



HAL
open science

Evidence for an Association Between Intrahepatic Vascular Changes and the Development of Hepatopulmonary Syndrome

Clément Lejealle, Valérie Paradis, Onorina Bruno, Emmanuelle de Raucourt, Claire Francoz, Olivier Soubrane, Didier Lebrec, Pierre Bedossa, Dominique Valla, Hervé Mal, et al.

► **To cite this version:**

Clément Lejealle, Valérie Paradis, Onorina Bruno, Emmanuelle de Raucourt, Claire Francoz, et al.. Evidence for an Association Between Intrahepatic Vascular Changes and the Development of Hepatopulmonary Syndrome. *Chest*, 2019, 155, pp.123 - 136. 10.1016/j.chest.2018.09.017 . hal-03486824

HAL Id: hal-03486824

<https://hal.science/hal-03486824v1>

Submitted on 20 Dec 2021

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License

1 **Body of manuscript word count:** 2645 words, not including the abstract, references,
2 tables, and figure legends

3 **Abstract word count:** 249 words

4

5 **Evidence for an association between intrahepatic vascular changes**
6 **and the development of hepatopulmonary syndrome**

7 **Running Head:** Liver vascular pattern of damage and HPS

8

9 Clément Lejealle^{1,5} MD, Valérie Paradis^{2,5,6} MD, PhD, Onorina Bruno³ MD, Emmanuelle de
10 Raucourt⁴ MD, PhD, Claire Francoz^{1,5} MD, PhD, Olivier Soubrane^{6,7} MD, PhD, Didier
11 Lebrech^{1,5,6} MD, PhD, Pierre Bedossa^{2,5,6} MD, PhD, Dominique Valla^{1,5,6} MD, PhD, Hervé
12 Mal^{6,8} MD, PhD, Valérie Vilgrain^{3,5,6} MD, PhD, François Durand^{1,5,6} MD, PhD, Pierre-
13 Emmanuel Rautou^{1,6,9} MD, PhD

14

15 ¹ Service d'Hépatologie, DHU Unity, Hôpital Beaujon, Assistance Publique-Hôpitaux de
16 Paris, Clichy, France

17 ² Service d'Anatomie Pathologique, Hôpital Beaujon, Assistance Publique-Hôpitaux de Paris,
18 Clichy, France

19 ³ Service d'imagerie, Hôpital Beaujon, Assistance Publique-Hôpitaux de Paris, Clichy, France

20 ⁴ Service d'Hématologie-Biologique, Hôpital Beaujon, Assistance Publique-Hôpitaux de
21 Paris, Clichy, France

22 ⁵ INSERM, UMR-1149, Centre de Recherche sur l'inflammation, Paris-Clichy, France

23 ⁶ Université Denis Diderot-Paris 7, Sorbonne Paris Cité, 75018 Paris, France

24 ⁷ Service de Chirurgie hépato-biliaire et Transplantation Hépatique, Hôpital Beaujon,
25 Assistance Publique-Hôpitaux de Paris, Clichy, France

1 ⁸ Service de Pneumologie B et Transplantation Pulmonaire, Hôpital Bichat, Assistance
2 Publique-Hôpitaux de Paris, Paris, France

3 ⁸ INSERM, UMR-970, Paris Cardiovascular Research Center - PARCC, Paris, France

4

5

6 **Corresponding author:**

7 Prof. Pierre-Emmanuel Rautou

8 Service d'Hépatologie,

9 Hôpital Beaujon,

10 100 boulevard du Général Leclerc,

11 92110 Clichy, France

12

13 **Disclosures:** none

14

15 **Financial support statement:** This work was supported by the Agence Nationale pour la
16 Recherche (ANR-14-CE12-0011 and ANR-14-CE35-0022) and by the Association Française
17 pour l'Etude du foie (AFEF 2009).

18

19 **Prior abstract presentation:** This article has been presented in oral communication at *the*
20 *Liver Meeting 2016 - American Association for the Study of Liver Diseases, 67th Annual*
21 *Meeting (November 11-15, 2016 - Boston, Massachusetts, USA)*

22

23

24

25 **Figures:** 3

26 **Tables:** 4

27 **References:** 41

28

1 **Abbreviations**

2 HPS: hepatopulmonary syndrome

3 MDCT: multidetector computed tomography

4 MELD: model for end-stage liver disease

5 PaO₂: partial pressure of arterial oxygen

6

7

1 **ABSTRACT**

2 **Backgrounds:** Hepatopulmonary syndrome (HPS) is characterized by an arterial
3 oxygenation defect - defined by an increased alveolar-arterial oxygen gradient - induced by
4 pulmonay vascular dilatations in the context of liver disease. The pathogenesis of HPS is
5 poorly understood. Morphological changes associated with HPS are unknown.

6 This study aimed at describing imaging and pathology changes associated with HPS.

7 **Methods:** We performed a case-control study in candidates for transplant with suspicion of
8 cirrhosis. Each patient with HPS ($\text{PaO}_2 \leq 70$ mm Hg) was matched to 3 controls for age,
9 cause and liver disease severity. Pretransplant thoracic and abdominal imaging and
10 explanted livers were reviewed.

11 **Results:** CT-scans and Doppler ultrasounds from 21 patients with HPS were compared with
12 those from 63 controls. HPS was associated with a 2 to 3-fold higher prevalence of
13 obstructed intrahepatic portal branches, of slowed or hepatofugal portal blood flow, and of
14 large abdominal portosystemic shunts. Hepatic artery diameter was also larger in patients
15 with HPS. Explanted livers from 19 patients with HPS were compared with those from 57
16 controls. HPS was associated with a 4-fold higher prevalence of portal venules thrombosis
17 and a nine fold higher prevalence of extensive vascular proliferation within fibrous septa.
18 Obstruction of centrilobular veins, sinusoidal dilatation and liver parenchymal extinction were
19 also more common in patients with HPS.

20 **Conclusions:** HPS is associated with intrahepatic vascular changes and with features
21 suggesting severe portal hypertension. These results raise the hypothesis that intrahepatic
22 vascular changes precipitate the development of HPS, opening new therapeutic perspectives
23 for HPS.

24 **Keywords:** Hepatopulmonary syndrome; cirrhosis; thrombosis; portal hypertension;
25 angiogenesis

26

1 **Introduction**

2 Hepatopulmonary syndrome (HPS) is characterized by an arterial oxygenation defect - as
3 defined by an increased alveolar-arterial partial pressure oxygen difference ≥ 15 mm Hg in
4 patients < 65 years and ≥ 20 mm Hg in patients ≥ 65 years - induced by pulmonary vascular
5 dilatations in the context of liver disease^{1,2}. This syndrome is observed in 5% to 32% of
6 patients with cirrhosis evaluated for liver transplant²⁻⁶.

7 The pathogenesis of HPS is still poorly understood, which hampers the development of
8 effective treatments. Data on the mechanisms leading to the key features of HPS, namely
9 pulmonary microvascular dilatations and angiogenesis, have been obtained in rats with
10 chronic common bile duct ligation⁷. In this model, pulmonary vasodilatation results from the
11 interaction between an increased release of endothelin-1 by the liver and an enhanced lung
12 endothelin B receptor expression due to the hyperdynamic circulation of cirrhosis⁸.
13 Pulmonary vasodilatation is also associated with increased activity of endothelial nitric oxide
14 (NO) synthase (eNOS) and inducible NO synthase (iNOS), and with enhanced carbon
15 monoxide (CO) production. Pulmonary angiogenesis is accompanied by the accumulation of
16 vascular endothelial growth factor (VEGF)-A in the lungs, and activation of VEGF-A
17 dependent signaling pathways. Placental growth factor (PIGF) also contributes to lung
18 angiogenesis in HPS⁹.

19 Attempts to clarify the pathophysiology of HPS in patients have been scarce. Patients with
20 HPS were found to have elevated levels of exhaled NO¹⁰, of venous endothelin-1¹¹, of
21 soluble VCAM-1 and ICAM-3¹² and of arterial carboxyhemoglobin¹³. However, the source of
22 these soluble mediators is unknown. Complete resolution or significant improvement in gas
23 exchange is almost constant following liver transplant suggesting that the liver itself, or the
24 gut though the portosystemic venous shunts, release mediators resulting in pulmonary
25 changes³.

26 In order to better understand the mechanisms involved in HPS, we aimed to characterize the
27 morphological changes occurring in patients with HPS both within the liver - based on
28 explant pathology - and within thorax and abdomen based on pre-transplant imaging.

1 This study has been approved by the Institutional Review Board of HUPNVS, Paris 7
2 University, AP-HP (#2017-013).

3

4

5 **Methods**

6 ***Patients***

7 This retrospective case-control study included all patients evaluated for liver transplant
8 between January 1997 and December 2015 at Beaujon hospital, Clichy, France. To facilitate
9 matching between cases (HPS) and controls, only patients with a pre-transplant diagnosis of
10 alcohol-related cirrhosis, hepatitis B or C virus-related cirrhosis, non-alcoholic
11 steatohepatitis-related cirrhosis or cryptogenic cirrhosis were included. Diagnosis of cirrhosis
12 was based on clinical examination, laboratory test, imaging and/or liver biopsy. The study
13 protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki.

14 Cases were patients with a diagnosis of HPS at least moderately severe based on the
15 following criteria: (i) diagnosis of cirrhosis, as mentioned above; (ii) abnormal arterial
16 oxygenation ($\text{PaO}_2 \leq 70$ mm Hg and alveolar-arterial oxygen gradient ≥ 15 mm Hg in patients
17 < 65 years and ≥ 20 mm Hg in patients ≥ 65 years) breathing room air, at rest, in the supine
18 and/or standing position; and (iii) contrast-enhanced transthoracic echocardiography showing
19 appearance of microbubbles in the left heart chambers 3 to 6 cycles after right atrial
20 passage, reflecting intrapulmonary vascular dilatations^{14,15}. All patients had a thoracic
21 multidetector computed tomography (MDCT) excluding large volume pleural effusion or
22 significant parenchymal changes that could explain hypoxemia. Patients with pulmonary
23 hypertension defined by mean pulmonary pressure > 25 mm Hg, pulmonary arterial
24 occlusion pressure < 15 mmHg and pulmonary vascular resistance > 240 dyn second cm^{-5}
25 were not included in the study.

26 Control patients had normal PaO_2 (> 85 mm Hg) in supine and upright position. Three
27 controls were matched with one patient with HPS according to the cause of liver disease,
28 calculated model for end-stage liver disease score (MELD) (± 3) at evaluation for liver

1 transplant, and age (\pm 5 years). In patients with several causes of cirrhosis, matching was
2 performed for the main cause of cirrhosis. MELD values mentioned all along the manuscript
3 are calculated using the formulae previously reported¹⁶ without extra points for hepatocellular
4 carcinoma or HPS.

5

6 ***Features analyzed***

7 Clinical, laboratory, hemodynamics features were analyzed. All thoracic and abdominal
8 contrast-enhanced triple phase MDCT performed at evaluation for liver transplant were
9 reviewed by a senior radiologist (OB) unaware of the clinical, laboratory and pathological
10 results. During the study period, samples from explants of liver transplant recipients were
11 systematically collected. For this study, liver samples from 6 or more liver segments were
12 selected. They were retrospectively reviewed by an expert pathologist (VP) unaware of the
13 presence or absence of HPS or of any other clinical, laboratory or imaging result. The extent
14 of liver fibrosis was evaluated by morphometry using picosirius staining, as reported
15 previously¹⁷. Factor V Leiden and G20210A prothrombin gene mutations were tested in
16 cases and controls after DNA extraction from frozen samples of explanted livers according to
17 previously reported methods¹⁸. All details regarding features analyzed are included in
18 supplementary material. (e-Text 1)

19

20 ***Statistical analysis***

21 Quantitative variables were expressed as median and interquartile range, and categorical
22 variables as absolute and relative frequencies. Comparisons between groups of quantitative
23 variables were performed using the Mann-Whitney U test. Comparisons between groups of
24 qualitative variables were performed using Chi-square and the Fisher exact tests, as
25 appropriate. All tests were two-sided, and significance was set at $p < 0.05$. All statistics
26 analyses were performed using the SPSS statistical package 20.0 software (SPSS Inc.,
27 Chicago, IL, United States).

28

1 **Results**

2 ***Patients' characteristics***

3 Out of the 2280 patients assessed for liver transplant at our hospital between January 1997
4 and December 2015, including 1355 patients meeting the above mentioned inclusion criteria,
5 23 had a diagnosis of HPS at least moderately severe. Twenty-one out of these 23 patients
6 had complete pre-transplant imaging. Nineteen patients were transplanted and had
7 explanted liver samples available for review. Finally, 17 patients had both imaging and
8 histological data available for review (e-figure S1: flow chart).

9 These 21 HPS patients with imaging data available and 19 patients with liver sample
10 available were compared with 63 and 57 matched control patients with a pretransplant
11 diagnosis of cirrhosis, respectively. Their clinical, laboratory and hemodynamic features are
12 shown in Table 1. Alveolar–arterial oxygen gradient was above 60 mmHg (corresponding to
13 $\text{PaO}_2 < 50$ mm Hg breathing room air with $\text{PaCO}_2 = 32$ mmHg) in 71% and 84% of the
14 patients with HPS with imaging data and with liver sample available, respectively. HPS
15 patients and control patients did not differ in age, cause and severity of cirrhosis. Alcohol
16 abuse was the leading cause of cirrhosis.

17 Large esophageal varices were more frequent in patients with HPS than in control patients.
18 Hepatocellular carcinoma was common in the control group. This difference can be
19 explained by the matching for the calculated MELD score at evaluation for transplant (no
20 including MELD exception points for HPS or hepatocellular carcinoma). Indeed, patients
21 listed for HPS had a relatively low calculated MELD score and patients listed with a similar
22 calculated MELD score and no HPS were more likely to have hepatocellular carcinoma as an
23 indication for transplant. Laboratory and hemodynamic data were similar in both groups,
24 except for serum creatinine and mean arterial pressure that were slightly higher in control
25 patients. Duration between evaluation before liver transplant and transplant was shorter in
26 HPS patients than in control patients.

27

28

1 Complete image analysis

2 Imaging findings are shown in Table 2. Patients with HPS had obstructed intrahepatic portal
3 vein branches, slowed or hepatofugal portal blood flow, and/or large abdominal portocaval
4 shunts two to three-fold more frequently than control patients. Moreover, patients with HPS
5 had larger paraumbilical vein diameter and hepatic artery diameter (Figure 1). Hepatic
6 venous system, right colon, spleen and thorax aspects were not different between the two
7 groups. All these differences, except slowed or hepatofugal hepatic portal blood flow,
8 remained significant when restricting the analyses to the 17 HPS patients with MDCT,
9 Doppler ultrasound and explanted liver samples available for review (data not shown).
10 Thoracic imaging features were not different between patients with HPS and control patients.

11

12 Explant pathology

13 Histological findings are shown in Tables 3 and 4. Pathological examination of the explanted
14 liver confirmed pretransplant diagnosis of cirrhosis or advanced fibrosis in all but 2 patients.
15 Details on these 2 patients are provided in online e-Table 2.

16 When comparing the two groups, we found that HPS was associated with a 4-fold higher
17 prevalence of intrahepatic portal venule thrombosis, and a 9-fold higher prevalence of
18 extensive vascular proliferation within fibrous septa. Thickening and thrombosis of
19 centrilobular veins, sinusoidal dilatation, liver parenchymal extinction and features consistent
20 with incomplete septal cirrhosis were also more common in patients with HPS than in control
21 patients (illustrated in Figures 2 and 3). Prevalence of other features was similar between the
22 two groups. When restricting the analyses to the 17 patients having both imaging and
23 histological data available for review, intrahepatic portal venule thrombosis, extensive
24 vascular proliferation within fibrous septa, features consistent with incomplete septal cirrhosis
25 and sinusoidal dilatation remained significantly more frequent in patients with HPS than in
26 control patients.

27

28

1 ***Prothrombotic states and effect of anticoagulation***

2 Given the high prevalence of intrahepatic venous obstruction in patients with HPS, we tested
3 Factor V Leiden and G20210A prothrombin gene mutations in 15 patients with HPS and in
4 52 control patients with available frozen liver. Prevalence of these mutations was not
5 different between the two groups.

6 Eight of 21 patients with HPS received anticoagulation (seven for portal thrombosis and one
7 for deep vein thrombosis). We studied changes in alveolar–arterial oxygen gradient reflecting
8 gas exchange, between evaluation for liver transplant and liver transplant according to the
9 administration or not of anticoagulation and observed no significant difference, but only three
10 patients had anticoagulation for more than 4 months between the two time-points.

11

12 **Discussion**

13 In this case control study, we found that HPS is associated with prominent changes in the
14 extrahepatic and intrahepatic vasculature.

15 Histological changes associated with HPS included intrahepatic portal venules thrombosis,
16 thickening and thrombosis of centrilobular veins, extensive vascular proliferation within
17 fibrous septa, sinusoidal dilatation, liver parenchymal extinction, and features consistent with
18 incomplete septal cirrhosis. Ma and colleagues previously assessed liver histological
19 alterations associated with HPS¹⁹. These investigators compared histological findings in
20 livers explanted from 8 patients with cirrhosis and HPS with those from 18 patients with
21 cirrhosis without HPS, matched for age, gender and cause of liver disease. The only
22 difference they observed was a lower prevalence of micronodular cirrhosis in patients with
23 HPS. A lack of power due to a small sample size and the absence of matching for the
24 severity of liver disease in the study by Ma and colleagues may explain the variance between
25 these findings and those of the present study.

26 In the present study, imaging changes associated with HPS included a higher prevalence of
27 obstructed intrahepatic portal branches, of slowed or hepatofugal portal blood flow, and of
28 large abdominal portosystemic shunts, as well as larger paraumbilical vein and hepatic artery

1 diameters. A similar systematic analysis of imaging findings was performed in patients with
2 portopulmonary hypertension and disclosed a high prevalence of large abdominal
3 portosystemic shunts, but we are not aware of any previous study in patients with HPS²⁰. In
4 particular, systematic imaging analyses have not been carried out in the large studies
5 investigating features associated with HPS^{5,6,21}. In the present study, obstructed intrahepatic
6 portal branches were observed both at the microscopic and at the macroscopic level
7 indicating a diffuse process of portal venous obstruction.

8 Despite the retrospective, cross-sectional, and observational nature of the present study, our
9 findings suggest that liver vessel involvement should be added to the list of the mechanisms
10 leading to HPS^{8,22}. Although our results cannot firmly establish that the intra- and
11 extrahepatic changes associated with HPS precede the development this syndrome, the
12 vascular pattern of damage we observed in patients with HPS raises the hypothesis that
13 obstruction of intrahepatic portal branches and hepatic venules are a primary event in the
14 development of pulmonary changes. Indeed, portal and hepatic venules obstructions have
15 been linked to parenchymal extinction in patients with cirrhosis, and with sinusoidal dilatation
16 in non-cirrhotic patients^{23,24}. These venular obstructions might also induce liver hypoxia
17 leading to an angiogenic response responsible for extensive vascular proliferation within
18 fibrous septa²⁵. Secondly, these intrahepatic vascular obstructions may increase
19 intrahepatic vascular resistance, thus worsening portal hypertension and explaining the large
20 esophageal varices, large paraumbilical veins and abdominal portosystemic shunts as well
21 as the slowed or hepatofugal portal blood flow and the liver hyperarterialization observed in
22 patients with HPS²⁶. The absence of difference in hepatic venous pressure gradient between
23 patients with HPS and control patients despite more pronounced signs of portal hypertension
24 in HPS patients may be explained by the frequent portal venule obstructions in patients with
25 HPS. Indeed, portosystemic gradient is underestimated by hepatic venous pressure gradient
26 measurement in case of presinusoidal lesions, even in the absence of hepatic venous
27 collaterals, as in our study²⁷⁻²⁹. The similar spleen size between patients with HPS and
28 control patients can be accounted for by the absent or weak correlation between spleen size

1 and portal pressure in patients with cirrhosis^{30–32}. Systemic vascular resistance could not be
2 interpreted in our study since patients with HPS tended to receive more commonly
3 betablockers as they more frequently had large varices. The reason why some patients
4 develop obstructions of intrahepatic portal and hepatic veins remains to be determined
5 although a particular hypercoagulable state can be suspected³³. Several of the lesions
6 observed in patients with HPS are also commonly encountered in patients with idiopathic
7 non-cirrhotic portal hypertension. Therefore, the identification of factors responsible for liver
8 vascular lesions in HPS might come in the future from a better understanding of the
9 pathophysiology of idiopathic non-cirrhotic portal hypertension. If confirmed by other groups,
10 our findings would provide the rationale for future studies testing anticoagulation in patients
11 with HPS. Since no dramatic improvement in hypoxemia was observed in the few patients
12 with HPS treated with anticoagulation in the present study, such a therapy would likely be
13 tested at early steps of HPS development to prevent HPS progression.

14

15 In addition to the previously demonstrated role of endothelin 1 and of bacterial translocation
16 in HPS development, the vascular pattern of damage we observed associated with HPS
17 suggests two possible scenarios explaining the pulmonary microvascular dilatations and
18 angiogenesis typical of this syndrome^{8,12}. A first possibility could be that the mediators
19 responsible for the pulmonary microvascular dilatations and angiogenesis derive from the gut
20 and reach directly the lungs through the major portosystemic shunts observed in patients
21 with HPS, without being cleared by the liver, as described in HPS associated with Abernethy
22 syndrome. VEGF is unlikely to be this mediator since VEGF levels are lower in the portal
23 vein than in hepatic veins in patients with cirrhosis³⁴. The rare development of HPS following
24 TIPS placement in patients with cirrhosis suggests that other factors than the pure derivation
25 of the blood from the gut to the lungs are however needed to induce HPS³⁵. A second
26 possibility is that intrahepatic portal vein obstructions in patients with HPS induce liver
27 hypoxia leading to the release by the hypoxic liver of pro-angiogenic/vasodilatory agents
28 into hepatic veins³⁶. The first vascular bed encountered by these mediators is the pulmonary

1 one. This hypothesis is supported by the activation of the VEGF pathway in the lungs of rats
2 with HPS ³⁷. The observation of more frequent HPS in patients with liver hypoxia induced by
3 Budd Chiari syndrome (28%) or hypoxic hepatitis (46%) than in patients with extrahepatic
4 portal vein thrombosis without cirrhosis (4%) is consistent with this view ³⁸⁻⁴¹.

5

6 **Conclusion**

7 This case-control study shows that HPS is associated with significant intrahepatic vascular
8 changes as well as with features suggesting a severe portal hypertension. Our findings invite
9 to give increased importance to - and to gain further insight into - the obstruction of
10 intrahepatic portal and hepatic venules as an additional pathophysiological mechanism
11 leading to HPS.

12

1 **Acknowledgements**

2 We thank Marion Tanguy, Nathalie Colnot and Miguel Albuquerque for superb technical
3 assistance.

4

5 **Authors' contribution:**

6 Dr Clément Lejealle and Pierre Emmanuel Rautou take responsibility for the content of the
7 manuscript including the data and analysis.

8 CL collected the data. CL and PER drafted the manuscript. VP and OB reviewed all explants
9 and imaging, respectively. All authors discussed and critically revised the manuscript.

10 We thank Marion Tanguy, Nathalie Colnot and Miguel Albuquerque for superb technical
11 assistance.

12

1 **References**

2

- 3 1. Rodríguez-Roisin R, Krowka MJ, Hervé P, Fallon MB. Pulmonary–Hepatic vascular
4 Disorders (PHD). *Eur Respir J* 2004;24(5):861–880.
- 5 2. Rodríguez-Roisin R, Krowka MJ. Hepatopulmonary Syndrome — A Liver-Induced Lung
6 Vascular Disorder. *N Engl J Med* 2008;358(22):2378–2387.
- 7 3. Machicao VI, Balakrishnan M, Fallon MB. Pulmonary complications in chronic liver
8 disease. *Hepatology* 2014;59(4):1627–1637.
- 9 4. Schenk P, Fuhrmann V, Madl C, et al. Hepatopulmonary syndrome: prevalence and
10 predictive value of various cut offs for arterial oxygenation and their clinical
11 consequences. *Gut* 2002;51(6):853–859.
- 12 5. Swanson KL, Wiesner RH, Krowka MJ. Natural history of hepatopulmonary syndrome:
13 Impact of liver transplantation. *Hepatology* 2005;41(5):1122–1129.
- 14 6. Fallon MB, Krowka MJ, Brown RS, et al. Impact of Hepatopulmonary Syndrome on
15 Quality of Life and Survival in Liver Transplant Candidates. *Gastroenterology*
16 2008;135(4):1168–1175.
- 17 7. Fallon MB, Abrams GA, McGrath JW, Hou Z, Luo B. Common bile duct ligation in the
18 rat: a model of intrapulmonary vasodilatation and hepatopulmonary syndrome. *Am J*
19 *Physiol - Gastrointest Liver Physiol* 1997;272(4):G779–G784.
- 20 8. Koch DG, Fallon MB. Hepatopulmonary syndrome. *Curr Opin Gastroenterol*
21 2014;30(3):260–264.
- 22 9. Raevens S, Geerts A, Paridaens A, et al. Placental growth factor inhibition targets
23 pulmonary angiogenesis and represents a novel therapy for hepatopulmonary
24 syndrome in mice. *Hepatology* 2017;
- 25 10. Rolla G, Brussino L, Colagrande P, et al. Exhaled nitric oxide and oxygenation
26 abnormalities in hepatic cirrhosis. *Hepatology* 1997;26(4):842–847.
- 27 11. Koch DG, Bogatkevich G, Ramshesh V, Lemasters JJ, Uflacker R, Reuben A. Elevated
28 levels of endothelin-1 in hepatic venous blood are associated with intrapulmonary
29 vasodilatation in humans. *Dig Dis Sci* 2012;57(2):516–523.
- 30 12. Raevens S, Coulon S, Van Steenkiste C, et al. Role of angiogenic factors/cell adhesion
31 markers in serum of cirrhotic patients with hepatopulmonary syndrome. *Liver Int Off J*
32 *Int Assoc Study Liver* 2015;35(5):1499–1507.
- 33 13. Arguedas MR, Drake BB, Kapoor A, Fallon MB. Carboxyhemoglobin levels in cirrhotic
34 patients with and without hepatopulmonary syndrome. *Gastroenterology*
35 2005;128(2):328–333.
- 36 14. Krowka MJ, Tajik AJ, Dickson ER, Wiesner RH, Cortese DA. Intrapulmonary vascular
37 dilatations (ipvd) in liver transplant candidates. screening by two-dimensional contrast-
38 enhanced echocardiography. *Chest* 1990;97(5):1165–1170.

- 1 15. Abrams GA, Jaffe CC, Hoffer PB, Binder HJ, Fallon MB. Diagnostic utility of contrast
2 echocardiography and lung perfusion scan in patients with hepatopulmonary syndrome.
3 *Gastroenterology* 1995;109(4):1283–1288.
- 4 16. Kamath PS, Wiesner RH, Malinchoc M, et al. A model to predict survival in patients with
5 end-stage liver disease. *Hepatol Baltim Md* 2001;33(2):464–470.
- 6 17. Caballero T, Pérez-Milena A, Masseroli M, et al. Liver fibrosis assessment with
7 semiquantitative indexes and image analysis quantification in sustained-responder and
8 non-responder interferon-treated patients with chronic hepatitis C. *J Hepatol*
9 2001;34(5):740–747.
- 10 18. Nery F, Chevret S, Condat B, et al. Causes and consequences of portal vein
11 thrombosis in 1,243 patients with cirrhosis: results of a longitudinal study. *Hepatol*
12 *Baltim Md* 2015;61(2):660–667.
- 13 19. Ma C, Crippin JS, Chapman WC, et al. Parenchymal alterations in cirrhotic livers in
14 patients with hepatopulmonary syndrome or portopulmonary hypertension. *Liver*
15 *Transpl* 2013;19(7):741–750.
- 16 20. Talwalkar JA, Swanson KL, Krowka MJ, Andrews JC, Kamath PS. Prevalence of
17 spontaneous portosystemic shunts in patients with portopulmonary hypertension and
18 effect on treatment. *Gastroenterology* 2011;141(5):1673–1679.
- 19 21. Pascasio JM, Grilo I, López-Pardo FJ, et al. Prevalence and Severity of
20 Hepatopulmonary Syndrome and Its Influence on Survival in Cirrhotic Patients
21 Evaluated for Liver Transplantation. *Am J Transplant* 2014;14(6):1391–1399.
- 22 22. Raevens S, Geerts A, Van Steenkiste C, Verhelst X, Van Vlierberghe H, Colle I.
23 Hepatopulmonary syndrome and portopulmonary hypertension: recent knowledge in
24 pathogenesis and overview of clinical assessment. *Liver Int Off J Int Assoc Study Liver*
25 2015;35(6):1646–1660.
- 26 23. Verheij J, Schouten JNL, Komuta M, et al. Histological features in western patients with
27 idiopathic non-cirrhotic portal hypertension. *Histopathology* 2013;62(7):1083–1091.
- 28 24. Marzano C, Cazals-Hatem D, Rautou P-E, Valla D-C. The significance of
29 nonobstructive sinusoidal dilatation of the liver: Impaired portal perfusion or
30 inflammatory reaction syndrome. *Hepatology* 2015;
- 31 25. Thabut D, Shah V. Intrahepatic angiogenesis and sinusoidal remodeling in chronic liver
32 disease: new targets for the treatment of portal hypertension? *J Hepatol*
33 2010;53(5):976–980.
- 34 26. Itai Y, Matsui O. Blood flow and liver imaging. *Radiology* 1997;202(2):306–314.
- 35 27. Sarin SK, Sethi KK, Nanda R. Measurement and correlation of wedged hepatic,
36 intrahepatic, intrasplenic and intravariceal pressures in patients with cirrhosis of liver
37 and non-cirrhotic portal fibrosis. *Gut* 1987;28(3):260–266.
- 38 28. Bissonnette J, Garcia-Pagán JC, Albillos A, et al. Role of the transjugular intrahepatic
39 portosystemic shunt in the management of severe complications of portal hypertension
40 in idiopathic noncirrhotic portal hypertension. *Hepatol Baltim Md* 2016;64(1):224–231.

- 1 29. Seijo S, Reverter E, Miquel R, et al. Role of hepatic vein catheterisation and transient
2 elastography in the diagnosis of idiopathic portal hypertension. *Dig Liver Dis Off J Ital*
3 *Soc Gastroenterol Ital Assoc Study Liver* 2012;44(10):855–860.
- 4 30. Westaby S, Wilkinson SP, Warren R, Williams R. Spleen size and portal hypertension in
5 cirrhosis. *Digestion* 1978;17(1):63–68.
- 6 31. Merkel C, Gatta A, Arnaboldi L, Zuin R. Splenic haemodynamics and portal
7 hypertension in patients with liver cirrhosis and spleen enlargement. *Clin Physiol Oxf*
8 *Engl* 1985;5(6):531–539.
- 9 32. Gusberg RJ, Peterec SM, Sumpio BE, Meier GH. Splenomegaly and variceal bleeding--
10 hemodynamic basis and treatment implications. *Hepatogastroenterology*
11 1994;41(6):573–577.
- 12 33. Tripodi A, Mannucci PM. The Coagulopathy of Chronic Liver Disease. *N Engl J Med*
13 2011;365(2):147–156.
- 14 34. Mortensen C, Karlsen S, Grønbaek H, et al. No difference in portal and hepatic venous
15 bacterial DNA in patients with cirrhosis undergoing transjugular intrahepatic
16 portosystemic shunt insertion. *Liver Int Off J Int Assoc Study Liver* 2013;33(9):1309–
17 1315.
- 18 35. Tsauo J, Weng N, Ma H, Jiang M, Zhao H, Li X. Role of Transjugular Intrahepatic
19 Portosystemic Shunts in the Management of Hepatopulmonary Syndrome: A Systemic
20 Literature Review. *J Vasc Interv Radiol JVIR* 2015;
- 21 36. Corpechot C, Barbu V, Wendum D, et al. Hypoxia-induced VEGF and collagen I
22 expressions are associated with angiogenesis and fibrogenesis in experimental
23 cirrhosis. *Hepatology* 2002;35(5):1010–1021.
- 24 37. Zhang J, Luo B, Tang L, et al. Pulmonary angiogenesis in a rat model of
25 hepatopulmonary syndrome. *Gastroenterology* 2009;136(3):1070–1080.
- 26 38. Krowka MJ. Hepatopulmonary syndrome and extrahepatic vascular abnormalities. *Liver*
27 *Transplant Off Publ Am Assoc Study Liver Dis Int Liver Transplant Soc* 2001;7(7):656–
28 657.
- 29 39. Gupta D, Vijaya DR, Gupta R, et al. Prevalence of hepatopulmonary syndrome in
30 cirrhosis and extrahepatic portal venous obstruction. *Am J Gastroenterol*
31 2001;96(12):3395–3399.
- 32 40. De BK, Sen S, Biswas† PK, et al. Occurrence of hepatopulmonary syndrome in Budd–
33 Chiari syndrome and the role of venous decompression. *Gastroenterology*
34 2002;122(4):897–903.
- 35 41. Fuhrmann V, Madl C, Mueller C, et al. Hepatopulmonary Syndrome in Patients With
36 Hypoxic Hepatitis. *Gastroenterology* 2006;131(1):69–75.

37

38

1 **TABLE 1 Patients' clinical, laboratory and hemodynamics features at**
 2 **evaluation for transplantation**
 3

Variable	Complete image analysis				Explant Pathology			
	n*	Control patients (n=63)	HPS patients (n=21)	p	n*	Control patients (n=57)	HPS patients (n=19)	p
Age (years)	84	56 (50-61)	53 (49-59)	0.20	76	53 (49-59)	51 (49-54)	0.25
Female gender	84	17 (27)	9 (43)	0.17	76	13 (23)	10 (53)	0.01
Arterial blood gas								
Upright PaO ₂ (mm Hg)	70	105 (98-118)	60 (49-67)	<0.01	65	106 (98-118)	52 (46-60)	<0.01
Upright A-a PO ₂ (mm Hg)	70	3 (0-12)	62 (50-66)	<0.01	65	2 (0-12)	66 (59-74)	<0.01
Upright SaO ₂ (%)	70	99 (98-99)	91 (88-95)	<0.01	73	99 (98-99)	88 (85-95)	<0.01
Hemodynamic data								
MAP (mm Hg)	70	89 (82-96)	84 (76-92)	0.046	62	90 (85-97)	83 (72-92)	0.046
HVPG (mm Hg)	67	16 (12-22)	17 (12-19)	0.77	57	16 (13-22)	13 (10.5-17.7)	0.18
RAP (mm Hg)	50	5 (3-10)	6 (3-8)	0.75	38	8 (3-10)	8 (5-9)	0.96
MPAP (mm Hg)	61	17 (13-23)	15 (12-20)	0.44	53	17 (14-23)	16 (13-19)	0.41
PWP (mm Hg)	61	10 (7-14)	10 (8-13)	0.84	53	10 (8-15)	10 (9-15)	0.97
CI (L/min/m ²)	61	3.5 (2.8-4.6)	4.2 (3-4.8)	0.29	50	3.8 (3.2-4.8)	3.8 (2.9-4.7)	0.75
SVR (dyn·s·cm ⁻⁵)	60	1060 (700-1300)	840 (630-1220)	0.21	50	910 (700-1170)	880 (630-1320)	0.65
PVR (dyn·s·cm ⁻⁵)	59	85 (54-144)	73 (47-122)	0.47	49	84.2 (51-146)	77.2 (47-115)	0.79
Causes of cirrhosis**								
Alcohol abuse	84	43 (68)	15 (71)	0.78	76	32 (56)	11 (58)	0.89
Hepatitis B or C virus	84	15 (24)	5 (24)	1.00	76	19 (33)	6 (32)	0.89
Cryptogenic	84	6 (10)	2 (10)	1.00	76	6 (10)	2 (10)	1.00
NASH	84	12 (19)	4 (19)	1.00	76	10 (18)	2 (10)	0.71
Severity of cirrhosis								
Child-Pugh A	84	12 (19)	3 (14)	0.75	76	12 (21)	3 (16)	1.00
Child-Pugh B	84	28 (44)	10 (48)	0.80	76	23 (40)	9 (47)	0.59
Child -Pugh C	84	23 (37)	8 (38)	0.90	76	22 (39)	7 (37)	0.89
MELD score (unadjusted)	84	13 (10-16)	13 (10-16)	0.89	76	13 (10-17)	14 (10-16)	0.88
Complications of cirrhosis								
Ascites	84	46 (73)	16 (76)	0.77	76	38 (67)	12 (63)	0.79
Refractory ascites	84	28 (44)	5 (24)	0.09	76	20 (35)	4 (21)	0.25
History of SBP	84	16 (25)	5 (24)	0.88	76	13 (23)	3 (16)	0.75
History of encephalopathy	84	28 (44)	12 (57)	0.31	76	22 (39)	9 (47)	0.50
Chronic encephalopathy	84	6 (10)	1 (5)	0.67	76	4 (7)	0 (0)	0.57
Large esophageal varices	83	38 (61)	18 (86)	0.04	76	37 (65)	16 (84)	0.11
History of variceal bleeding	84	18 (29)	10 (48)	0.11	76	19 (33)	9 (47)	0.27
HCC	84	28 (44)	5 (24)	0.09	76	27 (47)	3 (16)	0.02
HCC treatment	84	20 (32)	2 (10)	0.04	76	22 (39)	1 (5)	< 0.01
TIPS	82	3 (5)	0 (0)	1.00	74	3 (5)	0 (0)	1.00
Hepatorenal syndrome	84	6 (10)	0 (0)	0.32	76	3 (5)	0 (0)	0.57
Hydrothorax	84	6 (10)	2 (10)	1.00	76	6 (10)	1 (5)	0.67
Comorbidities								
BMI (kg/m ²)	75	26 (23-29)	24 (22-29)	0.7	75	26 (23-29)	25 (22-28)	0.26
Smoking	82	35 (56)	11 (58)	0.86	74	34 (60)	10 (56)	0.95
COPD	83	4 (6)	3 (15)	0.35	75	4 (7)	3 (16)	0.35

Diabetes	83	16 (25)	5 (25)	0.97	75	14 (25)	3 (17)	0.75
Arterial hypertension	83	24 (38)	6 (30)	0.51	75	18 (32)	4 (22)	0.45
Coronary artery disease	82	6 (10)	2 (10)	1.00	74	7 (12)	0 (0)	0.19
History of VTE	83	2 (3)	2 (10)	0.24	75	2 (4)	2 (11)	0.24
Laboratory data								
Serum bilirubin ($\mu\text{mol/L}$)	84	32 (16-46)	38 (22-58)	0.09	76	36 (17-51)	38 (23-57)	0.24
Serum creatinine ($\mu\text{mol/L}$)	84	71 (63-91)	65 (55-75)	0.06	76	71 (62-90)	60 (54-73)	<0.01
Serum albumin (g/L)	79	30 (25-35)	28 (23-35)	0.86	72	30 (25-33)	31 (25-37)	0.40
INR	84	1.4 (1.2-1.6)	1.4 (1.2-1.5)	0.73	76	1.4 (1.2-1.7)	1.4 (1.2-1.6)	0.88
Platelet count ($10^9/\text{L}$)	83	89 (68-127)	89 (59-120)	0.68	75	81 (66-116)	89 (58-124)	0.77
Alphafetoprotein ($\mu\text{g/L}$)	76	5 (3-13)	3 (2-5)	0.15	69	5 (3-15)	3 (2-6)	0.15
Treatment								
Diuretics	84	34 (54)	11 (52)	0.90	76	31 (54)	9 (47)	0.60
Prophylactic antibiotics	84	13 (21)	3 (14)	0.75	76	11 (19)	3 (16)	1.00
Beta blockers	84	37 (59)	16 (76)	0.15	76	34 (60)	14 (74)	0.27
Anticoagulation	84	14 (22)	8 (38)	0.15	76	12 (21)	7 (37)	0.22
Interval between evaluation before LT and LT	82	7.5 (5-11)	4.4 (2-8)	0.03	75	7.5 (5-11)	4.3 (2-8)	0.01

1 * Number of patients with available data, ** Some patients had several causes of cirrhosis
2 Variables are expressed as median (interquartile range) or n (%)
3 Abbreviations: A-a PO_2 , alveolar–arterial gradient BMI, body mass index; CI, cardiac index; COPD, chronic
4 obstructive pulmonary disease; HCC, hepatocellular carcinoma; HPS, hepatopulmonary syndrome; HVP, hepatic
5 venous pressure gradient; EV, esophageal variceal; EVL, endoscopic variceal ligation; INR, international
6 normalized ratio; LT, liver transplant; MAP, mean arterial pressure; MPAP, mean pulmonary artery pressure;
7 PaO_2 , arterial partial pressure of oxygen; PVR, pulmonary vascular resistance; PWP, pulmonary wedge pressure;
8 RAP, right atrial pressure; SaO_2 , arterial oxygen saturation; SBP, spontaneous bacterial peritonitis; SVR,
9 systemic vascular resistance; TIPS, transjugular intrahepatic portosystemic shunt; VTE, venous
10 thromboembolism;
11

TABLE 2 Abdominal and thoracic imaging in patients with HPS and in control patients

Variable	Number of patients with available data	Control patients (n=63)	HPS patients (n=21)	<i>p</i>
Liver morphology				
Liver morphologic changes	84	62 (99)	21 (100)	1.00
Irregular liver surface	84	57 (90)	17 (81)	0.26
Large parenchymal extinction	84	16 (25)	6 (29)	0.77
Arterial vascularization				
Hepatic artery diameter (mm)	83	5.6 (5.0-6.7)	7.0 (6.0-7.5)	0.001
Heterogeneous liver perfusion pattern	83	2 (3)	1 (5)	1.00
Arteriportal or arteriovenous shunts	83	3 (5)	1 (5)	1.00
Portal venous system				
Main portal vein thrombosis	84	15 (24)	7 (33)	0.39
Portal vein diameter (mm)	83	15 (12-17)	15 (10-18)	1.00
Portal branch thrombosis	84	10 (16)	3 (14)	1.00
Obstructed intrahepatic portal branches	82	15 (24)	12 (60)	0.03
Splenic and/or mesenteric venous thrombosis	84	6 (10)	11 (17)	0.35
Portal cavernoma	84	6 (10)	1 (5)	0.67
Slowed or hepatofugal portal blood flow	65	14 (27)	8 (57)	0.05
Hepatic venous system				
Hepatic vein thrombosis	84	1 (1.5)	0 (0)	1.00
Obstructed hepatic vein	84	22 (35)	6 (29)	0.59
Hepatic venous collaterals	84	0 (0)	0 (0)	1.00
Portovenous shunts	83	1 (1.5)	1 (5)	0.44
Abdominal portosystemic shunts				
Paraumbilical vein diameter (mm)	82	2 (0-5)	4.5 (2-6.5)	0.01
Portosystemic shunts >10 mm	82	16 (25)	13 (65)	0.01
Spleen				
Height (mm)	84	144 (130-170)	137 (124-171)	0.44
Width (mm)	84	61 (52-70)	60 (52-71)	0.72
Right colon wall thickness				
Wall thickness (mm)	84	2 (2-2)	2 (2-12)	0.08
Intrathoracic changes				
Pulmonary artery diameter (mm)	83	28 (27-31)	28 (27-30)	0.79
Azygos vein diameter (mm)	83	10 (9-11)	10 (9-11)	0.88
Intrathoracic portosystemic shunts	84	14 (22)	7 (33)	0.30
Hydrothorax	84	10 (16)	6 (29)	0.21

Variables are expressed as median (interquartile range) or n (%).

Abbreviations: HPS, hepatopulmonary syndrome

TABLE 3 Histological liver vascular changes in patients with HPS and in control patients

Variable	Number of patients with available data	Control patients (n=57)	HPS patients (n=19)	<i>p</i>
Hepatic artery thrombosis	76	2 (3)	1 (5)	1.00
Hepatic artery wall thickening	76	5 (9)	1 (5)	1.00
Main portal vein thrombosis				
Absence	76	40 (70)	11 (58)	
Partial	76	15 (27)	8 (42)	0.34
Complete	76	2 (3)	0 (0)	
Main portal vein wall thickening	76	8 (14)	4 (21)	0.48
Hepatic vein thrombosis	76	2 (3)	0 (0)	1.00
Hepatic vein wall thickening	76	1 (2)	0 (0)	1.00
Intrahepatic portal venule thrombosis				
Absence	76	50 (88)	10 (53)	
Mild	76	6 (10)	8 (42)	0.005
Severe or diffuse	76	1 (2)	1 (5)	
Intrahepatic portal venule wall thickening				
Absence	76	21 (37)	5 (26)	
Mild	76	29 (51)	7 (37)	0.06
Severe or diffuse	76	7 (12)	7 (37)	
Centrilobular venule thrombosis				
Absence	76	42 (74)	11 (58)	
Mild	76	13 (23)	3 (16)	0.01
Severe or diffuse	76	2 (3)	5 (26)	
Centrilobular venule wall thickening				
Absence	76	34 (60)	7 (37)	
Mild	76	17 (30)	5 (26)	0.03
Severe or diffuse	76	6 (10)	7 (37)	
Sinusoidal dilatation				
Absence	76	32 (56)	5 (26)	0.02
Present	76	25 (44)	14 (74)	
Vascular proliferation within fibrous septa				
Absence	76	16 (28)	1 (6)	
Mild	76	38 (67)	9 (47)	<0.001
Extensive	76	3 (5)	9 (47)	

Variables are expressed as median (interquartile range) or n (%).
Abbreviations: HPS, hepatopulmonary syndrome

1
2 **TABLE 4 Other liver histological features in patients with HPS and in control**
3 **patients**
4

Variable	Number of patients with available data	Control patients (n=57)	HPS patients (n=19)	<i>p</i>
Liver weight (gram)	74	1227 (1025 - 1605)	1117 (915-1462)	0.35
Liver aspect				
Macronodular	73	13 (24)	2 (12)	0.49
Micronodular	73	30 (54)	12 (76)	0.21
Mixed	73	12 (22)	2 (12)	0.50
Activity score				
A0, no activity	71	12 (22)	6 (35)	0.37
A1, mild activity	71	34 (63)	10 (59)	
A2, moderate activity	71	6 (11)	1 (6)	
A3, severe activity	71	2 (4)	0 (0)	
Fibrosis score				
F2, portal fibrosis with few septa	76	1 (2)	1 (5)	0.66
F3, numerous septa without cirrhosis	76	2 (4)	1 (5)	
F4, cirrhosis	76	54 (94)	17 (90)	
Laennec score				
4a mild	71	24 (44)	5 (29)	0.51
4b moderate	71	23 (43)	8 (47)	
4c severe	71	7 (13)	4 (24)	
Perisinusoidal fibrosis				
Absence	76	15 (26)	5 (26)	0.95
Mild	76	29 (51)	9 (48)	
Severe or diffuse	76	13 (23)	5 (26)	
Morphometric analysis				
Fibrosis (%)	76	30 (23-36)	35 (24-45)	0.38
Incomplete septal cirrhosis	76	1 (2)	3 (16)	0.046
Parenchymal extinction areas	76	16 (28)	10 (53)	0.05
Steatosis				
< 5 %	76	36 (63)	14 (74)	0.36
5-33 %	76	18 (31)	3 (16)	
34-66 %	76	2 (4)	2 (10)	
> 67 %	76	1 (2)	0 (0)	
Hepatocytes ballooning				
Absence	76	26 (45)	14 (74)	0.09
Mild (size > N, < 2N)	76	20 (35)	4 (21)	
Severe (size >2N)	76	11 (20)	1 (5)	
Lobular inflammation				
Absence	76	40 (70)	14 (74)	0.71
Mild (≤ 2 foci / 20 x field)	76	15 (26)	5 (26)	
Severe (> 2 foci/20 x field)	76	2 (4)	0 (0)	
Ductular proliferation				

Absence	76	27 (47)	10 (53)	
Mild	76	22 (39)	7 (37)	0.89
Severe or diffuse	76	8 (14)	2 (10)	
Bile deposition	76	13 (23)	1 (5)	0.17
Iron deposition	76	17 (30)	4 (21)	0.46

1
2
3
4

Variables are expressed as median (interquartile range) or n (%).
Abbreviations: HPS, hepatopulmonary syndrome

1 **Figure legends**

2

3 **FIGURE 1 Imaging features associated with hepatopulmonary syndrome (HPS).**

4 Axial abdominal contrast-enhanced multidetector computed tomography during portal phase (A, B, C,
5 D, G, H) and arterial phase (E, F) in patients with cirrhosis without (A, C, E, G) and with (B, D, F, H)
6 HPS.

7 (A) Visible portal branches (arrowheads); (B) Invisible portal branches (arrows); (C) Thin splenorenal
8 shunts (arrow); (D) Large splenorenal shunts (arrow); (E) Thin paraumbilical vein (arrowhead); (F)
9 Large paraumbilical vein (arrow); (G) "Normal" hepatic artery (arrowhead); (H) Enlarged hepatic artery
10 (arrow).

11

12 **FIGURE 2 Intrahepatic vascular changes associated with hepatopulmonary syndrome (HPS).**

13 Haematoxylin and eosin staining of liver explants from patients with cirrhosis without (A, C, E, G) and
14 with (B, D, F, H) HPS.

15 (A) Patent intrahepatic portal venule (arrowhead) (Magnification x140); (B) Intrahepatic portal venules
16 thrombosis (arrows) (Magnification x280); (C) Fibrous septa without vascular proliferation
17 (arrowheads) (Magnification x80); (D) Vascular proliferation (increased number of venous channels)
18 within fibrous septa (arrow) (Magnification x80); (E) "Normal" centrilobular venule (arrowheads)
19 (Magnification x140); (F) Wall thickening of centrilobular venule (arrows) (Magnification x140); (G)
20 Permeable intrahepatic hepatic venule (arrowheads) (Magnification x280); (H) Intrahepatic hepatic
21 venule thrombosis (arrows) (Magnification x140).

22

23 **FIGURE 3 Architectural and lobular changes associated with hepatopulmonary syndrome**

24 **(HPS).** Haematoxylin and eosin (A, B, E, F) and Picrosirius (C, D) staining of liver explants from
25 patients with cirrhosis without (A, C, E) and with (B, D, F) HPS.

26 (A) No dilated liver sinusoids (arrowheads) (Magnification x190); (B) Centrilobular sinusoidal dilatation
27 (arrows) (Magnification x190); (C) "Usual" fibrous septa (arrows) surrounding hepatocytes nodules
28 (arrowheads) (Magnification x28); (D) Large area of confluent fibrosis (arrows) with small nodules of
29 hepatocytes (arrowheads) (Magnification x28); (E) "Usual" complete septa delimiting hepatocytes
30 nodules (arrowheads) (Magnification x56); (F) Thin and incomplete septa (arrows) delimiting
31 hepatocytes nodules (Magnification x56).

32

Figure 1

Control patients

HPS patients

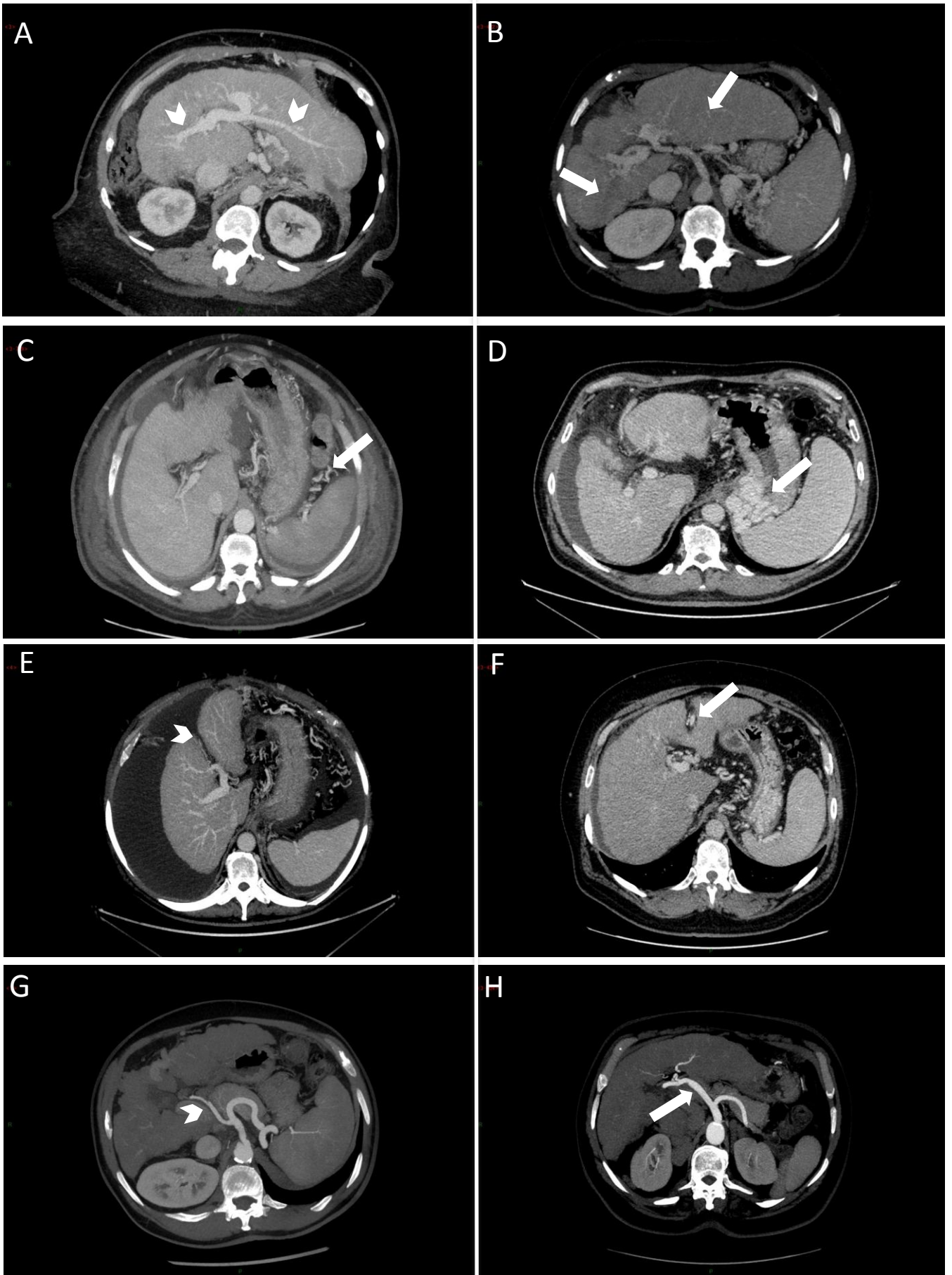


Figure 2

Control patients

HPS patients

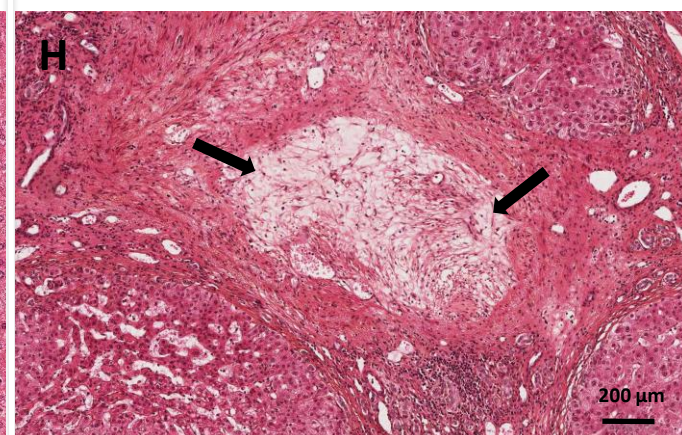
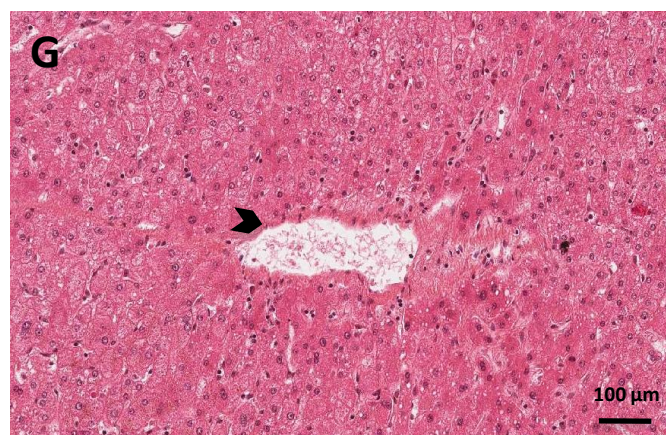
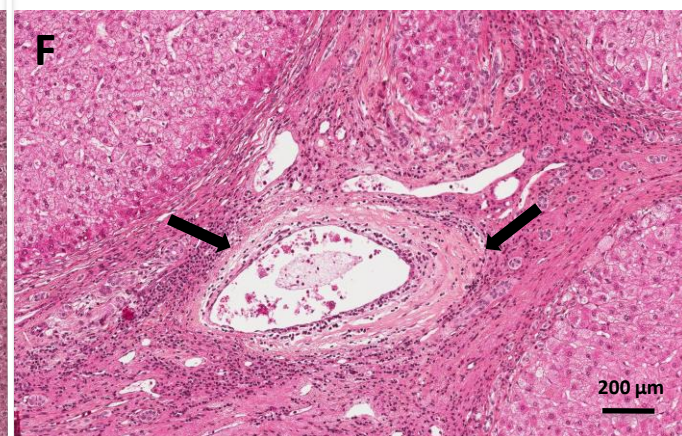
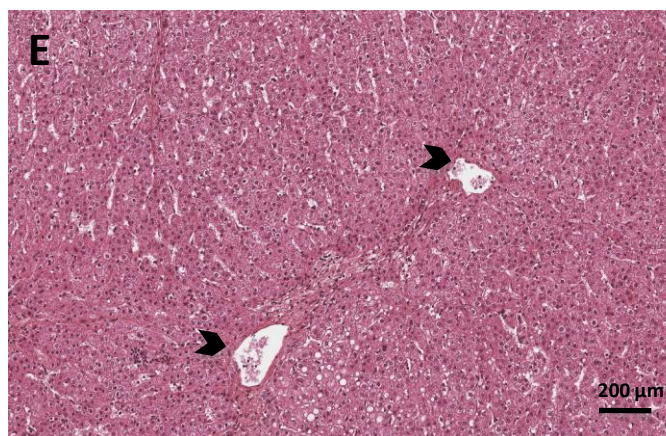
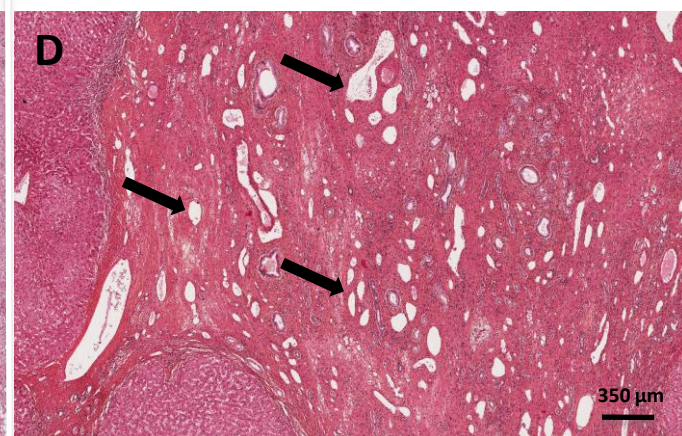
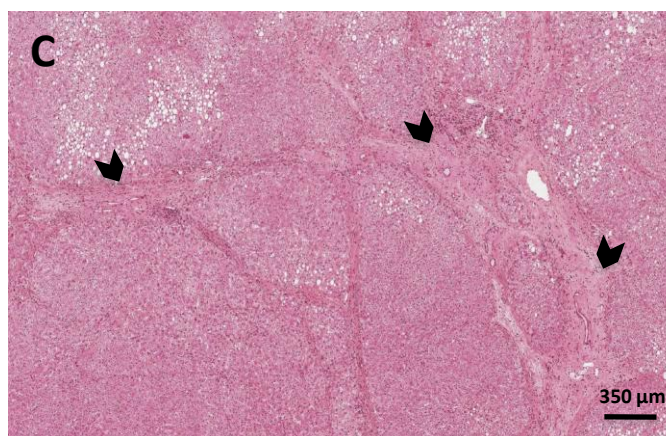
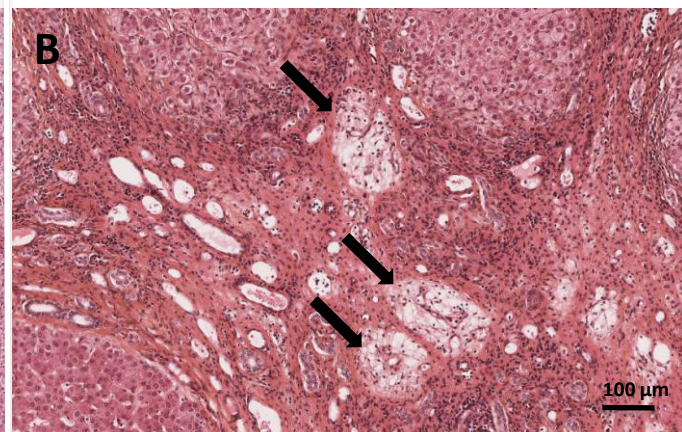
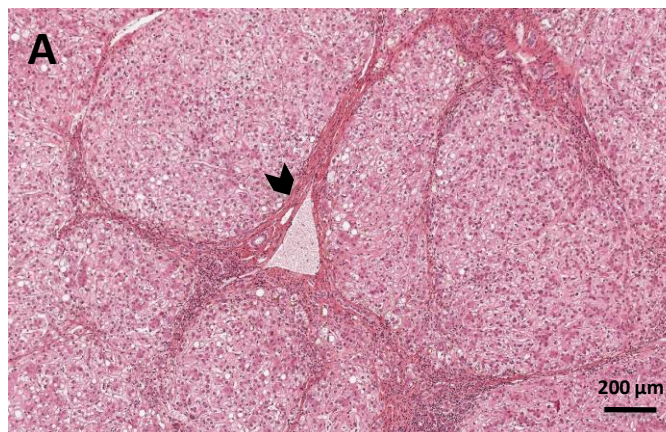


Figure 3

Control patients

HPS patients

