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Serum Endothilin-1 Level, Pulse Oximetry and Echocardiography for Diagnosis of Hepatopulmonary Syndrome

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Abstarct
Liver cirrhosis is a condition in which there is development of regenerative nodules surrounded by fibrous bands in response to chronic liver injury that leads to portal hypertension and end stage liver disease. Hepatopulmonary syndrome (HPS) is a triad of portal hypertension, intrapulmonary vascular dilatation or shunting, and hypoxemia. The prevalence of HPS in patients with liver cirrhosis varies from 4%- 47% with adverse out come and increase mortality in comparison to those without HPS especially when sever hypoxemia is present. The aim of the present work was to study the significance of serum endothelin-1 level, digital pulse oximetry, arterial blood gases analysis and contrast enhanced transthoracic echocardiography in diagnosis of HPS among Egyptian patients with liver cirrhosis.
Keywords: Hepatopulmonary syndrome (HPS), serum endothilin-1 level, pulse oximetry, arterial blood gases analysis, echocardiography

INTRODUCTION

Hepatopulmonary syndrome (HPS) is an uncommon condition with widened alveolar-arterial oxygen tension difference [$P(A–a)O_2$] in room air >15 mmHg, or >20 mmHg in patients >64 years of age, resulting from intrapulmonary vasodilatation in the presence of hepatic dysfunction or portal hypertension. (1) Its prevalence among patients with liver cirrhosis varies from 4%-47%. (2)

The pathogenesis of HPS include dilatation of the intrapulmonary blood vessels due to impaired liver function with defect in the synthesis and metabolism of pulmonary vasoactive substances which lead to imbalance between vasodilatation and vasoconstriction. [3, 4] Also, increased cardiac output and hyperdynamic circulation associated with liver disease reduce transit time of blood in the lung vasculature, which lead to reduction in the time through which the blood is exposed to oxygen diffusion. [5]

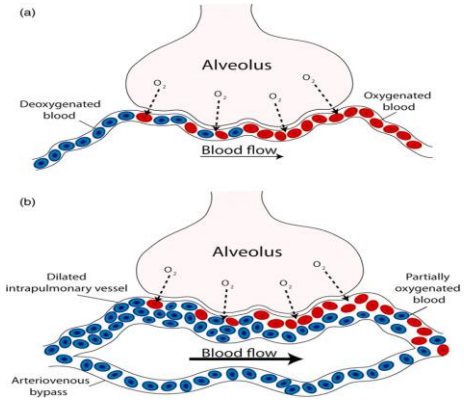

Figure (1): The pathophysiology of impaired gas exchange in HPS. [6]

(a) Represents the healthy gas exchange unite
(b) Represents the gas exchange unite in HPS.

Patients with HPS may be asymptomatic, [7] however, they may develop insidious onset of dyspnea which may be exertional or induced by the upright position and relieved by recumbence (platypnea), arterial hypoxemia assessed by arterial blood gases analysis and enhanced by the upright position (orthodeoxia). Moreover, finger clubbing and spider nevi are other clinical features of patients with HPS. [8]

Some patients with intrapulmonary vascular dilatations do not develop hypoxemia, whereas other patients develop severe hypoxemia with minimal dilatations. [9] Intrapulmonary vascular dilatations in HPS do not have tendency to bleed and result in pulmonary hemorrhage; also, they are reversible with liver transplantation. [10]

Endothelin-1 (ET-1) is a 21–amino acid component synthesized by endothelial cells, with powerful vasoconstrictive effects. It is formed as pre–pro ET-1, and through the action of specific metalloproteinases called endothelin-converting enzymes, pro ET-1 is generated then active ET-1 is formed. [11]

The biological effects of ET-1 are transduced by two pharmacologically distinguishable receptor subtypes, ETA and ETB receptors. [12] The ETA receptors located on vascular smooth muscle cells and mediate potent vasoconstriction. The ETB receptors are primarily located on endothelial cells, but may also be present on vascular smooth muscle cells. Stimulation of the endothelial ETB receptors result in release of nitric oxide (NO) and prostacyclin which cause vasodilatation, whereas stimulation of the vascular smooth muscle cell ETB receptors result in vasoconstriction. Thus, the net effect produced by ET-1 is determined on the receptor localization and the balance between ETA and ETB receptors. [13]

Circulating ET-1 level is increased in cirrhosis, not only from increased ET-1 production and release by the injured liver, but also from reduced ET-1 clearance, or from a combination of both. [14, 15] Elevated level of ET-1 in cirrhosis occurs in the setting of systemic vasodilatation and is not associated with measurable vasoconstrictive effects. This observation suggested that the effects mediated by ET-1 in chronic liver disease may include stimulation of NOS activity through the ETB receptors on endothelial cells or modulation of vasoactive peptide expression. [16]

HPS was suspected in cirrhotic patients who had persistent dyspnea after a normal chest film or after optimal treatment of the underlying conditions. Screening was done with digital pulse oximetry for each suspected patient, where oxygen saturation in sitting position and after 10 minutes of standing position was assessed. Oxygen saturation (SpO_2) <96% and/or decrease of ≥4% after 10 minutes of changing the position raise the suspicion. [17]

Arterial blood gases analysis to suspected patients with diminished O_2 saturation is beneficial in detecting cirrhotic patients with hypoxemia and HPS, where PaO_2 <80 mmHg is a good cutoff value for diagnosis of HPS (normal PaO_2 is ≥80 mmHg). [18] Moreover, the alveolar-arterial oxygen tension difference $P(A–a)O_2$ can be calculated where $P(A-a)O_2$ >15 mmHg at room air and sea level can diagnose HPS. [19] Also, its use is important because it increases abnormally before the partial pressure of oxygen itself becomes abnormally low. [20]

Transthoracic echocardiography is the most sensitive test for detection of intrapulmonary vascular dilatation (IPVD) and it has the additional advantage of distinguishing intracardiac from intrapulmonary shunting and allowing additional screening for pulmonary hypertension during testing. [21]

AIM OF THE WORK

The aim of this work was to study the significance of serum endothelin-1 (ET-1) level, digital pulse oximetry, arterial blood gases analysis and contrast enhanced echocardiography in the diagnosis of hepatopulmonary syndrome (HPS) among Egyptian cirrhotic patients.

SUBJECTS AND METHODS

The present study included 40 patients with liver cirrhosis; they were divided into two groups, **Group I**: 20 patients with liver cirrhosis, **Group II**: 20 patients with liver cirrhosis and HPS. Moreover, 10 age and sex matched healthy subjects with no evidence of liver disease were included as a control group (**Group III**).

Exclusion criteria included patients with heart diseases, lung diseases, renal impairment, hypertension, any kind of malignancy, infections or inflammatory disorders.

All patients included in this study were subjected to:

*Proper history taking and clinical evaluation focusing on signs and symptoms of chronic liver disease and HPS. Moreover, diagnosis of liver cirrhosis was confirmed by liver profile and abdominal ultrasound.

*Screening was done with digital pulse oximetry for each suspected patient, where oxygen saturation in sitting position and after 10 minutes of standing position was assessed. Oxygen saturation (SpO_2) <96% and/or decrease of ≥4% after 10 minutes of changing the position raise the suspicion.

*Arterial blood gases analysis was done to suspected patients with diminished O_2 saturation where PaO_2 <80 mmHg was the cutoff value used in the present study for diagnosis of HPS (normal PaO_2 is ≥80 mmHg). Also, calculation of the alveolar-arterial oxygen tension difference $P(A–a)O_2$ was done with the following equation:

$P(A\text{-}a)O_2=(FiO_2\%/100)*(Patm–47)–(PaCO_2/0.8)–PaO_2$. (Units in mmHg) [19] Where, Patm is atmospheric pressure at sea level=760 mmHg, FiO_2 is fraction of inspired oxygen= 21% at room air.

*Contrast enhanced transthoracic echocardiography was performed by intravenous injection of hand agitated saline (vigorously shaken to produce sonographically visible microbubbles 60-90 µm in diameter) during routine trans-thoracic echocardiography. Following administration of agitated saline into a peripheral arm vein, microbubbles opacification of the left atrium within 3-6 cardiac cycles following right atrium opacification indicates microbubbles passage through an abnormally dilated pulmonary vascular bed as normally the microbubbles are dissolved and absorbed in pulmonary capillaries (8 - 15 µm in diameter). On the other hand, immediate visualization of microbubbles in the left atrium (within 3 cardiac cycles) indicates intracardiac right-to-left shunting. Appearance of the microbubbles in the left cardiac chambers 3-6 cardiac cycles after administration is considered a positive test for intrapulmonary shunting. Moreover, trans-thorathic echocardiography allows measurement of pulmonary artery acceleration time (PAAT), which is the time in milliseconds (msec) from the onset of systolic pulmonary arterial flow to the peak flow velocity. PAAT was used for measurement of the mean pulmonary artery pressure (MPAP) using the following equation: MPAP=90-(0.62×PAAT) mmHg for those with PAAT less than 120 msec or Mahan's regression equation: MPAP=79-(0.45×PAAT) for those with PAAT more than 120 msec. Also, the peak velocity of the pulmonary arterial flow and the peak pulmonary artery pressure gradient were reported. [22, 23]

*Serum endotheline-1 (ET-1) level was measured in all studied subjects.

Written consent was taken from all participants included in the study before starting the research in accordance with the principles of the Declaration of Helsinki (revision of Edinburgh,2000). Approval of the ethical

committee of the Faculty of Medicine, Alexandria University was obtained.

RESULTS

Presenting symptoms and signs of HPS:

In the present study, dyspnea was the common presenting symptom among patients with HPS (90%), followed by clubbing and cyanosis (55% and 35% respectively). A statistical significant difference was observed between cirrhotic patients with and without HPS as regard studied symptoms and signs of HPS. **(Table 1)**

Table (1): Symptoms and signs of HPS in cirrhotic patients.

	Without HPS (GI) (n = 20)		With HPS (GII) (n = 20)		χ^2	P
	No	%	No	%		
Dyspnea	2	10.0	18	90.0	25.600*	<0.001*
Clubbing	3	15.0	11	55.0	7.033*	0.008*
Cyanosis	0	0.0	7	35.0	8.485*	FE p =0.008*

p: p value for comparing between the two studied groups

χ^2: value for Chi square FE: Fisher Exact test

*: Statistically significant at $p \leq 0.05$

Pulse oximetry findings:

Orthodeoxia which is a difference in O_2 saturation (measured by pulse oximetry) between both sitting and standing positions of more than 4%, was a common finding among patients with HPS where it was reported in 80% of these patients. On the other hand, none of the patients without HPS showed this finding with a statistically significant difference between both studied groups.

O_2 saturation in patients without HPS at sitting position ranged from 93-99%, while at standing position it ranged from 94-99% with a median of 97.5% in both positions. On the other hand, patients with HPS had O_2 saturation at sitting position ranged from 94-96% and at standing position ranged from 89-94% with a median of 95% and 91.5% in both positions respectively. A statistically significant difference was observed between the two studied groups according to O_2 saturation. **(Table 2)**

Table (2): Comparison between the two studied groups according to O_2 saturation using pulse oximetry.

	Without HPD (GI) (n = 20)		With HPD (GII) (n = 20)		Test of sig.	p
	No	%	No	%		
Orthodeoxia						
-ve	20	100.0	4	20.0	Z=26.667*	<0.001*
+ve	0	0.0	16	80.0		
O_2 saturation (sitting)						
Min. – Max.	93.0 – 99.0		94.0 – 96.0		Z=4.647*	<0.001*
Mean ± SD	97.35 ± 1.42		95.30 ± 0.66			
Median	97.50		95.0			
O_2 saturation (standing)						
Min. – Max.	94.0 – 99.0		89.0 – 94.0		Z=5.441	<0.001*
Mean ± SD	97.10 ± 1.48		91.55 ± 1.19			
Median	97.50		91.50			

*Statistically significant at $p \leq 0.05$

p: p value for comparing between the two studied groups

Z: Z for Mann Whitney test

t: Student t-test

Arterial blood gases analysis:

In the present study, the PH in patients without HPS ranged from 7.39-7.54 with median of 7.42, while, in patients with HPS it ranged from 7.30-7.50 with a median of 7.41.

PaO_2 in patients without HPS ranged from 83-110 mmHg with a median of 100 mmHg, while in patients with HPS it ranged from 56-80 mmHg with a median of 69.5 mmHg. Moreover, a statistically significant difference was noticed between both groups as regard PH and PaO_2.

$P(A–a)O_2$ had a median of 12.23 mmHg in patients without HPS, and 36.61 mmHg in patients with HPS with an evident statistically

significant difference between both studied groups. **(Table 3)**

Table (3): Comparison between the two studied groups according to arterial blood gases analysis (ABG).

	Without HPS (G I) (n = 20)	With HPS (G II) (n = 20)	Test of sig.	P
PH				
Min. – Max.	7.39 – 7.54	7.30 – 7.50		
Mean ± SD	7.44 ± 0.04	7.41 ± 0.05	Z =1.949*	0.049*
Median	7.42	7.41		
PaO_2				
Min. – Max.	83.0 – 110.0	56.0 – 80.0		
Mean ± SD	98.12 ± 7.65	69.15 ± 7.02	t = 12.477*	<0.001*
Median	100.0	69.50		
$PaCO_2$				
Min. – Max.	22.0 – 44.0	28.0 - 49.0		
Mean ± SD	32.26 ± 5.67	34.45 ± 6.17	t = 1.172	0.248
Median	31.0	33.50		
$P(A–a)O_2$				
Min. – Max.	5.23 ± 14.73	23.73 - 57.73		
Mean ± SD	11.75 ± 2.79	37.29 ± 10.67	t = 10.354*	<0.001*
Median	12.23	36.61		

p: p value for comparing between the two studied groups Z: Z for Mann Whitney test

t: Student t-test

*: Statistically significant at $p \leq 0.05$

Contrast enhanced transthoracic echocardiography:

In this study, contrast enhanced echocardiography was positive (the agitated saline microbubbles were visualized in the left atrium after 3-6 cardiac cycles) in 100% of patients with HPS, while it was negative in patients without HPS and control subjects. A statistically significant difference was reported between different studied groups.

The peak velocity of the pulmonary flow was almost equal in all groups with no statistical significant difference between different studied groups. On the other hand, the peak gradient was significantly elevated in patients with HPS in comparison to other groups.

The pulmonary artery acceleration time (PAAT) was significantly longer in patients without HPS in comparison to patients with HPS and control subjects. It was used to measure the mean pulmonary artery pressure (MPAP) where the median of MPAP was equal in both groups of patients and slightly diminished in the control group. MPAP was more than 25 mmHg in 30% of patients with HPS, while only 5% of patients without HPS had elevated MPAP and none of the control subjects had elevated pressure with a statistical significant difference between different studied groups. **(Table 4)**

Table (4): Comparison between different studied groups according to transthoracic echocardiography findings.

	Without HPD (G I) (n = 20)		With HPD (G II) (n = 20)		Control (G III) (n = 10)		Test of sig.	p
	No.	%	No.	%	No.	%		
Contrast enhanced echocardiography	0	0.0	20	100.0	0	0.0	$\chi^2 = 50.0^*$	$<0.001^*$
Peak velocity m/sec								
Min. – Max.	0.69 - 1.48		0.69 – 1.61		0.70 – 1.28		F= 2.165	0.126
Mean ± SD	1.09 ± 0.18		1.18 ± 0.24		1.02 ± 0.18			
Median	1.11		1.18		1.10			
Gradient Min. – Max.	1.84 – 8.76		4.55 – 10.40		2.81 – 6.60		F= 7.928*	0.001*

Mean ± SD	4.84 ± 1.56		6.50 ± 1.65		4.48 ± 1.40			
Median	5.0		5.85		4.19			
Acceleration time (msec)								
Min. – Max.	94.0 – 148.0		80.0 – 142.0		105.0 – 142.0			
Mean ± SD	123.90 ± 12.43		112.40 ± 16.66		120.10 ± 11.69		F=3.367*	0.043*
Median	121.0		115.0		118.0			
Mean pulmonary artery preasure								
Min. – Max.	12.40 – 31.72		14.98 – 40.40		15.10 – 24.90			
Mean ± SD	18.49 ± 4.39		22.19 ± 8.24		18.08 ± 3.04		$^{KW}\chi^2$=1.659	0.436
Median	18.70		18.70		16.96			
Increase mean pulmonary artery pressure	1	5.0	6	30.0	0	0.0	χ^2 = 7.226	^{MC}p = 0.056

p: p value for comparing between the three studied groups

χ^2: value for Chi square

F: F test (ANOVA)

^{KW}: Kruskal Wallis test

*: Statistically significant at $p \leq 0.05$

Serum endothelin-1 level:

The median value of serum endothelin-1 (ET-1) in normal subjects was 1.15ng/ml ranging from 0.4-1.6 ng/ml, an increase in this value was found in cirrhotic patients without HPS (**Group I)** where ET-1 level ranged from 0.5-8.7 ng/ml with a median value of 2.6 ng/ml. Highest levels were found among HPS patients **Group II**, as ET-1 level ranged from 2.2-12.1 ng/ml with a median value of 4.05 ng/ml. A statistically significant difference was reported between different studied groups as regard serum ET-1 level.

Table (5): Comparison between different studied groups according to serum endothelin-1 (ET-1) level.

	Without HPD (GI) (n = 20)	With HPD (GII) (n = 20)	Control (GIII) (n = 10)	$^{KW}\chi^2$	p
Serum Endothelin-1					
Min. – Max.	0.50 – 8.70	2.20 – 12.10	0.40 – 1.60		
Mean ± SD	3.64 ± 2.50	5.11 ± 2.75	1.08 ± 0.50	22.271*	<0.001*
Median	2.60	4.05	1.15		
p_1		0.036*	0.001*		
p_2		<0.001*			

^{KW}: Kruskal Wallis test

p_1 : p value for Mann Whitney test for comparing between group I and each other group

p_2 : p value for Mann Whitney test for comparing between group II and group III

*: Statistically significant at $p \leq 0.05$

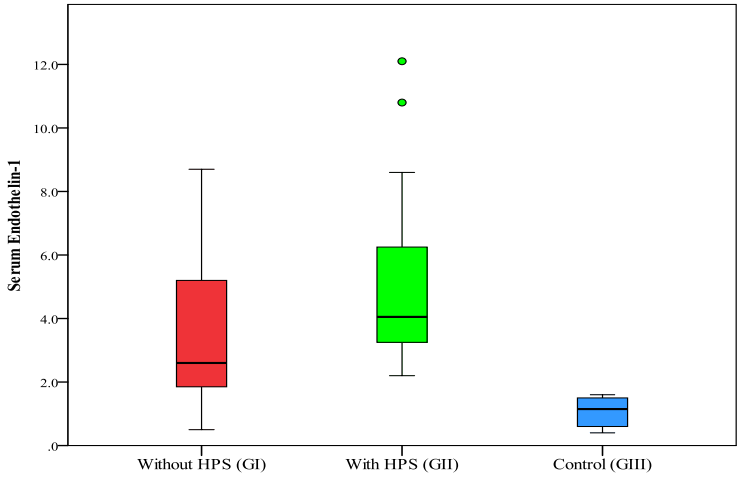

Figure (2): Comparison between the different studied groups according to serum endothelin-1 (ET-1) level.

DISCUSSION

Hepatopulmonary syndrome (HPS) is a triad of portal hypertension, intrapulmonary vascular dilatation or shunting, and hypoxemia. [24] It is an important complication of hepatic dysfunction with increase mortality in comparison to those without HPS especially when sever hypoxemia is present. [25]

In the present study, dyspnea was the most prevalent clinical feature in HPS patients (**Group II**) where it was present in 90% of these patients in comparison to 10% of cirrhotic patients without HPS **(Group I)**. This was in agreement with Hira HS et al [26] who reported that dyspnea is the most common symptom in HPS. However, Zakaria A et al [27] stated that ascites by elevating the diaphragm and impairing the ventilation/perfusion match might lead to mild hypoxemia and dyspnea in up to 10% of cirrhotic patients without HPS.

Clubbing was observed in 55% of patients with HPS (**Group II**) in comparison to 15% of cirrhotic patients without HPS **(Group I),** and this is closely similar to Anand AC et al (2001) [28] who observed clubbing in 60 % of their patients with HPS. Also, cyanosis was present in 35% of patients with HPS (**Group II**) where it was correlated with the degree of hypoxia as reported by Hira HS et al. [26]

A statistical significant difference was found between both groups as regard dyspnea, clubbing and cyanosis, this was in agreement with Lee JH et al (2001) [29] who observed that these signs and symptoms are specific for HPS.

In our study, digital pulse oximetry was used as a screening tool for detection of patients with diminished O_2 saturation (≤96%) who underwent further investigations by arterial blood gases analysis and transthoracic contrast enhanced echocardiography to confirm the diagnosis of HPS. Our results were similar to those made by Abrams GA et al [30] who reported that patients with HPS showed low O_2 saturation (≤96%) in comparison to those without HPS.

Moreover, there was a significant difference in O_2 saturation measured by digital pulse oximetry between sitting and standing positions among patients with HPS **(Group II)** while no difference was reported with changing position among patients without HPS **(Group I)**. This indicated orthodeoxia which was reported in 80% of our patients with HPS while none of the patients without HPS showed this finding with a statistically significant difference between both groups. This was in agreement with Hira HS et al [26] and Gómez FP et al [31] who stated that pulmonary vascular abnormalities were suggested to predominate in the middle and lower lung fields, gravitational effect was expected to increase the blood flow and worsen the ventilation-perfusion mismatch and finally resulted in deterioration of arterial oxygenation when the upright position was attained by the patient.

In our study, Hypoxemia was defined by a recumbent arterial PaO_2 cutoff value of less than 80 mmHg in an arterial blood sample to pick up HPS patients for further evaluation by contrast enhanced transthoracic echocardiography. This cutoff value was suggested by Pastor CM et al [32] who found that patients with PaO_2 more than 80 mmHg were unlikely to have HPS, this was in agreement with our results where the arterial PaO_2 of all included patients with HPS was less than 80 mmHg. In contrary, Hira HS et al [26] defined hypoxemia by recumbent arterial PaO_2 value of less than 70 mmHg.

The alveolar-arterial O_2 gradient [$P(A–a)O_2$] at room air showed a median of 12.23 mmHg in patients without HPS, and 36.61 mmHg in patients with HPS with an evident statistically significant difference between both studied groups. This was in agreement with Schenk P et al [33] and Arguedas MR et al [34] reported that O_2 saturation and PaO_2 showed a significant inverse correlations with $P(A-a)O_2$.

In this study, contrast enhanced echocardiography was positive in all patients with HPS, while it was negative in patients without HPS and control subjects. A statistically significant difference was reported between different studied groups. The same results were observed by Lenci I et al [21] who reported that contrast enhanced echocardiography is a good diagnostic tool for HPS.

The mean pulmonary artery pressure (MPAP) showed an equal median in both groups of patients while it was slightly diminished in the control group. Also, MPAP was more than 25 mmHg in 30% of patients with HPS, while only 5% of patients without HPS had elevated MPAP and none of the control subjects had elevated pressure with a statistically significant difference between different studied groups. This was in agreement with Castro M et al (1996) [35] who observed that the usual hyperdynamic state in liver disease (driven by splanchnic bed vasodilatation) is not associated with obstruction to pulmonary blood flow and the pulmonary vascular resistance (PVR) is normal or low simply due to high cardiac output., such a pulmonary hemodynamic pattern was associated with increased MPAP.

The peak velocity of the pulmonary flow was almost equal in all groups with no statistically significant difference between different studied groups. On the other hand, the peak gradient was significantly elevated in patients with HPS in comparison to other groups.

In the present study, The median value of endothelin-1 (ET-1) in normal subjects was 1.15ng/ml ranging from 0.4-1.6 ng/ml, an increase in this value was found in cirrhotic patients without HPS (**Group I)** where ET-1 level ranged from 0.4-8.2 ng/ml with a median value of 2.55 ng/ml. Highest levels were found among HPS patients **(Group II)**, as ET-1 level ranged from 1.6-12.1 ng/ml with a median value of 4.05 ng/ml.

In our results, ET-1 was elevated in patients with liver cirrhosis both (**Group I)** and (**Group II)** in comparison to control group, this agreed with Helmy A [(36)] who reported that ET-1 increased with cirrhosis due to decreased excretion. Moreover, an evident statistically significant difference between different studied groups was observed which agreed with Widyantoro B et al [(37)] who concluded that elevation of ET-1 level occurs evidently in patients with HPS. In contrary, Khoshbaten M et al [(38)] stated that the development of HPS may be dependent upon increase ET-1 receptors expression rather than increase serum ET-1 concentrations.

CONCLUSION:

Serum endothilin-1 (ET-1) level, digital pulse oximetry and contrast enhanced transthoracic echocardiography are beneficial tools for diagnosis of HPS in cirrhotic patients.

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