Outcome of liver transplantation for hepatopulmonary syndrome: a Eurotransplant experience

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 hypoxaemia to very severe hypoxaemia [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-month waiting list mortality and is used by Eurotransplant for prioritising 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]. Hypoxaemia 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 prioritise patients with severe HPS (arterial oxygen tension (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.* [1] reported that HPS is associated with a doubled risk of mortality compared to patients without HPS. In 2014, Goldberg *et al.* [5] 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. The European outcomes for patients with SE for HPS have never been explored. In this retrospective study, we analysed 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 anonymised 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 waiting list candidates aged ⩾18 years registered for their first LT with SE approved by Eurotransplant, according to disease- and country-specific criteria [8]. The exceptional MELD is expressed as percentage 3-month probability of death on the waiting list. 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, aetiology 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 and the ethical committee of the Faculty of Medicine and Health Sciences, Ghent University (Ghent, Belgium) 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 (hazard ratio (HR) 1.32, 95% CI 0.93–1.88; p=0.13) *versus* non-HPS patients (figure 1a). Fine and Gray regression models were used to evaluate pre-transplantation outcome, considering transplantation as a competing risk [9]. Pre-transplant mortality risk was similar in HPS and non-HPS waiting list candidates (HR 0.88, 95% CI 0.52–1.47; p=0.62) (figure 1b). A total of 128 (24%) patients died on the waiting list: 17 (19%) out of 88 HPS and

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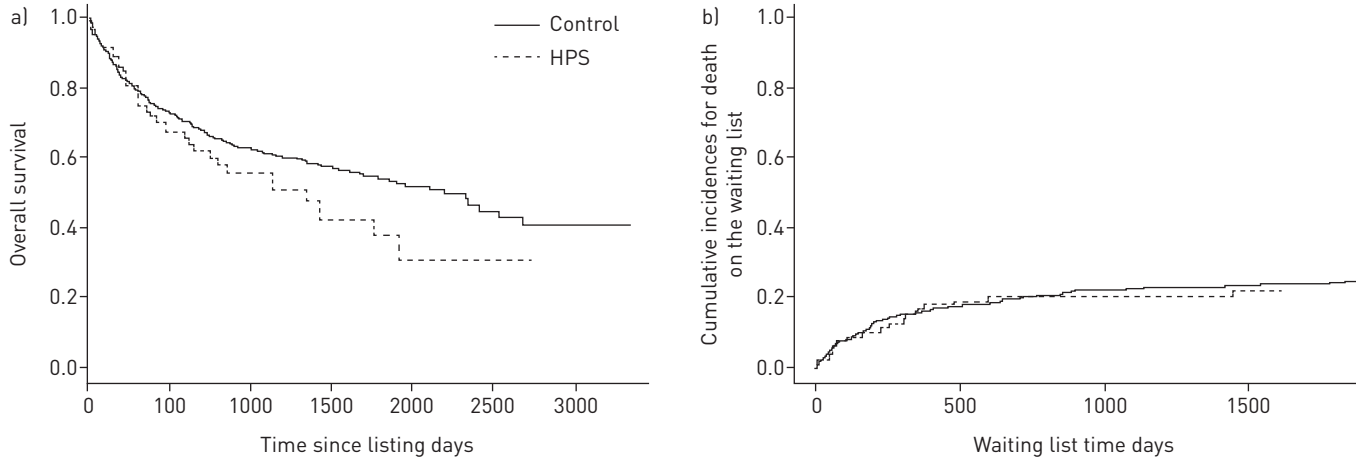

FIGURE 1 a) Overall patient survival of hepatopulmonary syndrome (HPS) *versus* non-HPS waiting list candidates. b) Competing risk curves for pre-transplantation waitlist survival in HPS *versus* non-HPS waiting list candidates. Unadjusted subdistribution hazard ratio for HPS 0.88 (95% CI 0.52–1.47, p=0.62).

111 (25%) out of 442 non-HPS patients. Causes of death did not differ between groups and mainly included infections (11 out of 17 HPS and 58 out of 111 non-HPS) and progression of liver disease (two out of 17 HPS and 13 out of 111 non-HPS). Patients with HPS were prioritised 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 *versus* 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 (three out of 88 HPS and 14 out of 442 non-HPS), and one (1%) HPS patient and 45 (10%) non-HPS patients were removed because their clinical status had improved.

Overall, 80 (27%) out of 298 transplanted patients had died at the time of data analysis (24 (39%) out of 61 HPS *versus* 56 (24%) out of 237 non-HPS; p=0.014). The median post-LT follow-up for HPS patients was 2 years. Survival analysis demonstrated 1- and 3-month post-LT survival rates of respectively 91% (95% CI 83–99%) and 84% (95% CI 74–96%) in HPS *versus* 96% (95% CI 93–98%) and 89% (95% CI 85–94%) in non-HPS patients. Death in the early post-operative 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 out of 61 *versus* 36 out of 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 the current exception policy may overprioritise 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 favourable 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), resulting 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 in the United Network for Organ Sharing (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 recognised 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 >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-LT 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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