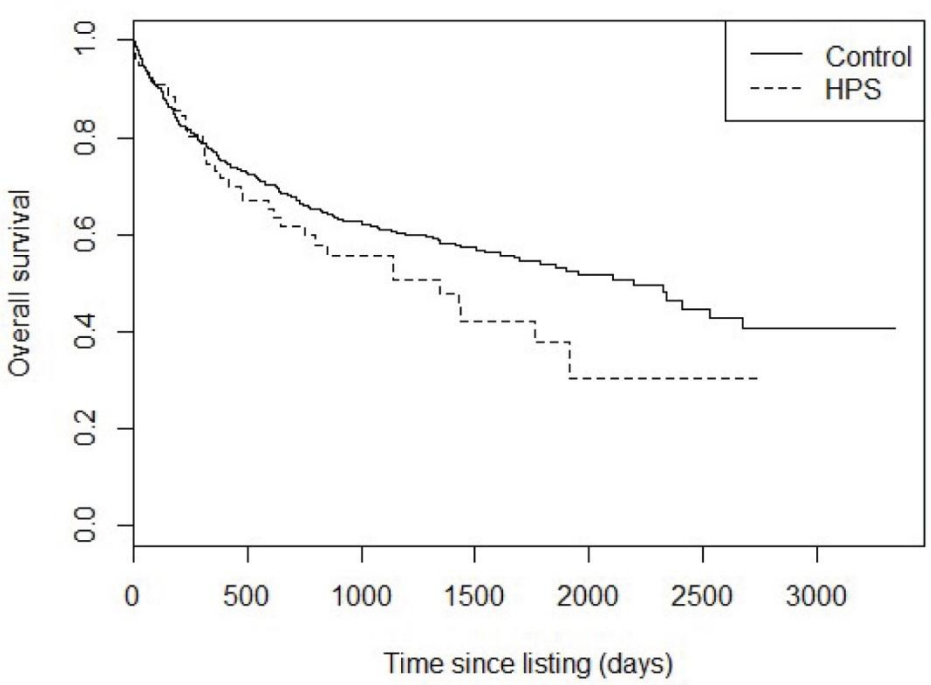
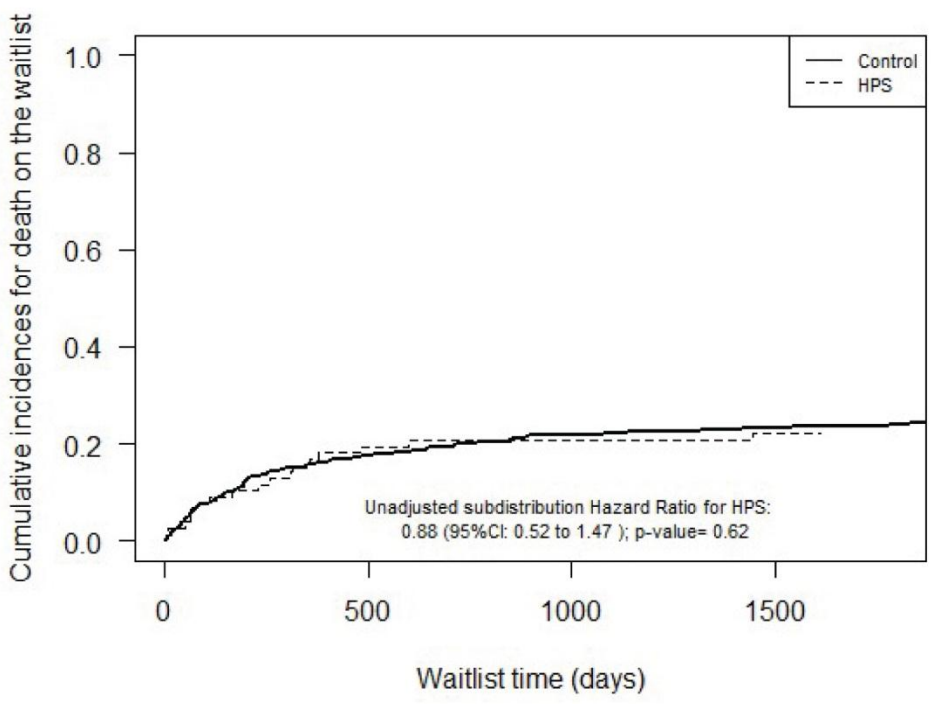
Figure legends

Figure 1. a) Overall patient survival of HPS vs non-HPS waitlist candidates. b) Competing risk curves for pre-transplantation waitlist survival in HPS vs non-HPS waitlist candidates.

a)


Control
HPS
Overall survival
0.0
0.2
0.4
0.6
0.8
1.0
0
500
1000
1500
2000
2500
3000
Time since listing (days)

b)


Control
HPS
Cumulative incidences for death on the waitlist
0.0
0.2
0.4
0.6
0.8
1.0
Unadjusted subdistribution Hazard Ratio for HPS:
0.88 (95%CI: 0.52 to 1.47); p-value= 0.62
0
500
1000
1500
Waitlist time (days)