**Turk J Gastroenterol** *2014; 25: 724-9*

# Report of seven children with hepatopulmonary syndrome

*Duygu Erge[1], Mukadder Ayşe Selimoğlu[2], Cemşit Karakurt[3], Hamza Karabiber[2], Özlem Elkıran[3], Ferat Çatal[1], Reyhan Koroğlu[4]*

[1]Division of Allergy, Department of Pediatrics, İnönü University Faculty of Medicine, Malatya, Turkey
[2]Division of Gastroenterology, Hepatology and Nutrition, Department of Pediatrics, İnönü University Faculty of Medicine, Malatya, Turkey
[3]Division of Cardiology, Department of Pediatrics, İnönü University Faculty of Medicine, Malatya, Turkey
[4]Department of Nuclear Medicine, İnönü University Faculty of Medicine, Malatya, Turkey

## ABSTRACT

Hepatopulmonary syndrome is an important pulmonary vascular complication of liver disease. Its diagnosis is based on the presence of hypoxaemia and the demonstration of intrapulmonary shunting by contrast-enhanced echocardiography or perfusion lung scanning. Awareness of this condition is critical to improve the outcomes of patients with chronic liver disease and/or portal hypertension because hepatopulmonary syndrome receives additional priority on the waiting list for transplantation. A non-invasive measurement of the blood oxygen saturation with pulse oximetry is recommended as a screening tool for this syndrome. The aim of this report was to present clinical and laboratory findings and follow-up of seven paediatric patients who were diagnosed with HPS at our centre.

**Keywords:** Hepatopulmonary syndrome, children, liver diseases

Case Report

## INTRODUCTION

Hepatopulmonary syndrome (HPS) is characterised by the triad of advanced chronic liver disease (CLD), arterial hypoxaemia and intrapulmonary arteriovenous shunting in the absence of a primary cardiopulmonary disease (1). The pathogenesis of this syndrome has been suggested to be an imbalance between the production and clearance of vasoactive circulating substances and the resultant microvascular dilatation within the pulmonary arterial circulation. Microvascular dilatation may lead to impaired ventilation-perfusion matching and an anatomical and functional shunt physiology, which causes arterial hypoxaemia (2). It has been reported that 13%-47% of patients with end-stage liver disease have intrapulmonary vascular abnormalities (3,4). Intrapulmonary vascular dilatations can be observed using contrast-enhanced echocardiography (CEE) or by performing a perfusion lung scan using technetium-99 m macroaggregated albumin (99 mTc-MAA) (5). The clinical course of the disease is characterised by dyspnoea and slowly progressive chronic hypoxaemia and depends on the progressive impairment of pulmonary circulation. It has been reported that about 50% of patients die within 41 months after the diagnosis of HPS (6). To date, the only proven therapy for patients with HPS has been liver transplantation (LT) (7).

Herein, we have presented clinical and laboratory findings and the follow-up details of seven paediatric patients diagnosed with HPS at our centre.

## MATERIALS AND METHODS

Paediatric patients diagnosed with HPS at Turgut Ozal Medical Centre of Inonu University have been presented in this paper. In the absence of a primary cardiopulmonary disease, the presence of advanced CLD, any evidence of hypoxaemia [in room-air pulse oximetry <93% (6) or arterial oxygen tension ($PaO_2$) of <70 mmHg on arterial blood gas (8)] and any intrapulmonary shunting observed on CEE or 99 mTc-MAA have been the diagnostic criteria for HPS (1,9). CEE was performed with the rapid injection of 10 mL of agitated normal saline solu-

**Address for Correspondence:** Duygu Erge, Division of Allergy, Department of Pediatrics, İnönü University Faculty of Medicine, Malatya, Turkey
E-mail: duyguolmez@hotmail.com
**Received:** 25 May, 2013 **Accepted:** 13 February, 2014
 • Available online at www.turkjgastroenterol.org • DOI: 10.5152/tjg.2014.5577

tion using a three-way venous cannula after the confirmation of normal cardiac anatomy with 2D and colour-coded transthoracic echocardiography (Vivid Pro 7; GE Healthcare, California, USA). The times at which contrast appeared in the right and left ventricles and the number of cardiac cycles between these times were recorded. An abnormal CEE scan was defined as the appearance of contrast in the left ventricle more than three cardiac cycles after its appearance in the right ventricle (10,11). A 99 mTc-MAA perfusion scan was performed with the injection of 0.05 mCi/kg 99 mTc-MAA (Pulmocis; CIS Bio International, Cedex, France) into a peripheral venous cannula while the child was in the upright or standing position. After 20 min, quantitative whole-body imaging was performed with a dual-head γ camera (Vertex V60; ADAC Laboratories, California, USA). The quantitative evaluation of the relative uptake was determined using regions of interest drawn over the brain, kidney, soft tissues and lungs. The shunt index (expressed as a ratio of the uptake in the lungs to the uptake in the total body minus kidney activity) was measured (11). A positive scan was defined as a shunt fraction greater than 4% (12). We used blood oxygen saturation ($SpO_2$) for the PaO2/ alveolar-arterial gradient as in other studies because an arterial blood gas analysis was not performed in all of our patients (9,13).

For the determination of liver disease severity, we used the Child–Pugh (CHILD), Paediatric End-Stage Liver Disease (PELD) and Model of End-Stage Liver Disease (MELD) scores (14).

## CASE PRESENTATIONS

### Case 1

A 16-year-old girl was referred to our hospital for central cyanosis, clubbing and growth retardation. Her evaluation revealed hypoxemia ($PaO_2$ = 61.6 mmHg). Cardiac evaluation with an echocardiogram and angiography showed mild aortic stenosis and aortic insufficiency. Chest radiography and computerized tomography (CT) of the thorax were normal. A pulmonary function test revealed that the percentages of vital capacity (VC%) and the forced expiratory volume in 1 s (FEV1%) were 73% and 59%, respectively. Because upper gastrointestinal bleeding developed during these evaluations, we performed an oesophagogastroduodenoscopy and discovered oesophageal varices. Detailed investigations including liver biopsy confirmed the diagnosis of chronic hepatitis (cryptogenic). The CHILD score was 5(A), and the MELD score was 12; the patient was diagnosed with HPS using CEE. Two years after admission, the intrapulmonary shunt ratio was 27%. Her $SpO_2$ was 82% in room air. The patient was placed on the national waiting list for LT.

### Case 2

The patient was a 15-year-old girl who had consulted with the paediatrics department before a tonsillectomy operation because of hepatosplenomegaly, central cyanosis, clubbing and dyspnoea. The patient had a history of abdominal distension and pain since one year of age. Seven years before admission, she was evaluated for liver disease at another centre, and a diagnosis of cirrhosis was confirmed using liver biopsy. The CHILD and MELD scores were 6(A) and 10, respectively. Oesophagogastroduodenoscopy revealed oesophageal varices. Her $SpO_2$ was 79% in room air. Chest radiography and CT of the thorax were normal. CEE revealed intracardiac shunting; the intrapulmonary shunt ratio was 19%. The patient underwent living donor liver transplantation (LDLT), receiving a graft from a maternal aunt. After LT, she required ventilatory support for 3 days. Decreased $SpO_2$ levels in the upright position, consistent with orthodeoxia, improved in the recumbent position. She received inhaled prostacyclin (Ilomedin; Schering AG, Berlin, Germany) therapy for 1 month because of the persistent low $SpO_2$ levels. The $SpO_2$ increased to 94% in room air 6 months after the operation.

### Case 3

The patient was a 13-year-old boy who had been treated in an intensive care unit of a hospital for encephalopathy two years prior to admission at our center. Because his assessments revealed hepatic failure as the cause of the encephalopathy, detailed investigations were performed; however, the aetiology of the hepatic failure could not be explained. A liver biopsy could not be performed because of severe coagulopathy. An LT was recommended for cryptogenic cirrhosis, but a living donor could not be found. When he was referred to our hospital, the CHILD and MELD scores were 7(B) and 14, respectively. The physical examination revealed splenomegaly, central cyanosis and clubbing. The $SpO_2$ was 86% in room air. Oesophagogastroduodenoscopy revealed grade 1 oesophageal varices. The echocardiogram revealed mild mitral and tricuspid insufficiency and a pulmonary arteriovenous fistula. However, the pulmonary arteriovenous fistula was not found on cardiac angiography. His VC% and FEV1% were 90% and 79%, respectively. Chest CT was normal, and the intrapulmonary shunt ratio was 21%. The patient was listed for LT and is still waiting.

### Case 4

A 2-month-old boy was diagnosed with biliary cirrhosis (cryptogenic) when he was evaluated for neonatal jaundice. His medical history revealed that two of his uncles had died from liver cirrhosis. He was admitted to our hospital for LT when he was 3 years old. The CHILD and PELD scores were 7(B) and 5, respectively. Grade 1 oesophageal varices were found on endoscopy. The $SpO_2$ was 94% in room air. The echocardiogram was consistent with mild mitral insufficiency. One year after admission, the CHILD and PELD scores had increased to 10(C) and 6. When he was 4 years old, he was admitted with central cyanosis and dyspnoea. Physical examination revealed clubbing, central cyanosis and hepatosplenomegaly. His respiratory findings were normal except for the cyanosis. He was treated for pneumonia initially, but the $SpO_2$ was still below 90% in room air in spite of antibiotic treatments. Thus, a CT of thorax was performed and was found to be normal. He was then evaluated for HPS; intracardiac shunting was observed on CEE. On

the 99 mTc-MAA perfusion scan, the intrapulmonary shunt ratio was 16%. The patient was discharged with at-home oxygen therapy as the $SpO_2$ was 84% in room air. He was also placed on the national waiting list for LT.

### Case 5

The patient was a 16-year-old girl admitted to our hospital for progressive dyspnoea, which she had first noticed 6 years earlier. During the examination, we detected central cyanosis and clubbing. The $SpO_2$ was 86% in room air. Her chest X-ray and chest CT scan revealed no abnormal findings. She could not perform the pulmonary function test. CEE showed intracardiac shunting. On the 99 mTc-MAA perfusion scan, the intrapulmonary shunt ratio was 32% (Figure 1). The liver biopsy was compatible with fibrosis, and grade 1 oesophageal varices and portal hypertensive gastropathy were found on endoscopy. The CHILD and MELD scores were 5(A) and 10, respectively; however, the aetiology of the liver fibrosis could not be clarified despite detailed studies. Increasing hypoxia restricted the patient's daily activity and necessitated at-home oxygen therapy. She is waiting for LT.

### Case 6

A 9-year-old girl who was diagnosed with cryptogenic cirrhosis at 6 years of age was admitted to our hospital. The CHILD and PELD scores were 6(A) and 3, respectively. Hepatosplenomegaly and oesophageal varices were detected at ages four and eight, respectively. During the follow-up, the child exhibited central cyanosis and clubbing. The $SpO_2$ was 89% in room air. Chest radiography was normal, and her VC% and FEV1% were 70% and 83%, respectively. CEE showed intracardiac shunting, but a 99 mTc-MAA perfusion scan could not be performed. She received a cadaveric transplant at the age of 10. The patient was extubated in the intensive care unit, but she developed a massive pleural effusion, atelectasis and persistent hypoxaemia despite the placement of a tube into the pleural space for drainage and mechanical ventilation on the second post-transplantation day. She died five days after LT because of severe hypoxaemia and multi-organ failure.

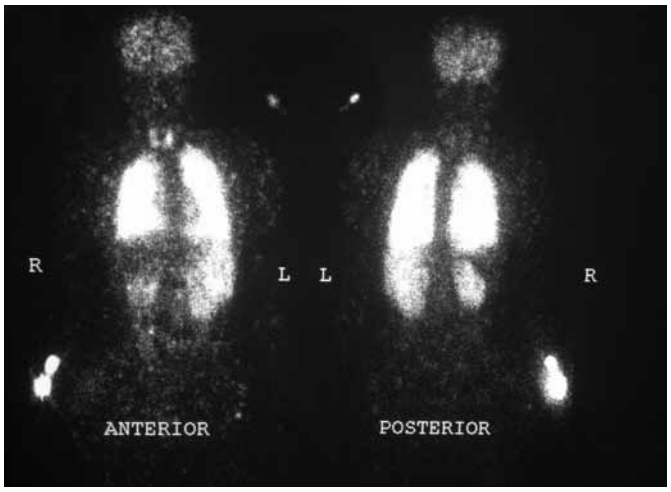


**Figure 1.** A high shunt index of 32% in Tc-99 m MAA perfusion lung scan of Case 5. In posterior positions, extrapulmonary activity is seen in kidneys, brain and spleen

### Case 7

A 6-month-old girl diagnosed with neonatal cholestasis during the newborn period was admitted to our hospital. Her physical examination revealed jaundice and hepatosplenomegaly. As the family did not give permission for the procedure, a liver biopsy could not be performed on admission. However, when she was 10 months old, we performed a biopsy that was consistent with biliary cirrhosis. The CHILD and PELD scores were 8(B) and 15, respectively. Although central cyanosis was not detected, and the $SpO_2$ was normal in room air, CEE showed intracardiac shunting. A 99 mTc-MAA perfusion scan and endoscopy were planned. The child is being prepared for the LT.

Some clinical and laboratory features of the cases presented above are shown in Table 1.

Written informed consent was obtained from patients and their parents who participated in this case.

## DISCUSSION

Hepatopulmonary syndrome is a disease of gas exchange secondary to intrapulmonary shunting associated with CLD (15). Although hypoxaemia is commonly reported in patients with liver cirrhosis, only a small number of patients exhibit respiratory symptoms (16). Thus, routine measurement of $SpO_2$ with pulse oximetry is recommended in patients with CLD (9). In our series, all of the patients except Case 7 had $SpO_2$s of 93% or less which is below the cut-off value (6,13) for the diagnosis of hypoxaemia. We did not draw blood for the arterial blood gas analysis as has been reported in other studies because of the invasive nature of this test (13,17). Abrams et al. (13) reported that an $SpO_2$ of 94% or less was detected in all subjects with an arterial $PaO_2$ of <60 mmHg.

In most patients with HPS, severe liver dysfunction and PHT is evident. The respiratory problems can occasionally be more relevant than the liver failure manifestations (18). Krowka et al. (19) reported that 82% of the patients with HPS showed the symptoms and findings of CLD. In the remaining 18%, dyspnoea was the primary symptom. Among our patients, Cases 1 and 5 had dyspnoea as a preceding symptom before the appearance of the liver disease findings. Besides the dyspnoea, we also found clubbing in all of our patients except Case 7, who was the youngest one. Clubbing may be a sign of CLD resulting from hyperdynamic circulation and arteriole–capillary dilatation, which is observed in all CLD patients with HPS (20).

The prevalence of HPS was 9%-20% in children with biliary atresia and 0.5% in children with portal vein thrombosis (21,22). HPS can also be seen in children with CLD, PHT and congenital anomalies of the portal vein (23,24). Noli et al. (11) detected HPS in 8% of 301 children with cirrhosis or severe PHT. We de-

Case Report

**Table 1.** Some clinical and laboratory features of the patients with HPS

| | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|---|
| Age/gender | 16/F | 15/F | 13/M | 4/M | 16/F | 10/F | 10 mo./F |
| Time for HPS diagnosis (yr) | 2 | 7 | 2 | 4 | 6 | 3 | 4 mo. |
| Cyanosis | + | + | + | + | + | + | – |
| Clubbing | + | + | + | + | + | + | – |
| Growth retardation | + | – | – | – | – | + | + |
| PHT/variceal bleeding | +/+ | +/– | +/– | +/– | +/– | +/– | NP |
| Liver biopsy | Chronic hepatitis | Cryptogenic cirrhosis | Cryptogenic cirrhosis | Cryptogenic biliary cirrhosis | Fibrosis | Cryptogenic cirrhosis | Biliary cirrhosis |
| CHILD score | 5(A) | 6(A) | 7(B) | 10(C) | 5(A) | 6(A) | 8(B) |
| PELD score | | | | 6 | | 3 | 15 |
| MELD score | 12 | 10 | 14 | | 10 | | |
| VC% | 73 | NP | 90 | NP | NP | 70 | NP |
| $FEV_1$% | 59 | NP | 79 | NP | NP | 83 | NP |
| Intrapulmonary shunt ratio (%) | 27 | 19 | 21 | 16 | 32 | NP | NP |
| $SpO_2$ | 82 | 79 | 86 | 84 | 86 | 89 | 95 |
| CEE | Positive CEE/ mild aortic stenosis and insufficiency | Positive CEE | Positive CEE / mild mitral and tricuspid insufficiency | Positive CEE / mild mitral insufficiency | Positive CEE | Positive CEE | Positive CEE |
| LT | - | + | - | - | - | + (exitus) | - |

NP: not performed; HPS: hepatopulmonary syndrome; PHT: portal hypertension; CHILD: child-pugh; PELD: pediatric end-stage liver disease; MELD: model of end-stage liver disease; VC%: percentage of vital capacity; $FEV_1$%: percentage of forced expiratory volume in 1 s; $SpO_2$: blood oxygen saturation; CEE: contrast enhanced echocardiography; LT: liver transplantation

termined that CLD was a cause of HPS in all of our patients except Case 4, who was diagnosed with biliary cirrhosis and Case 7, who was diagnosed with extrahepatic biliary atresia and fibrosis.

In our series, intrapulmonary shunting was observed using CEE or 99 mTc-MAA perfusion lung scan. In some of our patients, both of these diagnostic studies were performed. It was reported that the 99 mTc-MAA perfusion lung scan was more sensitive than CEE in the diagnosis of shunts because perfusion scans can detect small shunts whereas CEE has no quantitative aspect and can miss smaller shunts (1). However, the European Respiratory Society Task Force on pulmonary-hepatic vascular disorders has recommended CEE as the first-line screening modality for HPS (25). Krowka et al. (26) reported that mild or subclinical intrapulmonary vasodilatations in cirrhotic patients might not alter the gas exchange. They found that 9.7% of 31 normoxaemic patients, who were candidates for LT, had a positive CEE. Therefore, CEE may be positive despite normal arterial blood gases. In Case 7, a positive CEE was observed despite the absence of hypoxaemia, which was consistent with the literature.

Clinical trials have shown that 99 mTc-MAA scans can be used to assess the severity of HPS to predict outcomes after LT (27). HPS was classified into three grades based on the degree of intrapulmonary shunting calculated by 99 mTcMAA pulmonary scintigraphy: mild (shunt ratio <20%), moderate (shunt ratio ≥20% and ≤40%) and severe (shunt ratio >40%) (28). It has been determined that a preoperative $PaO_2$ of <50 mmHg in room air and a MAA shunt fraction of ≥30% are the strongest predictors of postoperative mortality (29). Also a relationship between the MAA shunt fraction and HPS resolution was found; the higher the shunt fraction, the longer the time needed for the reversal of HPS (23). Since it is thought that severe hypoxaemia due to HPS may be a relative contraindication for LT, an early operation is suggested in the presence of HPS (30). Among our patients who had MAA scans, none had severe HPS based on the degree of intrapulmonary shunting. However, we do not know the shunt fraction value of Case 6, who died of respiratory problems after LT.

The CHILD classification, which reflects the degree of liver failure, is used in determining the prognosis in cirrhotic patients (31). No correlation has been reported between the severity of hepatic dysfunction and that of HPS (23). When the CHILD and PELD scores and the presence of PHT were evaluated, we also concluded that HPS was not related to the severity of liver disease but rather to the presence of PHT.

While HPS improves after LT in the majority of patients, there seems to be an increase in postoperative complications and mortality in transplanted cases (26). In patients with HPS, portal venous thrombosis, intracranial events and multi-organ failure have been seen more commonly (32). Because hypoxaemia can cause polycythaemia and increased blood viscosity, supplemental oxygen before LT can be given to prevent or minimize the risk of polycythaemia and the subsequent risk of vascular thrombosis (23). We recommended at-home oxygen therapy for our patients while waiting for LT. Intraoperative fluid overloading, atelectasis and restrictive disorders due to abdominal distension and/or pleural effusion after LT are some of the factors leading to postoperative hypoxaemia (33). In our Case 6, a massive pleural effusion and atelectasis did not respond to therapies, and the patient died five days after LT due to severe hypoxaemia and multi-organ failure.

It has been reported that the time required for HPS resolution negatively correlated with the oxygenation parameters. HPS takes longer to resolve when hypoxaemia is severe before LT (23). It has been reported that a complete resolution may take as long as 1 year (8). In Case 2, the respiratory complaints slowly improved after LT, and the $SpO_2$ was 94% in room air 6 months after the operation.

In summary, a non-invasive measurement of $SpO_2$ with pulse oximetry should be used as a screening tool for HPS. If hypoxaemia is evident, intrapulmonary shunting can be assessed using either CEE or 99 mTc-MAA scan. It must be kept in mind that mild or subclinical intrapulmonary vasodilatations in cirrhotic patients may not alter gas exchange, as in Case 7. Because HPS increases morbidity and mortality among waiting list patients, those with HPS should receive additional priority on the waiting list, and an early transplantation program should be suggested. Oxygen therapy can be an effective prophylactic strategy before transplantation. In the postoperative period, the recumbent position must be preferred in order to prevent hypoxaemia.

In conclusion, in order to improve the long- and short-term outcomes, HPS should be considered in all children with CLD and/or PHT, and if present, it should be an indication for LT even in the absence of liver failure.

**Ethics Committee Approval:** N/A.

**Informed Consent:** Written informed consent was obtained from patients and their parents who participated in this case.

**Peer-review:** Externally peer-reviewed.

**Author contributions:** Concept - D.E., M.A.S., H.K.; Design - D.E., M.A.S, C.K.; Supervision - D.E., M.A.S., F.C.; Resource - C.K., F.C., R.K.; Materials - C.K, H.K, O.E.; Data Collection &/or Processing - C.K., H.K., O.E., R.K.; Analysis &/or Interpretation - D.E., M.A.S.; F.C.; Literature Search - D.E., F.C., R.K.; Writing - D.E., M.A.S., C.K.; Critical Reviews - O.E., R.K., H.K.

**Conflict of Interest:** No conflict of interest was declared by the authors.

**Financial Disclosure:** The authors declared that this study has received no financial support.

## REFERENCES

1. El-Shabrawi MH, Omran S, Wageeh S, et al. (99 m)Technetium-macroaggregated albumin perfusion lung scan versus contrast enhanced echocardiography in the diagnosis of the hepatopulmonary syndrome in children with chronic liver disease. Eur J Gastroenterol Hepatol 2010; 22: 1006-12. **[CrossRef]**
2. Ho V. Current concepts in management of hepatopulmonary syndrome. Vasc Health Risk Manage 2008; 4: 1035-41.
3. Naeije R. Hepatopulmonary syndrome and portopulmonary hypertension. Swiss Med Wkly 2003; 133: 163-9.
4. Whyte MK, Hughes JM, Peters AM, et al. Analysis of intrapulmonary right to left shunt in the hepatopulmonary syndrome. J Hepatol 1998; 29: 85-93. **[CrossRef]**
5. Abrams GA, Jaffe CC, Hoffer PB, Binder HJ, Fallon MB. Diagnostic utility of contrast echocardiography and lung perfusion scan in patients with hepatopulmonary syndrome. Gastroenterology 1995; 109: 1283-8. **[CrossRef]**
6. Schenk P, Schoniger-Hekele M, Fuhrmann V, et al. Prognostic significance of the hepatopulmonary syndrome in patients with cirrhosis. Gastroenterology 2003; 125: 1042-52. **[CrossRef]**
7. Tumgor G, Arikan C, Yuksekkaya HA, et al. Childhood cirrhosis, hepatopulmonary syndrome and liver transplantation. Pediatr Transplant 2008; 12: 353-7. **[CrossRef]**
8. Battaglia SE, Pretto JJ, Irving LB, et al. Resolution of gas exchange abnormalities and intrapulmonary shunting following liver transplantation. Hepatology 1997; 25: 1228-32. **[CrossRef]**
9. Willis AD, Miloh TA, Arnon R, Iyer KR, Suchy FJ, Kerkar N. Hepatopulmonary syndrome in children - is conventional liver transplantation always needed? Clin Transplant 2011; 25: 849-55. **[CrossRef]**
10. Krowka MJ, Tajik AJ, Dickson ER, Wiesner RH, Cortese DA. Intrapulmonary vascular dilatations (IPVD) in liver transplant candidates: screening by two-dimensional contrast-enhanced echocardiography. Chest 1990; 97: 1165-70. **[CrossRef]**
11. Noli K, Solomon M, Golding F, Charron M, Ling SC. Prevalence of hepatopulmonary syndrome in children. Pediatrics 2008; 121: 522-7. **[CrossRef]**
12. Wolfe JD, Tashkin DP, Holly FE, Brachman MB, Genovesi MG. Hypoxemia of cirrhosis: detection of abnormal small pulmonary vascular channels by a quantitative radionuclide method. Am J Med 1977; 63: 746-54. **[CrossRef]**
13. Abrams GA, Sanders MK, Fallon MB. Utility of pulse oximetry in the detection of arterial hypoxemia in liver transplant candidates. Liver Transpl 2002; 8: 391-6. **[CrossRef]**
14. Mcdiarmid SV, Anand R, Lindblad AS; Principal Investigators and Institutions of the Studies of Pediatric Liver Transplantation (SPLIT) Research Group. Development of a paediatric end-stage liver disease score to predict poor outcome in children awaiting liver transplantation. Transplantation 2002; 74: 173-81. **[CrossRef]**
15. Castro M, Krowka MJ. Hepatopulmonary syndrome. A pulmonary vascular complication of liver disease. Clin Chest Med 1996; 17: 35-48. **[CrossRef]**
16. Krowka MJ, Dickson ER, Cortese DA. Hepatopulmonary syndrome. Clinical observations and the lack of a therapeutic response to somatostatin analogues. Chest 1993; 104: 515-21. **[CrossRef]**
17. Arguedas MR, Singh H, Faulk DK, Fallon MB. Utility of pulse oximetry screening for hepatopulmonary syndrome. Clin Gastroenterol Hepatol 2007; 5: 749-54. **[CrossRef]**

18. Marti´nez Palli G, Barberà JA, Visa J, et al. Hepatopulmonary syndrome in candidates for liver transplantation. J Hepatol 2001; 34: 651-7. **[CrossRef]**
19. Krowka MJ, Dickson R, Wiesner RH, et al. A prospective study of pulmonary function and gas exchange following liver transplantation. Chest 1992; 102: 1161-6. **[CrossRef]**
20. Williams A, Trewby P, Williams R, Reid L. Structural alterations to the pulmonary circulation in fulminant hepatic failure. Thorax 1979; 34: 447-53. **[CrossRef]**
21. Sasaki T, Hasegawa T, Kimura T, Okada A, Mushiake S, Matsushita T. Development of intrapulmonary arteriovenous shunting in postoperative biliary atresia: evaluation by contrast-enhanced echocardiography. J Pediatr Surg 2000; 35: 1647-50. **[CrossRef]**
22. Barbe´ T, Losay J, Grimon G, et al. Pulmonary arteriovenous shunting in children with liver disease. J Pediatr 1995; 126: 571-9. **[CrossRef]**
23. Al-Hussaini A, Taylor RM, Samyn M, et al. Long-term outcome and management of hepatopulmonary syndrome in children. Pediatr Transplant 2010; 14: 276-82. **[CrossRef]**
24. Morikawa N, Honna T, Kuroda T, et al. Resolution of hepatopulmonary syndrome after ligation of a portosystemic shunt in a paediatric patient with an Abernethy malformation. J Pediatr Surg 2008; 43: 35-8. **[CrossRef]**
25. Rodri'guez-Roisin R, Krowka MJ, Herve P, Fallon MB. Pulmonary-hepatic vascular disorders (PHD). Eur Respir J 2004; 24: 861-80. **[CrossRef]**
26. Krowka MJ, Mandell MS, Ramsay MA, et al. Hepatopulmonary syndrome and portopulmonary hypertension: A report of the multicenter liver transplant database. Liver Transpl 2004; 10: 174-82. **[CrossRef]**
27. Arguedas MR, Abrams GA, Krowka MJ, Fallon MB. Prospective evaluation of outcomes and predictors of mortality in patients with hepatopulmonary syndrome undergoing liver transplantation. Hepatology 2003; 37: 192-7. **[CrossRef]**
28. Egawa H, Kasahara M, Inomata Y, et al. Long-term outcome of living related liver transplantation for patients with intrapulmonary shunting and strategy for complications. Transplantation 1999; 67: 712-7. **[CrossRef]**
29. Tiao GM, Alonso MH, Ryckman FC. Pediatric liver transplantation. Sem Pediatr Surg 2006; 15: 218-27. **[CrossRef]**
30. Umeda A, Tagawa M, Kohsaka T, et al. Hepatopulmonary syndrome can show spontaneous resolution: possible mechanism of portopulmonary hypertension overlap? Respirology 2006; 11: 120-3. **[CrossRef]**
31. Yigit IP, Hacievliyagil SS, Seckin Y, Oner RI, Karincaoglu M. The relationship between severity of liver cirrhosis and pulmonary function tests. Dig Dis Sci 2008; 53: 1951-6. **[CrossRef]**
32. Martinez G, Barbera JA, Navasa M, et al. Hepatopulmonary syndrome associated with cardiorespiratory disease. J Hepatol 1999; 30: 882-9. **[CrossRef]**
33. Chihara Y, Egawa H, Tsuboi T, et al. Immediate noninvasive ventilation may improve mortality in patients with hepatopulmonary syndrome after liver transplantation. Liver Transpl 2011; 17: 144-8. **[CrossRef]**