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FTWU Title	HPS Waiting list Prioritisation
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Objectives set by LAG	There have been concerns expressed about prioritisation of patients with Hepatopulmonary Syndrome which may depending on its severity affect waiting list (M1) and post-transplant (M2) survival. But is not currently factored into the offering process. As a consequence HPS patients fall into 3 broad categories: • CLD patients with high UKELD/TBS who will likely be offered organs relatively quickly due to the severity of their liver disease and calculated benefit from OLT regardless of the HPS • CLD patients with low UKELD /TBS (but meet minimal listing criteria) or HCC where HPS may or may not determine prognosis on the waiting list according to its severity but it is unlikely the patient will get a named offer. This is a particular concern if the patient has severe HPS which may determine survival on the list and be at risk of being deemed too high risk to proceed with OLT. • Variant patients with HPS as the indication where likely the HPS determines the prognosis on the list and the perioperative risk and existing waiting timings are potentially too long. We request that the group will: 1. To confirm the appropriate timescales for transplantation for each of those indications according to HPS severity and nature and severity of underlying liver disease. 2. To undertake an options appraisal for prioritisation of each of these indications. 3. To make recommendations on the preferred options for prioritisation for each indication. 4. Consideration will also be given to determining futility of transplantation in patients with HPS
Reporting Date	November LAG 2020

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Hepatopulmonary Syndrome (HPS) - Internationally accepted definitions

Diagnostic criteria (3):
1. Liver disease (portal hypertension)
2. Arterial de-oxygenation - alveolar-arterial oxygen gradient ≥15mmHg/≥2kPa, or if >64 yrs ≥20mmHg/2.7kPa
3. Evidence of intrapulmonary vascular dilatation (IPVD) on contrast enhanced echo (microbubbles seen in left heart ≥3 cardiac cycles after right atrium)

Grading (3)

	PaO2 (mmHg)*	PaO2 (kPa)*
Mild	≥80	≥10.7
Moderate	60-79.9	8-10.6
Severe	50-59.9	6.7-7.9
Very severe	<50	<6.7

**PaO2 on air, at rest whilst sitting*

NB Assessment of the severity of IPVD is difficult by means of CEE because this technique does not provide a quantitative evaluation. Extrapulmonary uptake of ^{99m}TcMAA can be quantified, but the procedure has not been sufficiently standardised beyond a few centres. The sensitivity of both approaches for the detection of anatomical pulmonary arteriovenous communications or diffuse or localised vascular dilatations alone is similar (3).

NHSBT selection criteria for HPS

HPS patients can be listed as chronic liver disease (CLD) with UKELD ≥49 or variant syndrome (1).

Variant syndrome criteria – "arterial pO2 <7.8, alveolar arterial oxygen gradient >20 mmHg, calculated shunt fraction >8% (brain uptake following TC macroaggregated albumin), pulmonary vascular dilatation documented by positive contrast enhanced transthoracic echo, in the absence of overt chronic lung disease."

HPS current method of wait list prioritisation

In the current system, HPS patients with a UKELD ≥49 are listed on the CLD/hepatocellular carcinoma (HCC) arm, and wait list prioritised as per the transplant benefit score.

Patients with HPS and a PaO2<7.8 kPa (in the absence of chronic lung disease) and a UKELD <49 are listed as a variant syndrome i.e. organs are allocated according to duration on the list.

Twenty-six percent of variant syndrome patients were transplanted by 6-months after listing during the 15-months after NLOS was implemented (compared to 68% of CLD patients and 66% of HCC patients) suggesting an expected wait after listing of approx. 2 years (Item 5.2 LAG (20) 4).

HPS is only recorded on the NHSBT database if patients are listed under the variant criteria, and not if the patient has a UKELD of 49 or above. Therefore, accurate data on the number of patients listed by each route is not currently available.

An active national collaborative study has observed that only 19/56 patients transplanted for HPS 2006-2016 were coded as such on the NHSBT database (additional patients identified retrospectively by individual units).

Severity of hypoxaemia data is also not consistently collected or updated whilst waiting.

Patients with HPS have a relatively low UKELD and transplant benefit score.

Of the 37 patients transplanted for HPS 2006-2016 with severe-very severe HPS, 49% of patients had a UKELD at listing of ≤50, and 30% had a UKELD of 51-54.
The transplant benefit score was generated for 5 random HPS patients assuming an average donor organ – the scores were as follows: 220 (UKELD 50, severe HPS), 345 (UKELD 53, severe HPS, HCC), 692 (UKELD 49, severe HPS), 429 (UKELD 52, severe HPS), 271 (UKELD 49, severe HPS).

Review of literature

HPS is a significant cause of morbidity and mortality that is reversed with liver transplantation. A summary of the literature is provided in Appendix 1, but the key points are as follows.

There is a suboptimal evidence base reflecting:

- Paucity of published data.
- Heterogeneity of cases.

Nevertheless, a reasonable summary seems to be:

1. Mild-moderate HPS (PaO2 ≥8kPa) has not been demonstrated to have a clear impact on symptoms/clinical picture.

2. Patients with mild-moderate HPS (PaO2 ≥8kPa) have similar natural history, wait list survival and post transplant survival to patients without HPS.

3. Patients with severe-very severe HPS (PaO2 <8kPa) probably have worse transplant free survival than patients without HPS. 1-year cumulative mortality was as high as 35-40% in

one early small study (5); but less at 80% by 3-years when the cohort was expanded in the later publication (16). The Eurotransplant competing risk data (in the MELD exception era) suggests an 18% risk of death after 1-year on the transplant waiting list – similar to non HPS patients (24).

4. Rate of progression of HPS – one small study of patients on the liver transplant waiting list reported that 13/15 (87%) had a decline in PaO2 from 60 to 50 mmHg (8 kPa to 6.7 kPa) during a mean followup time of 13 months; with a mean rate of decline of 1.8 +/-2.2 kPa/yr (17).

5. Overall there is increased short term mortality after liver transplantation for HPS, but this relationship is not maintained long term – HPS and non HPS patients have relatively comparable long term survival. Very severe hypoxaemia (PaO2<6kPa) however is an independent predictor of post transplant death; although the estimated 5-year post transplant survival is still 60% for this subgroup (15).

6. HPS will resolve after liver transplantation in approx. 3/4 recipients (17,23).

Conclusions on review of UK/Ireland data

An analysis of UK/Ireland data is provided in Appendix 2.

The patient numbers are small but the data is in keeping with peer reviewed literature. The relevant observations are as follows.

1. Patients with severe-very severe HPS (PaO2<8 kPa) at listing had increased short term post transplant morbidity and mortality compared to non HPS patients, but comparable long term post transplant survival.

2. Patients with severe-very severe HPS (PaO2<8 kPa) had similar 1-year estimated wait list survival (censored at time of transplantation) to non HPS patients, despite a lower UKELD at listing.

3. HPS patients had a longer waiting time to transplantation, and were more likely to die/be removed from the list because of deterioration.

Consensus recommendations of the FTWU

The FTWU when considering wait list prioritisation for HPS patients were conscious that we are in a transplant benefit rather than needs based system.

All recommendations are based on a PaO2 on air, at rest whilst sitting in keeping with international guidelines.

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Following review of the published literature and the available UK/Ireland data, the FTWU consensus recommendations are:

1. Given the lack of evidence to show that mild-moderate HPS (PaO2 ≥8 kPa) in isolation is associated with significant morbidity and mortality, the FTWU suggests that only severe-very severe HPS (PaO2 <8 kPa) should be viewed as an indication for liver transplantation in the absence of liver failure/HCC.

2. Similarly, given that mild-moderate HPS (PaO2 ≥8 kPa) is not associated with increased wait-list mortality, the recommendation is that HPS status does not impact on wait list prioritisation in this group. Instead, the FTWU suggests that patients with mild-moderate HPS (PaO2 ≥8 kPa) are wait-list prioritised as per the standard transplant benefit score. Should a patient with mild-moderate HPS (PaO2 ≥8 kPa) at listing demonstrate progressive hypoxaemia and drop down into the severe-very severe HPS category (PaO2 <8 kPa) then their mode of prioritisation should change to that of the severe-very severe HPS (PaO2 <8 kPa).

3. The FTWU believe that the severe-very severe HPS patients (PaO2 <8 kPa) are not best served by the variant syndrome method of prioritisation because of their significant mortality rate. Moreover, it is important that HPS patients are transplanted before they develop very severe hypoxaemia (PaO2 ≤5.9 kPa) because of the increased post transplant mortality – waiting time of >1 year at a progression rate of 1.8 +/-2.2 kPa/yr could feasibly mean that many patients develop very severe hypoxaemia. The FTWU recommend that patients are listed on the CLD/HCC arm and prioritised according to a transplant benefit score. The FTWU recommend that ideally all severe-very severe HPS patients (PaO2 <8 kPa) are transplanted within 1-year of listing.

4. The patients with severe-very severe HPS (PaO2 <8 kPa) frequently have disproportionately low transplant benefit scores reflecting their relatively compensated liver disease otherwise. As such, patients wait longer than the patients without HPS, increasing their risk of pre and post transplant mortality. Of added relevance is the theoretical increased risk of ischaemic graft complications influencing donor decision making. The FTWU recommend that consideration is given to weighting the transplant benefit score for the impact of severe-very severe HPS (PaO2 <8 kPa) - we envisage that HPS status will increase the transplant benefit score. The ideal scenario is that HPS is included in the transplant benefit score modelling; but in the absence of complete data, the FTWU wonder if it is possible to run the model including the HPS patients identified retrospectively for the national study? An alternative strategy might be to give an arbitrary added weight, although it would be important to avoid the unfair advantage that has been linked with MELD exception points as per the OPTN and Eurotransplant studies.

5. With regards to predicting futility, the FTWU's view is that there is no single strong predictor of futility in patients with HPS other than standard parameters associated with worse outcome. Patients with very severe hypoxaemia (PaO2 ≤5.9 kPa) have greater post transplant mortality, although their 5-year estimated survival remains acceptable at 60%.

6. The FTWU favour that the diagnostic criteria for HPS is in keeping with international guidelines i.e. liver disease with an alveolar-arterial oxygen gradient ≥15mmHg (≥2kPa) (or if >64 yrs, ≥20mmHg/2.7kPa) and a positive contrast enhanced echocardiogram; with severe-very severe HPS being defined as a PaO2 <8 kPa (rather than <7.8 kPa). Shunt size estimation by MAA scan should be viewed as optional for listing because it is not available in all units, its accuracy is not certain and it is not one of the diagnostic criteria; but it is useful to collect this data.

7. Given the paucity of national and peer-reviewed published data, the FTWU recommend that the following information is collected routinely for all listed HPS patients (mild-moderate and severe-very severe): diagnostic criteria for HPS achieved, including alveolar-arterial oxygen gradient; shunt size estimation by MAA scan (if available/optional); PaO2 (on air, at rest, whilst sitting) at listing, and then repeated intervals whilst on the transplant waiting list (no less frequently than 3-monthly) until transplantation; PaO2 on 100% oxygen, at rest, whilst sitting at time of listing. It is important to collect this data in the mild-moderate HPS patients (PaO2 ≥8 kPa) as well as the severe-very severe HPS patients (PaO2 <8 kPa) to confirm the current evidence base/decision making. We suggest a re-run of transplant benefit modelling including all HPS data after a 5-year interval.

8. The FTWU recommend further detailed data collection to aid management decisions: in the short term, completion of the national review of transplanted HPS patients including collection of individual patient data; and longer term, the prospective collection of relevant data via a national service evaluation.

9. Finally, the question of bridging ECMO was raised during the discussions. The FTWU believe that bridging ECMO may have a role in extremely hypoxaemic patients but it's use remains a rarity having been performed in only one unit in the UK to our knowledge. The ideal is that that patients are transplanted before they reach the need for ECMO. Nevertheless, the FTWU acknowledged that ECMO might rarely be viewed as beneficial and in this instance rapid transplantation may warrant request via the appeals panel.

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Appendix 1 – Review of literature

ILTS guidelines

1. Screening for severe HPS is advised in individuals otherwise suitable for candidates for liver transplantation because of the impact on QofL and survival (2B).

2. Diagnosis:
- Pulse oximetry (O_2 saturation < 96%) is a reasonable screening test to detect hypoxemia in adults who are otherwise suitable LT candidates, however ABG determination of oxygenation is necessary to diagnose HPS (1C).
- CE-TTE is the optimal screening test and criterion in adults for detection of IPVD (1B).
- MAA scans clarify the contribution of HPS-related hypoxmia in coexistent intrinsic cardiopulmonary disease (1C).

3. Severe hypoxemia due to HPS (PaO_2 < 60 mm Hg) should be considered an indication for LT and such individuals should have expedited LT consideration (1B).

4. Multicenter data and recent UNOS data suggest that pre-LT PaO_2 less than 45 to 50 mm Hg, has been associated with increased risk of transplant hospital mortality, morbidity, and severe hypoxemia post-LT (1B). Prospective center-specific data show that selected HPS patients with pre-LT PaO_2 less than 50 mm Hg (6.7kPa) may have good outcomes, suggesting center-specific excellence (1C).

5. Standard MELD exception scores should be given if PaO_2 is less than 60 mm Hg due to HPS (1B). Increased MELD exception score (higher MELD points if PaO_2 < 50 mm Hg) should be considered in view of recent UNOS post-LT data analysis (1B).

HPS– defining clinical significance

Case series documented frequency of HPS in patients undergoing liver transplant assessment.

1. 14/78 (17.9%) fulfilled the diagnostic criteria of “HPS” (although only 3 had a pO2<8kPa); a further 25 (32%) had an elevated A-a gradient but negative CEE (4).
2. In 98 patients undergoing liver transplant assessment, 34% had a positive CEE although only 80% of these patients had an elevated A-a gradient. 19/33 (58%) patients with a positive CEE had a pO2 <10.7, and only 9 had a pO2 <8kPa (27%, 9% of whole) (5). See table 2 below. Patients with a positive CEE had a higher CPS.
3. 75 of 363 undergoing liver transplant assessment (Mayo/Texas) fulfilled the diagnostic criteria for HPS as per the ERS taskforce (21%) (9). “HPS” patients had a higher bilirubin, lower albumin and CPS than non HPS patients. Median PaO2 of the HPS patients was 80mmHg (IQ 72-88).

4. In a prospective study, 27% of patients fulfilled the diagnostic criteria for HPS. Mean PaO2 67 (range 45-80) – looks like 6/31 HPS patients had a pO2<60mmHg. HPS patients had a higher MELD and CPS, than non (13).
5. Another prospective study, of predominantly mild-mod (only 7% had a PaO2<8): on multivariate modelling, CPS was the only factor associated with HPS. If CPS was removed, then ascites was the only variable associated (NB bacterial translocation associated in another paper) (14).

Table 2 Frequency of different cut off values for arterial oxygenation in cirrhotics with and without a positive contrast echocardiogram, the resulting prevalence of the hepatopulmonary syndrome (HPS)*, positive and negative predictive values, and overall accuracy for diagnosis of this syndrome

	Positive contrast echocardiogram (n=33)	Negative contrast echocardiogram (n=65)	Prevalence of HPS* (%) (95% CI)	Positive predictive value for diagnosis of HPS* (%) (95% CI)	Negative predictive value† for exclusion of HPS* (%) (95% CI)	Overall accuracy (95% CI)
PaO_2 <80 mm Hg[14]	19 (58%)	24 (37%)	19 (12–29)	44 (29–60)	75 (61–85)	61 (51–71)
PaO_2 <70 mm Hg[5 7 8 13]	14 (42%)	1 (1%)	15 (9–24)	93 (68–100)	77 (67–86)	80 (70–87)
PaO_2 <age related threshold value mm Hg	15 (45%)	1 (1%)	15 (9–24)	94 (70–100)	78 (68–86)	81 (71–88)
PaO_2 <65 mm Hg	13 (39%)	0	13 (7–22)	100 (75–100)	76 (66–85)	80 (70–87)
PaO_2 <60 mm Hg	9 (27%)	0	12 (6–20)	100 (66–100)	73 (63–82)	76 (66–84)
$AaDO_2$ >15 mm Hg[10 15]	31 (94%)	59 (91%)	32 (23–42)	34 (25–45)	75 (34–97)	38 (28–48)
$AaDO_2$ >20 mm Hg[16]	30 (91%)	50 (77%)	31 (22–41)	37 (27–49)	83 (59–96)	46 (36–56)
$AaDO_2$ >age related threshold value mm Hg[6 11]	27 (81%)	24 (37%)	28 (19–37)	53 (38–67)	87 (74–95)	69 (59–78)

*Defined as: chronic liver disease and arterial hypoxaemia and pulmonary vasodilation (measured by contrast echocardiography).
†For negative predictive values the oxygenation cut off values are: PaO_2 ≥80 mm Hg, ≥70 mm Hg, ≥age related threshold value, ≥65 mm Hg, ≥60 mm Hg; $AaDO_2$ ≤15 mm Hg, ≤20 mm Hg, ≤age related threshold value.

ERS taskforce state “More severe HPS causes greater clinical symptoms.” Referencing: Martinez (4) – no symptoms or measures of morbidity or mortality (only PFTs, etc). Schenk (5) – subdivided patients into “clinically significant HPS” (PaO2<9.3kPa) and “subclinical HPS” (PaO2 ≥9.3 but increased A-a gradient as per age). See table 3 below. Seems to be an arbitrary cutoff.

Table 3 Clinical features of cirrhotics with “clinically significant” hepatopulmonary syndrome (HPS), “subclinical” HPS, and no HPS

	“Clinically significant” HPS* (n=14) and positive contrast echo	“Subclinical” HPS† (n=13) and positive contrast echo	No HPS (n=71)	p Value
Dyspnoea	8 (57%)	1 (8%)	4 (6%)	<0.001
Spider naevi	11 (79%)	7 (54%)	28 (39%)	<0.05
Palmar erythema	8 (57%)	4 (31%)	35 (49%)	NS
Child-Score	11.6 (1.9)	10.5 (3.1)	9 (2.5)	<0.05
OLT	2 (14%)	5 (38%)	12 (17%)	
Complications	0	Embolic brain infarct 2; wound infection 1; prolonged weaning 1	0	
Outcome	Both died, 2 and 10 months after OLT	1 died, 6.5 months after OLT	2 died, 7.5 and 9 months after OLT	

*Defined as hypoxaemia (PaO_2 <70 mm Hg).
†Defined as normoxaemia (PaO_2 ≥70 mm Hg and $AaDO_2$ >age related threshold).

NB

1. Some patients with a positive CEE do not have an elevated A-a gradient, meaning they do not fulfil the diagnostic criteria of HPS. In one study of 365 patients enrolled in the Pulmonary Vascular Complications of Liver disease study – 76 patients had HPS and a further 46 had a positive CEE but a normal A-a gradient (25). 85% of the latter had mild IPVD based on the density of bubbles. Median PaO2 was 98mmHg. The IPVD group had a higher

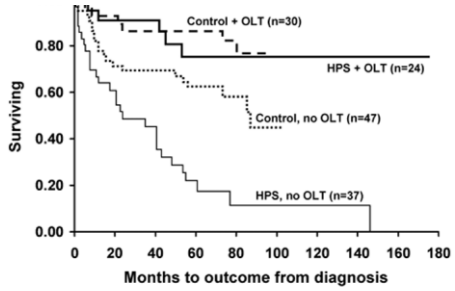
CPS and MELD score than patients with a negative CEE, and a trend towards a higher CI and TAPSE; there was no difference in symptoms.

2. Healthy controls demonstrate positive CEE during exercise (52/55 SUBJECTS) (7). During exercise there is a progressive increase in PASP and reduction in PVR – patients with a greater shunt (more positive CEE) demonstrated a lower exercise induced increase in PASP and greater reduction in PVR, higher cardiac output and improved LV function, and greater VO2 max. The authors speculated that pulmonary transit of agitated saline during exercise is in keeping with the recruitment of larger- calibre pulmonary vessels to allow lower afterload/greater flow i.e. reflects pulmonary vascular reserve and could be important in maximizing cardiac output during exercise. No association between degree of positivity of CEE and PaO2.

Therefore in cirrhosis is there may be:
1. "True HPS" i.e. positive CEE associated with hypoxaemia and symptoms with impact on prognosis. Feasibly in this group there may be a local factor exacerbating vasodilatation/diffusion.
2. Positive CEE in the context of the "hyperdynamic state" of portal hypertension. Explaining the correlation of a positive CEE with markers of severity of liver disease, and lack of impact of non hypoxaemic "HPS" on outcome.

HPS – natural history (see table below; most relevant papers with more info available summarised)

Swanson KL (6)
61 patients with HPS evaluated at the Mayo 1985-2002 (6).
37 did not undergo liver transplantation, 5 of whom were listed but died on the list. Multiple different reasons for not listing.
pO2 ≥8, 10 patients; pO26.7-7.9, 8; <6.7, 19.
No patient died of progressive, isolated hypoxemic respiratory failure. The primary reasons for deaths were GI bleeds followed with or without respiratory failure, progressive hepatic failure with wasting/encephalopathy/aspiration pneumonitis, neoplasms (oropharyngeal/lung/hematological), hepatorenal syndrome, and aspiration pneumonia.
See Kaplan Meier below :
NB Controls –patients with cirrhosis matched to HPS in terms of age, aetiology, MELD and CPS.



Estimated 1-year survival approx. 60-65% for HPS and approx. 75% for controls.

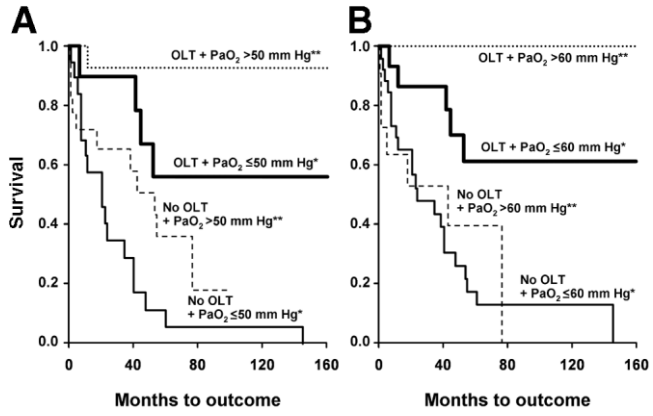
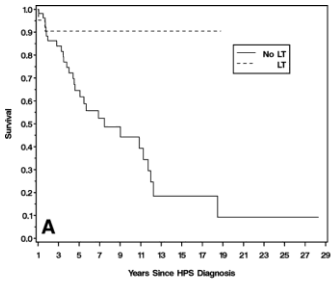


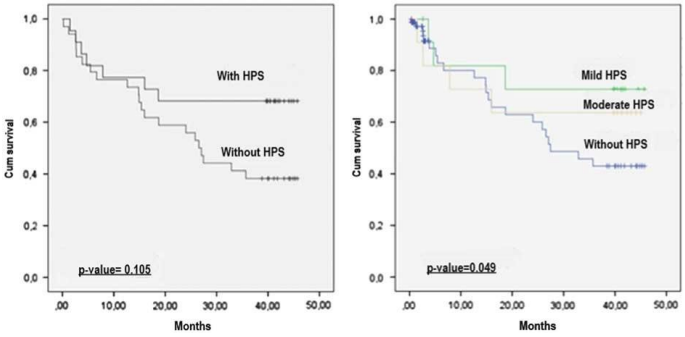
Fig. 2. Survival based on initial PaO_2 determinations at the time of HPS diagnosis in patients with HPS based on transplant status. (A) Survival differences between HPS patients undergoing OLT or not with $PaO_2 \leq 50$ mm Hg (10, OLT; 19, no OLT) and $PaO_2 > 50$ mm Hg (14, OLT; 18, no OLT) (*$P = .001$; **$P = .002$); (B) Survival differences with $PaO_2 \leq 60$ mm Hg (15, OLT; 26, no OLT) and with $PaO_2 > 60$ mm Hg (9, OLT; 11, no OLT) (*$P = .002$; **$P = .002$). PaO_2 measurements were taken in the standing position.

Arbitrary cut offs of PaO2 not useful in predicting short-term mortality relevant to liver transplant waiting list.

Iyer VN (16). Updated Mayo data (1986-2010) (includes the Swanson patients above (6)).
106 patients with HPS, 49 of which underwent liver transplantation.
Median PaO2 50, range 31-70; 55% PaO2<6.6; 77% PaO2<8 (82 patients).
Estimated 5-year survival after HPS diagnosis based on Kaplan Meier approx. 50%,



Fragaki (10). FU data on mild- moderate HPS (i.e. PaO2>8). Kaplan meiers below – no difference to patients without "HPS". NB HPS defined as per cirrhosis, elevated A-a gradient and positive MAA scan.



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Schenk (22).
27/111 patients undergoing liver transplant assessment had HPS.
HPS patients had higher MELD and CPS. 9/27 patients had a PaO2<8. None had very severe HPS.
7 patients were transplanted – none of these patients had a PaO2<8.
On univariate analysis, HPS patients had worse survival from point of diagnosis including when subdivided as per CP class. But looks like sicker patients.

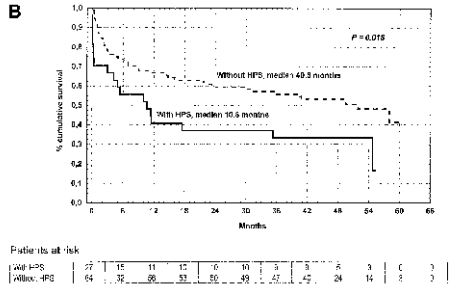


Figure 2. (A) Cumulative survival rate of all the 111 patients with cirrhosis included in the study. (B) Cumulative survival of patients with (n = 27) and without HPS (n = 84). Survival was significantly different (log rank test).

Fallon QOL paper widely quoted (18):
Screening of "potential liver transplant candidates" picked up prevalence of HPS of 72/146 (49%) – mean MELD 13, mean PaO2 77mmHg (10.3). No difference between HPS and non HPS in terms of MELD or components of CPS.
However HPS were more likely to report dyspnoea (48% vs 29%) and orthopnoea, had worse New York Heart Association functional class , and had significantly worse quality of life in certain questionnaire domains compared with patients without HPS.
No info about respiratory muscle strength (Katsakas 2013). FEV1 and FVC were both less than non HPS, and proportionate suggesting muscle strength may be relevant.
HPS an independent predictor of long term survival although curves run close…

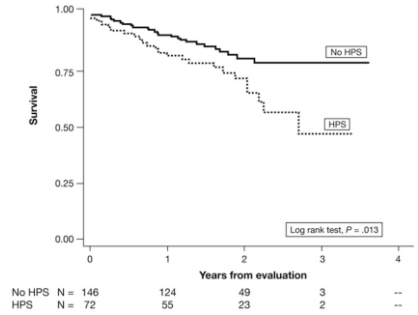


Figure 2.
Kaplan–Meier survival estimates of patients with HPS and patients without HPS (No HPS) (n = 218).

HPS – evidence with respect to waiting list (see table below; most relevant papers with more info available summarised)

Iyer VN (16). Updated Mayo data (1986-2010) (includes the Swanson patients above (6)). Authors comment that survival post transplant seemed to improve after the introduction of MELD exception (however not sure that they can say this given the improved survival over the years in all liver transplant recipients).

COD on the waiting list were described for the MELD exception point era (from 2002 onwards) – 3 HPS patients died on the list; COD renal abscess/sepsis, peritonitis/sepsis, pneumonia/ARDS.

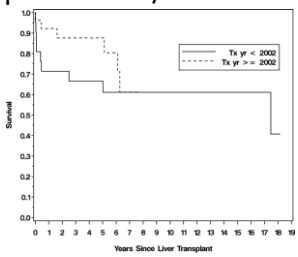


Fig. 4. Post-LT survival by MELD era (MELD exception for HPS began in 2002). There were 28 HPS transplanted patients from 2002 onward.

**Pascasio et al, AJT (14). CEE was done in all patients assessed for liver transplantation with an elevated A-a gradient. 81/316 fulfilled HPS diagnostic criteria (25.6%): mild 33 (41%), moderate, 42 (52%), severe 5 (6%), very severe 1 (1%).

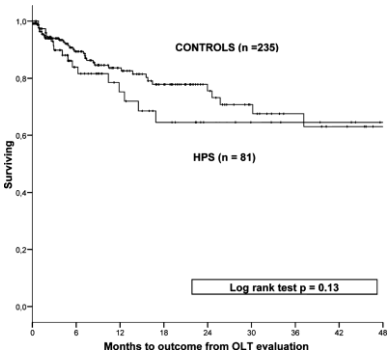


Figure 2: Liver transplantation waiting list survival. Survival curve from the preliver transplantation evaluation of patients with hepatopulmonary syndrome and without hepatopulmonary syndrome (controls).

No difference in 1-year survival on waiting list, possible trend to reduced survival by 2-years. Predominant mild/mod HPS was not an independent predictor of death on the transplant waiting list:

Table 4: Variables included in the multivariate analysis related to liver transplantation waiting list survival

Variables	RR	95% CI	p-Value
MAP	0.99	0.96–1.01	0.34
Child-Pugh score	1.633	1.20–2.22	0.02
MELD score	0.92	0.81–1.03	0.16
HPS	0.67	0.61–2.152	0.66
Restrictive respiratory disease	24.28	5.01–117.5	<0.001
Mixed respiratory disease	2.489	1.21–5.12	0.01

HPS, hepatopulmonary syndrome; MAP, mean arterial pressure; MELD, Model for End-Stage Liver Disease; RR, relative risk. Significant variables in the univariate were included in multivariate analysis. Cox regression was used for the multivariate analysis.

Gupta (17):
In 15 HPS patients on the transplant waiting list with sequential PaO2s (median 5 ABGs/person) – over 1.6-45.5 months (mean 13 months), 13/15 patients (87%) had a

decline in PaO2 from 60 to 50 mmHg. Mean rate of decline 13.5 +/- 16.5 mmHg/yr (1.8 kPa +/-2.2kPa/yr).

**Goldberg et al. UNOS database.
HPS defined as patients who received MELD exception points for HPS based on:
1. Strict HPS criteria (as per ERS taskforce definition) – <5% of exception applications included the primary data to confirm this so additional definitions were used as follows.
2. Hypoxaemia (PaO2<70mmHg or sats <=96%) and intrapulmonary shunting (confirmed CEE of "intrapulmonary shunting written on form…) and no cardiopulmonary disease.
3. HPS defined by centre with no evidence.
973/59619 patients transplanted 2002-2012 fulfilled this definition (1.6%). 522/610 (86%) patients with PaO2 data had a PaO2 at time of exception point application of <8kPa.
Patients had a lower mELD score than the non HPS patients.
Survival on wait list provided but median time to transplantation after MELD exception was only 55 days. 9% patients died within 90 days. "No association between oxygenation and wait list survival". No further wait list data provided.

Sulieman (19).
OPTN database. Patients who received HPS exception points were transplanted quicker than non HPS patients (median time of 200 days), were more likely to be transplanted (93% vs46%) and less likely to die whilst waiting (1% vs 14%). In keeping with exception points for HPS patients resulting in unfair advantage. Similar post transplant outcome.

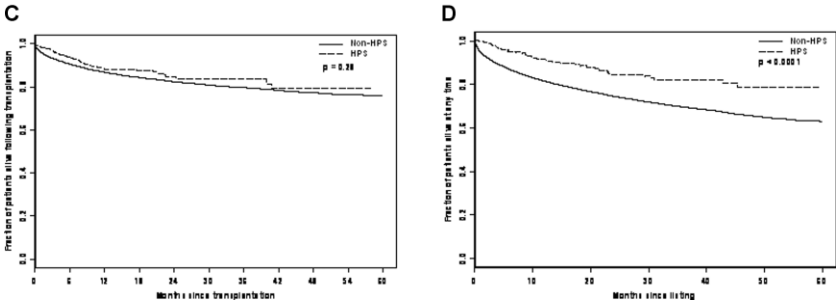


Figure 2: (A) Fraction of patients remaining on waiting list. (B) Fraction of patients alive on waiting list. (C) Fraction of transplanted patients alive after transplantation. (D) Fraction of patients alive from time of listing (overall survival).

Eurotransplant data (11) – n=80, 0.5% of all patients were documented to have HPS exception points. 25% of patients with HPS exception points died/were removed from the liver transplant database vs 34% of patients without exception points. Patients with HPS exception points had a statistically significant lower risk of adverse outcome after listing i..e. unfairly advantaged by the method.

Raevens Eurotransplant data (24)
88 patients with severe-very severe HPS (PaO2 <8). 61 were transplanted.
On competing risk analysis, HPS MELD exception point patients had similar pre transplant mortality to non HPS patients. The main causes of death with infection and liver failure.

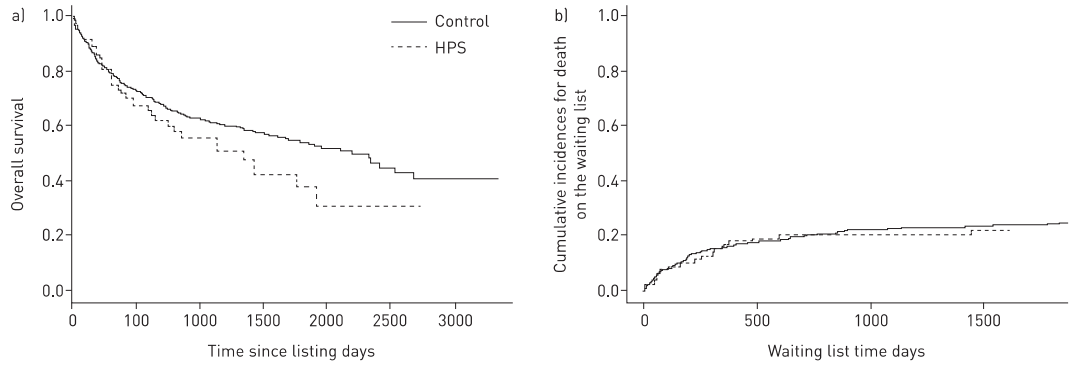
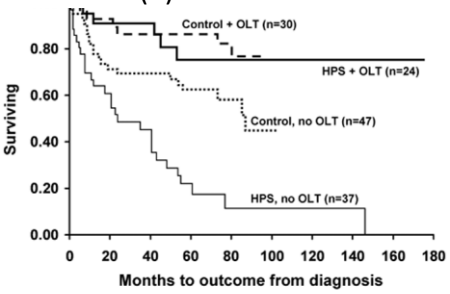


FIGURE 1 a) Overall patient survival of hepatopulmonary syndrome (HPS) *versus* non-HPS waiting list candidates. b) Competing risk curves for pre-transplantation waitlist survival in HPS *versus* non-HPS waiting list candidates. Unadjusted subdistribution hazard ratio for HPS 0.88 (95% CI 0.52–1.47,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

HPS – evidence with respect to outcomes after liver transplantation (see table below; most relevant papers with more info available summarised)

Swanson KL (6) as above and:



Overall HPS patients had similar long term post transplant survival to controls, and superior survival to non OLT patients.

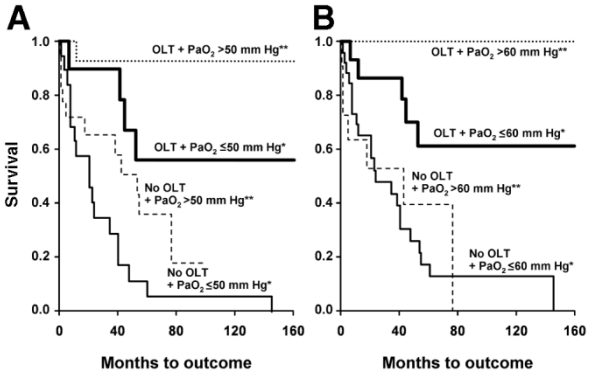


Fig. 2. Survival based on initial PaO_2 determinations at the time of HPS diagnosis in patients with HPS based on transplant status. (A) Survival differences between HPS patients undergoing OLT or not with $PaO_2 \leq 50$ mm Hg (10, OLT; 19, no OLT) and $PaO_2 > 50$ mm Hg (14, OLT; 18, no OLT) (*$P = .001$; **$P = .002$); (B) Survival differences with $PaO_2 \leq 60$ mm Hg (15, OLT; 26, no OLT) and with $PaO_2 > 60$ mm Hg (9, OLT; 11, no OLT) (*$P = .002$; **$P = .002$). PaO_2 measurements were taken in the standing position.

Trend towards reduced survival PaO2<60 (8kPa) vs PaO2 ≥8, 5-year survival being 60%.

Iyer VN (16). Updated Mayo data (1986-2010) (includes the Swanson patients above (6)). 106 patients with HPS, 49 of which underwent liver transplantation.
Pa02 data available in 32/49 transplanted patients (looks like PaO2 at time of HPS diagnosis – not clear): 21/32 PaO2<60/8 (65%), 11/32 PaO2 <50/6.7 (34%).
Post transplant survival not predicted by baseline (ie at time of HPS diagnosis) PaO2.

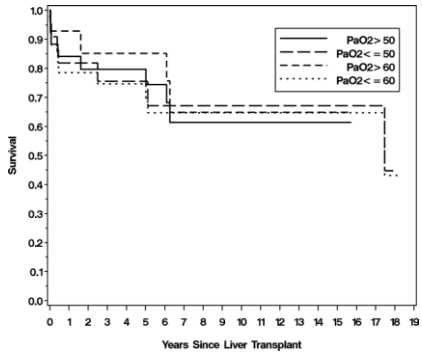


Fig. 3. Post-LT survival based on baseline PaO_2 values. The graphs shown are for PaO_2 $\leq$50 mmHg, $>$50 mmHg, $\leq$60 mmHg, and $>$60 mmHg.

**Pascasio et al, AJT (14). CEE was done in all patients assessed for liver transplantation with an elevated A-a gradient. 81/316 fulfilled HPS diagnostic criteria (25.6%): mild 33 (41%), moderate, 42 (52%), severe 5 (6%), very severe 1 (1%).
49/81 HPS patients were transplanted (4/49 with PaO2<8). HPS did not impact on post transplant survival. 96% and 100% of patients had reversal of HPS by 6-months and 12-months post transplant, respectively.

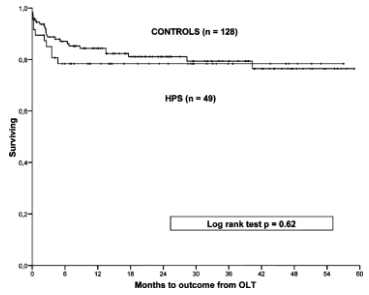


Figure 3: Postliver transplantation survival. Survival curve after liver transplantation in patients with hepatopulmonary syndrome and without hepatopulmonary syndrome (controls).

**Goldberg et al. UNOS database.
HPS defined as patients who received MELD exception points for HPS based on:
1. Strict HPS criteria (as per ERS taskforce definition) – <5% of exception applications included the primary data to confirm this so additional definitions were used as follows.
2. Hypoxaemia (PaO2<70mmHg or sats <=96%) and intrapulmonary shunting (confirmed CEE of "intrapulmonary shunting written on form…) and no cardiopulmonary disease.
3. HPS defined by centre with no evidence.

973/59619 patients transplanted 2002-2012 fulfilled this definition (1.6%). 522/610 (86%) patients with PaO2 data had a PaO2 at time of exception point application of <8kPa.
Patients had a lower mELD score than the non HPS patients.
Survival on wait list provided but median time to transplantation after MELD exception was only 55 days. 9% patients died within 90 days. “No association between oxygenation and wait list survival”. No further wait list data provided.
Identified the optimal cut off of PaO2 (at time of exception point application) to determine post transplant survival: on multivariate modelling patients with a PaO2<=44mmHg (<=5.9kPa) had increased post transplant mortality (HR 1.58 (95% CI 1.15-2.18).
Estimated survival below (5-year survival if PaO2<6 still 60%):

Table 3. Unadjusted 1-, 3-, and 5-Year Post-Transplantation Survival Rates of HPS Transplant Recipients by PaO_2 Category and HPS vs Non-HPS Transplant Recipients

PaO_2 category	1-Year survival, 95% CI	3-Year survival, 95% CI	5-Year survival, 95% CI
Standard categories			
<50 mm Hg	87.2 (81.1–91.5)	75.0 (66.6–81.5)	69.3 (59.6–77.1)
50–59 mm Hg	93.1 (89.8–95.4)	85.9 (81.0–89.6)	80.1 (73.4–85.0)
60–69 mm Hg	87.0 (77.8–92.6)	79.8 (68.9–87.2)	77.7 (66.3–85.7)
Cubic spline categories[a]			
≤44.0 mm Hg	84.4 (72.2–91.6)	68.1 (52.9–79.4)	59.0 (40.9–73.3)
44.1–54.0 mm Hg	91.8 (87.4–94.7)	83.6 (77.4–88.2)	77.9 (70.3–83.7)
54.1–61.0 mm Hg	92.5 (88.3–95.3)	86.4 (80.3–90.7)	81.7 (74.0–87.3)
≥61.1 mm Hg	84.8 (73.6–91.5)	70.6 (57.3–80.5)	68.4 (54.8–78.7)
HPS vs non-HPS recipients			
All HPS recipients	90.6 (88.1–92.6)	81.2 (77.6–84.3)	75.5 (71.2–79.3)
HPS lowest risk[b]	92.3 (89.4–94.4)	84.7 (80.6–88.1)	79.7 (74.6–83.9)
Non-HPS DDLT recipients	88.7 (88.3–89.1)	80.7 (80.2–81.3)	74.3 (73.6–75.1)

DDLT, deceased donor liver transplant.
[a]Cubic spline categories determined by fitting cubic spline logistic regression models for the binary outcome of post-transplantation mortality (yes/no), with pre-transplantation room-air PaO_2 as a continuous variable. Cut points determined based on the best model fit. The 15 transplant recipients with a PaO_2 >70 mm Hg were excluded.
[b]Lowest-risk HPS transplant recipients defined as HPS transplant recipients with the best post-transplantation outcomes based on the cubic spline analysis—those with an initial room-air PaO_2 of 44.1–61.0 mm Hg.

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Table of papers showing survival data – natural history
Blue highlighter – most relevant studies of patients a large proportion of severe/very severe HPS.
Mild/mod HPS does not look to impact on survival.

	No.	Grade	Cohort	Survival	Predictors of outcome	Other comments
Schenk (22). 2003	27	9/27 patients had a PaO2<8, none very severe		On univariate analysis, HPS patients had worse survival from point of diagnosis including when subdivided as per CP class.		But looks like sicker patients
Swanson KL (6), Mayo 2005	37/61	pO2 ≥8, 10 patients; pO2 6.7-7.9, 8; <6.7, 19. 2/3 severe/ Very severe	Mixed bag	HPS patients had worse long term survival (up to 20 yr FU) than matched controls. Estimated 1-year survival approx. 60-65% for HPS and approx. 75% for controls.	Cut offs of PaO2 were not useful in predicting short-term mortality relevant to liver transplant waiting list.	No patient died of progressive, isolated hypoxemic respiratory failure.
Fallon (18), USA 2008	72	Mean PaO2 77mmHg (10.3)	NAD	HPS an independent predictor of worse long term survival.		KM curves run close… PFTs raise question of muscle weakness/sarcopenia contributing – not commented on.
Iyer VN (16) Mayo (includes Swanson pts) 2013	106	55% PaO2<6.6; 77% PaO2<8 (82 patients).		Estimated 3-year survival after HPS diagnosis based on Kaplan Meier approx. 80%. Estimated 5-year about 50%.		1986-2010

Pascasio (14), Spain 2014	81	6/81 had a PaO2 <8.	Liver transplant waiting list	Comparable 1-year wait list survival, looking like trend towards reduced survival at 2-years (see KM above). HPS not independent predictor of death on waiting list.		
Goldberg (15), UNOS 2014	973 with "HPS"	522/610 (86%) had PaO2<8	Liver transplant waiting list	Survival on wait list from time of exception approval to transplant/death provided - but median time to transplantation was only 55 days. 9% patients died within 90 days of exception.	"No association between oxygenation and wait list survival". No further wait list data provided.	Imprecise definition of HPS, and short wait list FU time after inclusion (median 55 days). But lower MELD and most PaO2<8. 2002-2012. Interpret with caution.
Voiosu (12), Romania 2015	17	7 mild, 10 mod (ie all PaO2>8)	NAD	No difference in survival to 1-year compared to patients without HPS.		Identical curve on KM.
Fragaki (10), Greece 2018	24	Mean PaO2 77	NAD	No difference in long term survival of patients with mild-mod HPS (ie PaO2>8) compared to non HPS patients.		HPS defined as liver disease with positive MAA scan and elevated A-a gradient. Same grades to ERS. HPS and controls matched by MELD and CPS.
Raevens (24) Eurotransplant 2019	88 with severe "HPS" – awarded HPS MELD exception points.	All had PaO2<8.	Liver transplant waiting list	On competing risk analysis, pre-transplant mortality risk was similar for HPS and non HPS patients. KM above – approx. an 18% cumulative incidence of death by 1-year.		2006-2013. PRS matched controls.

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Table of papers showing survival data – post transplant
Blue highlighter – most relevant studies of patients a large proportion of severe/very severe HPS.
Mild/mod HPS does not look to impact on survival.

	No.	Grade	Cohort	Survival	Predictors of outcome	Other comments
Schenk (5), Austria 2002	7	2 PaO2<9.3	NAD	Both PaO2 <9.3 died, 1/5 PaO2 ≥9.3 died.		Subdivided patients into "clinically significant HPS" (PaO2<9.3kPa) and "subclinical HPS" (PaO2 ≥9.3 but increased A-a gradient as per age).
Taille C (23) Paris 2003	23	18/24 PaO2<8	NAD	8.5% 3-month mortality (2 patients, both of refractory hypoxaemia and MOF – PaO2 going was 32 and 52). A further 22% had late mortality. 15/21 with LT FU achieved a post op PaO2 >70mmHg.	No variables predictive of death but small nos.	1991-2000 4 centres
Krowka (21) 2004	32/40 transplanted (16 paed, 24 adult).	PaO2<50mmHg in 50% of 40.		16% died prior to hospital discharge.	Patients who died had a lower PaO2 pre transplant (37 vs 55mmHg).	Multinational (USA/Canada/Japan/Germany). 10 centres. 3 patients/centre transplanted on average. 1996-2001. Information difficult to take out of paper.
Swanson KL (6), Mayo 2005	24	Mean PaO2 57mmHg	NAD	21% died, all within 6 months of transplantation.	Mean PaO2 5.5 (3.6-7.2) in patients who died at any time compared to 8.1	Causes of death – abdominal sepsis x 2, opportunistic pulmonary infection, ICH, new

					(7.2-9) in patients who survived. However using a cut off of Pa)2 of <8 or < 6.6 did not predict survival post transplant – trend towards lower long term survival c PaO2<8 group vs PaO2 ≥8.	onset AF with stroke/cardiac complications. Not contemporary.
Schiffer (20), Geneva 2006	9	Mod-severe (mean 60mmHg). No patients had PaO2 <6.7.		Mortality rate at 6 months post transplant 33% vs 9% in non transplant patients.	No difference in PaO2, but MELD was higher (19-28 in patients who died).	1999-2003 Small no of patients, and only 90 transplanted in total/4 years.
Gupta S (17), Canada 2010	21	11/21 PaO2<6.7; 18 on home O2		1/21 died (1/11 with PaO2<6.7) during a median FU of 20 months. Of 16 patients with 3 months FU minimum, 15 were off O2 support by a median of 4 months post op; 75% were off by 6 months post op.		2000-2008
Iyer VN (16) Mayo (includes Swanson pts) 2013	49	Data available on 32/49.		Similar post transplant survival to non HPS patients – 5-	Baseline PaO2 levels (ie at point of HPS diagnosis) did not predict outcome	Not contemporary (1986-2010) PaO2 taken from point of HPS diagnosis rather than

		21/32 PaO2<60/8 (65%), 11/32 PaO2 <50/6.7 (34%).		year 78%, 10-year 64%,	after transplantation. (KM identical – above)	transplantation. Time to transplant not provided.
Pascasio (14), Spain 2014	49	45 had mild/mod, 4 had PaO2<8	NAD	Comparable 5-year survival.		Cumulative 5-year post transplant survival approx. 80% for HPS and non HPS patients.
Goldberg DS, UNOS (15) 2014	973 with "HPS" – awarded HPS MELD exception points.	522/610 (86%) had a PaO2<8.	NAD	Comparable survival of HPS to non HPS patients: 1-year, 91% for HPS vs 89% for non HPS; 5-year, 76% for HPS vs 74% for non HPS.	PaO2<6kPa an independent predictor of death post transplant, but these patients still had an estimated 5-year survival of 60%.	Imprecise definition of HPS. But lower MELD and most PaO2<8. 2002-2012. Interpret with caution.
Kotera Y (8), Japan 2019	48 (47 living donor, 1 deceased)	11 Severe (PaO2 6.7-8), 7 very severe (<6.7)	NAD	Overall provided only. 87% 1-year, 82% 5-year and 10-year survival.	NA	
Raevens (24) Eurotransplant 2019	61 with severe "HPS" – awarded HPS MELD exception points.	All had PaO2<8.		70% and 81% 1-year post transplant survival for HPS and non HPS patients respectively.		2006-2013. PRS matched controls. Median post transplant FU 2 years. PaO2 levels not available through the registry so no further analyses done.

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Appendix 2 – UK/Ireland experience

- **Patients who reached transplantation**

Methods:

Liver transplant recipients over a 10-year time period – 2006-2016.
19 HPS patients were identified via the NHSBT database and a further 37 patients were identified retrospectively via the 8 UK/Irish units, giving a total of 56 HPS patients – 19 moderate, 37 severe/very severe.
Comparison group – all single organ first elective liver transplant recipients over the same time period.
Propensity risk score matching - A PRS of the presence of HPS over non HPS generated by nonparsimonious multiple logistic regression, including all recipient variables of clinical relevance to the outcome measure death. Included in the model – recipient age, gender, BMI, aetiology, HCC, albumin, UKELD, eGFR, donor type, donor age, time since transplant. C-statistic 0.770 (0.716-0.823).
Interactions: Gender*HCC (p=0.062); Gender*UKELD (0.080); aetiology*albumin (0.093); aetiology*UKELD (0.097). No statistically significant interactions and trends not included.

Results:

Entire cohort.

	HPS N=56	No HPS N=5570	P value
Age	52.9 (9.4)	52.6 (11.2)	0.848
Female gender	23 (41.2)	1866 (33.5)	0.233
Aetiology			
- ALD	23 (41.1)	1603 (28.8)	
- Cholestatic	2 (3.6)	1251 (22.5)	
- HCV	11 (19.6)	1104 (19.8)	
- NASH/Crypto	12 (21.4)	581 (10.4)	
- Other	8 (14.3)	1031 (18.5)	**0.001**
HCC	5 (8.9)	1356 (24.3)	**0.007**
BMI	27.7 (5.4)	27.1 (5.2)	0.359
Hb	12.3(9.3-14.1)	10.9(9.3-12.6)	**0.013**
Plts	79(52-109)	90(63-136)	**0.027**
Albumin	30(25-35)	31(27-36)	0.111
Bilirubin	36(25-54)	47(24-96)	0.145
INR	1.35(1.20-1.68)	1.40(1.20-1.70)	0.797
Creatinine	73(60-89)	79(64-99)	**0.027**
Sodium	139(134-142)	137(134-140)	**0.040**
eGFR	90(72-122)	87(66-110)	0.149
UKELD	52(49-57)	54(51-58)	**0.020**
MELD	13(11-18)	16(12-20)	0.083
Time since transplant (yrs – 2019-yr)	7(5-10)	8(6-10)	0.314
UK Donor Liver Index	1.09(0.98-1.26)	1.16(0.98-1.43)	0.089

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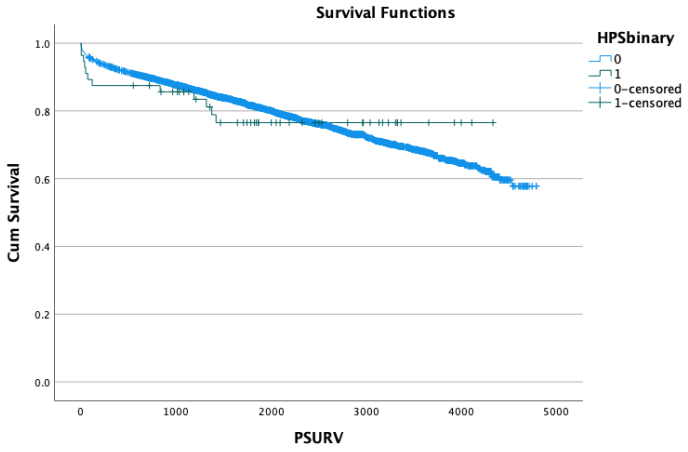
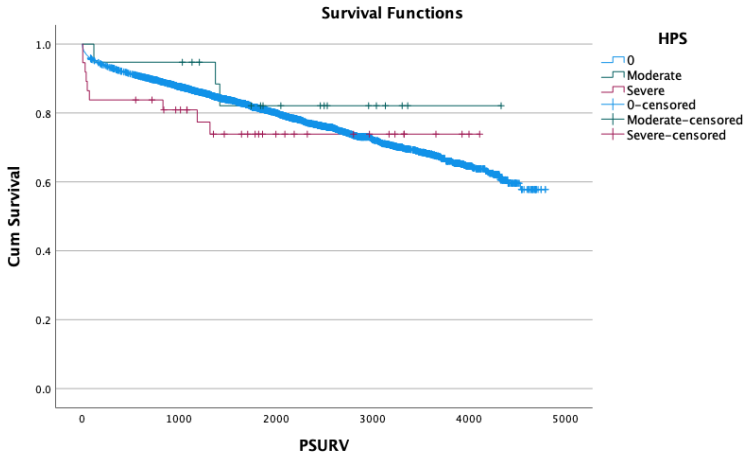
Feng DRI	1.53(1.35-1.79)	1.58(1.33-1.86))	0.512
Donor type			
- DBD	48 (85.7)	4422 (79.4)	
- DCD	7 (12.5)	1066 (19.1)	
- Living	1 (1.8)	51 (0.9)	
- Domino	0	31 (0.6)	0.508
Donor age	47.4(13.3)	47.6(16.0)	0.922
Donor BMI	26.2(4.8)	26.2(4.9)	0.933
CIT	545(425-643)	504(407-616)	0.310



Log rank p=0.964.

On multivariate modelling (adjusting for age, gender, aetiology, HCC, UKELD, eGFR AND UK DLI there was no association between HPS and post transplant death (HR 1.05; 95% CI 0.58-1.90, P=0.883). If UK DLI replaced by Feng, HR 1.11 (95% CI 0.63-1.97, p=0.708).



Log rank p=0.633.

Cumulative incidence of mortality by 1-year after transplantation for non HPS, moderate HPS and severe/very severe HPS was 92.4%, 94.7% and 83.8%, respectively.

PRS matched cohort:

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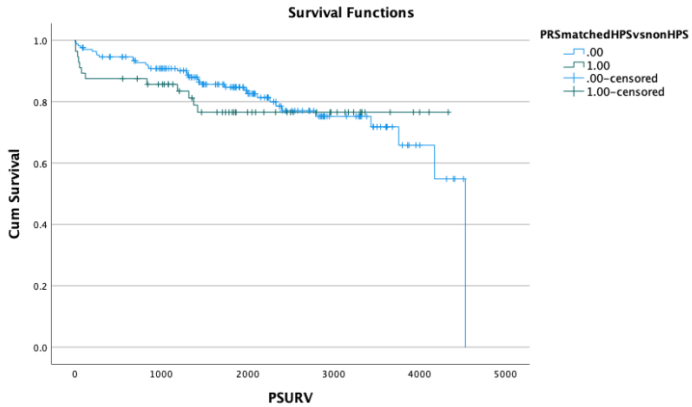
	HPS N=56	Matched no HPS N=168	P value
Age	52.9 (9.4)	53.0 (10.8)	0.950
Female gender	23 (41.2)	73(43.5)	0.755
Aetiology			
- ALD	23 (41.1)	75 (44.6)	
- Cholestatic	2 (3.6)	3 (1.8)	
- HCV	11 (19.6)	27 (16.1)	
- NASH/Crypto	12 (21.4)	48 (28.6)	
- Other	8 (14.3)	15 (10.7)	0.556
HCC	5 (8.9)	16 (9.5)	0.895
BMI	27.7 (5.4)	28.1 (5.1)	0.639
Hb	12.3(9.3-14.1)	10.8(9.1-12.1)	**0.003**
Plts	79(52-109)	89(66-122)	0.082
Albumin	30(25-35)	30(25-34)	0.971
Bilirubin	36(25-54)	40(25-76)	0.553
INR	1.35(1.20-1.68)	1.40(1.20-1.70)	0.330
Creatinine	73(60-89)	75(61-95)	0.373
Sodium	139(134-142)	138(134-141)	0.259
eGFR	90(72-122)	86(65-119)	0.317
UKELD	52(49-57)	53(50-58)	0.190
MELD	13(11-18)	15(12-19)	0.304
Time since transplant (yrs – 2019-yr)	7(5-10)	7(6-10)	0.759
UK Donor Liver Index	1.09(0.98-1.25)	1.16(0.97-1.35)	0.143
Feng DRI	1.53(1.35-1.79)	1.60(1.35-1.83)	0.426
Donor type			
- DBD	48 (85.7)	143 (85.1)	
- DCD	7 (12.5)	25 (14.9)	
- Living	1 (1.8)	0	
- Domino	0	0	0.229
Donor age	47.4(13.3)	49.5(16.5)	0.375
Donor BMI	26.2(4.8)	26.4(5.2)	0.801
CIT	545(425-643)	508(404-603)	0.370



Log rank p=0.630.

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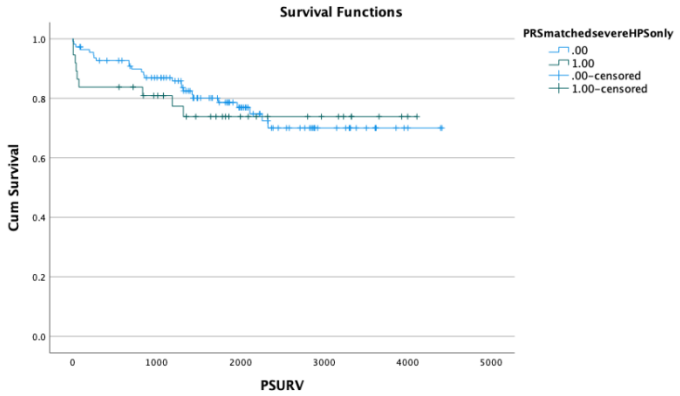

Log rank p=0.685.

Early post op outcomes:

	Severe HPS N=37	Matched no HPS N=111	P value
Days ventilated	1(1-3)	1(1-2)	0.010
Days in ITU	3(2-13)	2(1-4)	0.026
Days in hospital	18(17-49)	16(12-29)	0.036
90-day survival	31(83.8)	108(97.3)	0.008

All values median(IQR), no (%).

After adjusting for age, MELD, eGFR, severe HPS remained associated with 3-month mortality (OR 9.97; 95% CI 2.06-48.33).

Variables associated with 3-moth mortality in HPS

	Mortality N=6	Survival N=44	P value
Age	52(48-62)	55(46-50)	0.969
MELD	13(11-18)	14(12-18)	0.560
UKELD	51(49-52)	52(50-57)	0.214
eGFR	104(75-154)	90(71-115)	0.399
Albumin	35(25-40)	29(25-35)	0.186
Haemoglobin	15.7(12.0-16.8)	12.0(9.3-13.9)	0.030
UK DLI	1.17(0.98-1.39)	1.09(1.00-1.19)	0.814

Further analysis has not been performed pending individual patient data – no information available regarding PaO2 at transplantation etc.

- **Patients listed for transplantation**

Methods:

All patients listed 1990-2019.
45 patients were coded as “HPS”, but this number increased to 104 when HPS was reported as other indication or other cause of death or the centre had previously identified the patient as HPS.

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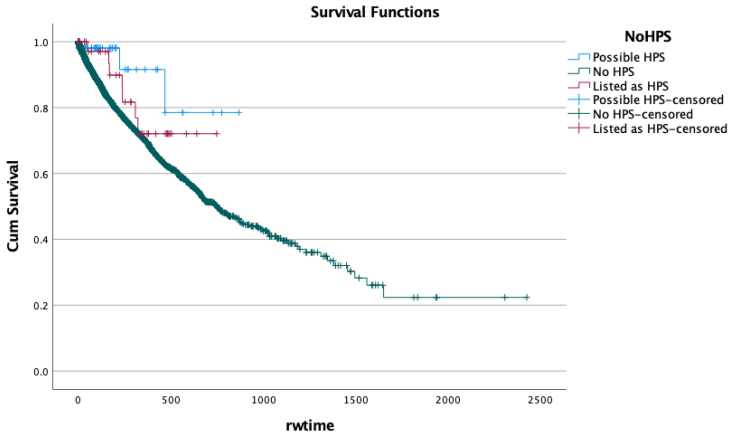
Of the 45 patients coded as “HPS”, no patient was listed under the CLD arm (43 variant syndrome, 2 not documented). Meaning that all patients were probably severe-very severe HPS.
Of the 104 patients where any reference to HPS, 45 were listed under the variant arm (59 not documented, 0 CLD). Using this method, 7 patients over and above the HPS patients picked up in the post transplant study were labelled as “HPS”. This may therefore be a heterogenous cohort.
Comparison group – 1st, adult, CLD, single organ.

Results:

	Listed as HPS	Heterogenous HPS	Non HPS
UKELD at listing	48(47-51)	51(48-53)	54(51-58)
Died/removed because of deterioration before transplantation (n=2178/17031)	7/39(17.9%)	10/92(10.9%)	2168/16939(12.8%)
Time to transplant (days)	284(112-476)	165(52-363)	55(17-143)
Time to death/removal (days)	237(164-308)	230(136-312)	78(26-181)
Waiting time >1 year	16/45(35.6%)	28/104(26.9%)	1178/16937(7.0%)
If waiting time > 1 year, died/removed because of deterioration before transplantation	0/12	1/20(5%)	219/1178(18.6%)



Survival on transplant waiting list (Univariate, non competing risk, censored at transplant). Estimated 1-year wait list survival for HPS and non HPS patients 72.1% and 69.6%, respectively.

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References

1. https://nhsbtdbe.blob.core.windows.net/umbraco-assets-corp/9440/pol195_7-liver-selection-policy.pdf
2. Krowka MJ, Fallon MB, Kawut SM, et al. International Liver Transplant Society Practice Guidelines: Diagnosis and Management of Hepatopulmonary Syndrome and Portopulmonary Syndrome. Transplantation 2016;100:1140-1452
3. Rodriguez-Roisin R, Krowka MJ, Herve Pj, et al. Pulmonary-Hepatic vascular disorders (PHD). Eur Resp J 2004;24:861-880.
4. Martinez GP, Barbera JA, Visa J, et al. Hepatopulmonary syndrome in candidates for liver transplantation. J Hepatol 2001;34:651-657.
5. Schenk P, Fuhrmann V, Madl C, et al. Hepatopulmonary syndrome: prevalence and predictive value of various cut-offs for arterial oxygenation and their clinical consequences. Gut 2002;51(6):853-9.
6. Swanson KL, Wiesner RH, Krowka MJ. Natural History of Hepatopulmonary Syndrome: Impact of Liver transplantation. Hepatology 2005;41(5):1122-
7. La Gerche A, MacIsaac AI, Burns AT, et al. Pulmonary transit of agitated contrast is associated with enhanced pulmonary vascular reserve and right ventricular function during exercise. J Appl Physio 2010;109(5):1307-17.
8. Kotera Y, Egawa H, Ogata S, et al. Current status of hepatopulmonary syndrome in liver transplantation in Japan: a Japanese multicentre analysis. J Hepatobiliary Pancreat Sci 2019;26(7):292-299.
9. Forde KA, Fallon MB, Krowka MJ, et al. Pulse oximetry is insensitive for detection of HPS in patients evaluated for liver transplantation. Hepatology 2019;69(1):270-81.
10. Fragaki M, Sifaki-Pistolla D, Samonakis DN, et al. Screening for Hepatopulmonary Syndorme in cirrhotic patietns using technetium 99m-macroaggregated albumin perfusion lung scan (Tc-MAA): Diagnostic approach and clinical correlations. J Clin Gastroenterol 2018;52(9):828-834.
11. Umgelter A, Hapfelmeier A, Wouter K, et al. Disparities in Eurotransplant liver transplantation wait-list outcome between patients with and without model for end-stage liver disease exeptions. Liver Transpl 2017;23(10):1256-1265.
12. Voiosu AM, Daha IC, Voiosu TA, et al. Prevalence and impact on survival of hepatopulmonary syndrome and cirrhotic cardiomyopathy in a cohort of patients with cirrhosis. Liver Int 2015;35(12):2547-.
13. Horvatits T, Drolz A, Roedl K, et al. Von Willebrand factor antigen for detection of HPS in patients with cirrhosis. J Hepatol 2014;61(3):544-9.
14.Pascasio JM, Grilo I, Lopez-Pardo FJ, et al. Prevalence and severity of HPS and its influene on survival in patients evaluation for liver transplantation. Am J Transplant 2014;14(6):1391-
15. Goldberg DS< Krok K, Batra S, et al. Impact of the hepatopulmonary syndrome MELD exception policy on outcomes of patients after liver transplantation: an analysis of the UNOS database. Gastroenterology 2014;146(5):1256-.
16. Iyer VN, Swanson KL, Cartin-Ceba R, et al. HPS: favourable outcomes in the MELD exception era. Hepatology 2013;57(6):2427-35.
17. Gupta S, Castel H, Rao RV, et al. Improved survival after liver transplantation in patients with HPS. Am J Transplant 2010;10(2):354-.
18. Fallon MB, Krowka MJ, Brown RS, et al. Impact of HPS on quality of life and survival in liver transplant candidates. Gastroenterology 2008;135(4):1168-75.

19. Sulieman BM, Hunsicker LG, Katz DA, et al. OPTN policy regarding prioritization of patients with HPS: does it provide equitable organ allocation? Am J Transplant 2008;8(5):954-64.
20. Schiffer E, Majno P, Mentha G, et al. HPS increases the postoperative mortality rate following liver transplantation: a prospective study in 90 patients. Am J Transplant 2006;6(6):1430-7.
21. Krowka MJ, Mandel MS, Ramsey MAE, et al. HPA and portopulmonary hypertension: a report of the multicentre liver transplant database. Liver Transpl 2004;10(2):174-82.
22. Schenk P, Schoniger-Hekele M, Fuhrmann V, et al. Prognostic significance of the HPS in patients with cirrhosis. Gastroenterology 2003;125(4):1042-52.
23. Taille C, Cadranel J, Bellocq A, et al. Liver transplantation for HPS: a ten-year experience in Paris, France. Transplantation 2003;75(9):1482-.
24. Raevens S, Rogiers X, Geerts A, et al. Outcome of liver transplantation for HPS: a Eurotransplant experience. Eur Respir J 2019;53(2):1801096.
25. DuBrock HM, Krowka MJ, Forde KA, et al. Clinical Impact of Intrapulmonary Vascular Dilatation in Candidates for Liver Transplant. Chest 2018;153(2):414-426.