Frequency of hepatopulmonary syndrome and portopulmonary hypertension in cirrhotic liver patients

Abbas S. El-Maraghy[a], Ahmed A. Abu Naglah[a], Ayman Amin[a], Kamal A. Merghany[b], Mohamed M. Khalil[a]

Background Chronic liver diseases may cause abnormal changes in the pulmonary vascular bed. There are two important and pathophysiologically different pulmonary vascular abnormalities – hepatopulmonary syndrome (HPS) and portopulmonary hypertension (PPHTN). Pathophysiologically, HPS results from vasodilatation, whereas PPHTN results from vasoconstriction.

Objective The objective of this study was to determine the frequency of HPS and PPHTN in dyspneic cirrhotic hepatic patients.

Patients and methods This study included 87 patients with cirrhotic liver disease admitted to Al-Azhar University Hospitals from September 2013 to September 2015. The diagnosis of cirrhosis was based on clinical, biochemical, serological, and metabolic workup, abdominal ultrasound, or liver biopsy. All patients in this study were subjected to complete medical history taking and clinical examination, liver function tests, plain chest radiography, and thoracic high-resolution computed tomography, abdominal ultrasonography, arterial blood gas analysis in the supine and standing positions, calculation of alveolar–arterial oxygen gradient, saline two-dimensional contrast-enhanced echocardiography, and right-heart catheterization only for all cases with PPHTN.

Results The present study showed that the prevalence of HPS was 25.28% (22 out of 87 cases) and was higher than the prevalence of PPHTN, which was 5.7% (5 out of 87 cases).

Conclusion HPS and PPHTN are not uncommon in patients with hypoxemia and chronic hepatic disease. Diagnoses of such disorders are essential, especially in patients who are listed for liver transplantation.

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Departments of, [a]Chest, [b]Cardiology, Faculty of Medicine, Al-Azhar University, Cairo, Egypt

Correspondence to Ayman Amin, MD, 20 Samir Abd Elraouf-Makram Ebeid, Nasr City, Cairo 11614, Egypt.
e-mail: aymanaminmo@yahoo.com

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Introduction

Hepatopulmonary syndrome (HPS) is defined as intrapulmonary vasodilatation at the capillary and precapillary levels, as well as impaired arterial oxygenation. Advanced liver disease is not required for HPS development, and the disease may worsen irrespective of hepatic function [1].

HPS is characterized by a triad of impaired arterial oxygenation, hepatic dysfunction, and the presence of intrapulmonary vascular dilatations (IPVDs). According to its pathophysiology, the vasodilatations may take the form of dilated precapillary and capillary vessels or direct arteriovenous communications termed type-1 HPS. If the discrete shunts are the major vascular abnormality, it is termed type-2 HPS [2].

Portopulmonary hypertension (PPHTN) is defined as pulmonary arterial hypertension associated with portal hypertension, with or without hepatic disease. True PPHTN is found in 3.1–4.7% patients with cirrhosis and, if untreated, is associated with high mortality. In moderate-to-severe stages of PPHTN, liver transplantation may not reverse the condition and may increase perioperative morbidity and mortality; this is being regarded by many authorities as a contraindication to liver transplantation [3].

Aim

The aim of this study was to determine the frequency of HPS and PPHTN in dyspneic cirrhotic hepatic patients.

Patients and methods

This study included 87 patients with cirrhotic liver disease admitted to Al-Azhar University Hospitals from September 2013 to September 2015. The diagnosis of cirrhosis was based on clinical, biochemical, serological, and metabolic workup, ultrasound abdomen, or liver biopsy.

Inclusion criteria

Patients with cirrhotic liver disease with unexplained dyspnea were included.

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Exclusion criteria

(1) Patients with chronic liver disease with an explained cause for dyspnea.
(2) Patients with pulmonary hypertension due to an obvious cause such as chronic obstructive pulmonary disease, idiopathic pulmonary fibrosis, and end-stage systemic disease other than liver cirrhosis.

All patients in this study were subjected to the following:

(1) Full history taking with special attention to dyspnea and any coexisting cardiopulmonary problems. Patients were assessed for dyspnea according to the Modified Medical Research Council (MMRC) dyspnea scale [4]:
Grade 0: not troubled by breathlessness except while performing strenuous exercises.
Grade 1: shortness of breath when hurrying on the level or walking up a hill.
Grade 2: walks slower than people of the same age on the level because of breathlessness or has to stop to breathe when walking at his or her own pace on the level.
Grade 3: stops to breathe after walking about 100 m or after a few minutes on the level.
Grade 4: too breathless to leave the house or breathless when dressing or undressing.
(2) Thorough general examination.
(3) Complete abdominal, cardiac, and chest examination.
(4) Laboratory investigations:
    (a) Complete blood count, blood urea, serum creatinine, alanine aminotransferase, aspartate aminotransferase, fasting, and 2-h postprandial blood glucose level, bilirubin (total and direct), alkaline phosphatase, serum albumin, prothrombin time and concentration, international normalized ratio, and erythrocyte sedimentation rate.
    (b) Arterial blood gas analysis: 1-ml arterial blood was taken from the radial artery after disinfecting the site of sampling with alcohol while the patient was in the supine position. Another sample was collected similarly while the patient was in the upright position with a time interval of 10 min [5].
(5) ECG.
(6) Plain chest radiography (posteroanterior view).
(7) Thoracic, high-resolution computed tomography.
(8) Pelvic–abdominal ultrasonography.
(9) Contrast-enhanced echocardiography [6]:
Ten milliliter of agitated saline, which provides a stream of microbubbles 60–90 μm in diameter that usually opacify only the right heart chambers, was injected slowly into a venous peripheral line (cannula) into patients' upper right or left limb, observing whether it will appear on the left side of the heart and after how many beats after its appearance on the right side of the heart.
Under normal circumstances, these microbubbles are filtered by the pulmonary capillary bed and do not appear in the left side of the heart. However, in the presence of an intrapulmonary or intracardiac right-to-left shunt, microbubbles will opacify the left heart chambers.
Patients were also assessed for the rest of the cardiac parameters such as ejection fraction, chambers size, valves, and systolic and diastolic dysfunction.
Echocardiograpic grading of shunt: Relative opacification of the left atrium (LA) was assessed semiquantitatively as follows: grade 0, no microbubbles in LA; grade I, a few bubbles in LA, indicating small intra pulmonary shunt (IPS); grade II, moderate bubbles without complete filling of the LA (moderate IPS); grade III, many bubbles filling the LA completely (large IPS); and grade IV, extensive bubbles as dense as in the right atrium (extensive HPS) [7].
(10) Transthoracic Doppler echocardiography (DE): it was performed on all the patients to detect PPHTN and to exclude cardiac causes of dyspnea.
(11) Right-heart catheterization (RHC) was performed for all cases of PPHTN, as it is considered the standard method for direct pressure measurement and hemodynamic assessment in pulmonary hypertension. The recorded parameters included the following:
    (a) Right atrial pressure (RAP) was directly measured; however, by echocardiography it was indirectly measured by the inferior vena cava diameter.
    (b) Right ventricular pressure: both systolic and diastolic right ventricular pressures were recorded. It is more important compared with echocardiography as right ventricular systolic pressure is used to estimate pulmonary artery systolic pressure (PASP) in the absence of a gradient across the right ventricular outflow tract or the pulmonary valve.
    (c) Pulmonary artery pressure (PAP): the systolic, diastolic, and mean PAPs were recorded.

(d) Hepatic venous pressure gradient, which is the difference between free hepatic venous pressure (should not differ with RAP by >1–2 mmHg) and wedged hepatic vein pressure, normally 1–5 mmHg, of greater than 10 mmHg indicates clinically significant portal hypertension, and a value more than 12 mmHg is considered the threshold pressure for variceal rupture. The main advantages of wedged hepatic vein pressure (WHVP) are simplicity, reproducibility, and safety [8].

(12) Alveolar–arterial oxygen tension difference $P(A–a)O_2$ was calculated as follows:
$(FIO_2 \times 713 - 5/4\ PaCO_2) - PaO_2$,
where FIO_2 is the fraction of inspired oxygen, $PaCO_2$ the partial arterial CO_2 tension, and PaO_2 the partial arterial oxygen tension [5].

Statistical analysis

Data analysis was performed using statistical package for the social sciences (SPSS, version 20.0; SPSS Inc., Chicago, Illinois, USA). *P*-value of 0.05 or less was considered statistically significant. Parametric data are expressed as mean±SD and were compared using the paired or independent Student's *t*-test. Pearson's correlation coefficient (*r*) was used to calculate correlations between different variables.

Results

In this study, 87 patients with liver cirrhosis and dyspnea were studied. After preliminary investigations, they were classified into the following groups:

Group 1 included 60 patients as controls who had neither HPS nor PPHTN.
Group 2 included 22 patients with HPS.
Group 3 included five patients with PPHTN.

The present study showed that the prevalence of PPHTN was 5.7% (five cases), whereas the prevalence of HPS was 25.28% (22 cases), which was slightly higher in females (12 cases) than in males (10 cases). The mean age at diagnosis was the fifth decade of life (Tables 1–3).

According to the MMRC dyspnea scale, 30 (50%) patients of group 1 (n=60) were of grade I, 20 (33.33%) patients were of grade II, eight (13.33%) patients were of grade III, and two (3.33%) patients were of grade IV. In group 2 (n=22), four (18.18%) patients were of grade II, 11 (50%) patients were of grade III, and seven (31.82%) patients were of grade IV. In group 3 (n=5), two (40%) patients were of grade II and three (60%) patients were of grade III (Table 4).

Table 1 Frequency of hepatopulmonary syndrome and portopulmonary hypertension in the studied groups

Findings	*N* (%)
HPS	22 (25.28)
IPVD	5 (5.75)
PPHTN	5 (5.75)

HPS, hepatopulmonary syndrome; IPVD, intrapulmonary vascular dilatation; PPHTN, portopulmonary hypertension.

There was a highly significant correlation between dyspnea grading and echocardiographic grading of shunt (P<0.001) (Table 5).

In group 2, 17 (77.27%) patients had orthodeoxia (Table 6). Regarding arterial blood gases, the mean value of PaO_2 in group 1 was 92.54±8.54 mmHg in the supine position and 94.21±10.58 mmHg in the standing position. On the other hand, the mean value of PaO_2 in group 2 was 65.45±9.05 mmHg in the supine position and 59.3±8.11 mmHg in the standing position, and in group 3 the mean value of PaO_2 was 87.85±7.55 mmHg in the supine position and 89.7±10.77 mmHg in the standing position (Table 7).

In the present study, we utilized the PaO_2 and $P(A–a)O_2$ gradients for detecting hypoxia using PaO_2 less than 70 mmHg and $P(A–a)O_2$ more than 15 mmHg as cutoff values. Therefore, in group 2, three (13.64%) cases had a $P(A–a)O_2$ gradient of 15–20 mmHg, nine (40.91%) cases had a $P(A–a)O_2$ gradient of 20–30 mmHg, and 10 (45.45%) cases had a $P(A–a)O_2$ gradient of more than 30 mmHg, with all the cases having PaO_2 less than 70 mmHg.

In group 3, two (40.00%) cases had a $P(A–a)O_2$ gradient of 15–20 mmHg, one (20.00%) case had a $P(A–a)O_2$ gradient of 20–30 mmHg, and two (40.00%) cases had a $P(A–a)O_2$ gradient of more than 30 mmHg, with all the cases having PaO_2 less than 70 mmHg (Tables 8 and 9).

On echocardiography, in group 1, diastolic dysfunction was reported in 10 cases and positive contrast echocardiography (bubble test) was found in five cases (subclinical HPS). In group 2, diastolic dysfunction was reported in six cases and positive contrast echocardiography (bubble test) was found in 22 cases (overt HPS), whereas in group 3 all cases had pulmonary hypertension (Table 10).

On echocardiographic grading of HPS, the present study showed that 27 cases had positive contrast

Table 2 Age distribution among patients of the studied groups

	Group 1 (mean±SD)	Group 2 (mean±SD)	Group 3 (mean±SD)	ANOVA	
				F	*P*-value
Age	51.651±2.462	50.943±1.866	49.624±4.228	1.779	0.118

Table 3 Sex distribution among the studied groups

Sex	Group 1 [*N* (%)]	Group 2 [*N* (%)]	Group 3 [*N* (%)]	Total [*N* (%)]	χ^2	*P*-value
Male	35 (58.33)	10 (45.45)	3 (60.00)	48 (55.17)	1.130	0.568
Female	25 (41.67)	12 (54.55)	2 (40.00)	39 (44.83)		
Total	60 (100.00)	22 (100.00)	5 (100.00)	87 (100.00)		

Table 4 Comparison between different groups with regard to the Modified Medical Research Council dyspnea scale

MMRC dyspnea scale	Group 1 [*N* (%)]	Group 2 [*N* (%)]	Group 3 [*N* (%)]	Total [*N* (%)]	χ^2	*P*-value
Grade 1	30 (50.00)	0 (0.00)	0 (0.00)	30 (34.48)	39.179	<0.001*
Grade 11	20 (33.33)	4 (18.18)	2 (40.00)	26 (29.89)		
Grade 111	8 (13.33)	11 (50.00)	3 (60.00)	22 (25.29)		
Grade 1V	2 (3.33)	7 (31.82)	0 (0.00)	9 (10.34)		
Total	60 (100.00)	22 (100.00)	5 (100.00)	87 (100.00)		

MMRC, Modified Medical Research Council. *Highly significant.

Table 5 Correlation between dyspnea grading and echocardiographic grading of shunt in patients

	Zero [*N* (%)]	Grade I [*N* (%)]	Grade II [*N* (%)]	Grade III [*N* (%)]	Grade IV [*N* (%)]	Total [*N* (%)]	χ^2	*P*-value
Dyspnea I	25 (83.33)	2 (6.66)	2 (6.66)	1 (3.33)	0 (0)	30 (34.5)	43.917	<0.001 (HS)
Dyspnea II	23 (88.46)	1 (3.84)	1 (3.84)	1 (3.84)	0 (0)	26 (29.9)		
Dyspnea III	10 (45)	0 (0)	2 (9.09)	3 (13.6)	5 (22.7)	20 (23)		
Dyspnea IV	2 (18.18)	0 (0)	0 (0)	2 (18.18)	7 (63.63)	11 (12.6)		
Total	60 (69)	3 (3.4)	5 (5.7)	7 (8)	12 (13.8)	87 (100)		

Correlation coefficient=0.583. HS, highly significant.

Table 6 Comparison between different groups with regard to orthodeoxia

Orthodeoxia	Group 1 [*N* (%)]	Group 2 [*N* (%)]	Group 3 [*N* (%)]	Total [*N* (%)]	χ^2	*P*-value
Negative	60 (100.00)	5 (22.73)	5 (100.00)	70 (80.46)	62.425	<0.001*
Positive	0 (0.00)	17 (77.27)	0 (0.00)	17 (19.54)		
Total	60 (100.00)	22 (100.00)	5 (100.00)	87 (100.00)		

Table 7 Comparison between different groups with regard to PaO_2 in supine and standing positions

Patients positions	PaO_2 (mean±SD) (mmHg)			ANOVA		Tukey's test		
	Group 1	Group 2	Group 3	*F*	*P*-value	I and II	I and III	II and III
Supine	92.54±8.54	65.45±9.05	87.85±7.55	18.450	0.000	0.000	0.088	0.000
Standing	94.21±10.58	59.3±8.11	89.7±10.77	22.870	0.000	0.000	0.154	0.000

Table 8 Comparison between different groups with regard to PaO_2

PaO_2 (mmHg)	Group 1 [*N* (%)]	Group 2 [*N* (%)]	Group 3 [*N* (%)]	Total [*N* (%)]	χ^2	*P*-value
<60	0 (0.00)	17 (77.27)	0 (0.00)	17 (19.54)	80.840	<0.001*
60–70	5 (8.33)	5 (22.73)	3 (60.00)	13 (14.94)		
>70	55 (91.67)	0 (0.00)	2 (40.00)	57 (65.52)		
Total	60 (100.00)	22 (100.00)	5 (100.00)	87 (100.00)		

echocardiography (bubble test), and out of them three cases had echocardiographic grade 1 positive bubble test. Five cases showed echocardiographic grade II positive bubble tests, seven cases showed echocardiographic grade III positive bubble tests, and 12 cases showed echocardiographic grade IV positive bubble tests (Table 11). Only 22 out of 27 cases met criteria for HPS, and five cases with positive contrast echocardiographic did not fulfill criteria for HPS and were diagnosed as subclinical HPS.

Table 9 Comparison between different groups with regard to $P(A–a)O_2$ gradient

$P(A–a)O_2$ gradient (mmHg)	Group 1 [*N* (%)]	Group 2 [*N* (%)]	Group 3 [*N* (%)]	Total [*N* (%)]	χ^2	*P*-value
<15	55 (91.67)	0 (0.00)	0 (0.00)	55 (63.22)	79.420	<0.001*
15–20	5 (8.33)	3 (13.64)	2 (40.00)	10 (11.49)		
30–20	0 (0.00)	9 (40.91)	1 (20.00)	10 (11.49)		
>30	0 (0.00)	10 (45.45)	2 (40.00)	12 (13.79)		
Total	60 (100.00)	22 (100.00)	5 (100.00)	87 (100.00)		

Table 10 Comparison between different groups with regard to echocardiographic findings

Echocardiographic findings	Group 1 [*N* (%)]	Group 2 [*N* (%)]	Group 3 [*N* (%)]	Total [*N* (%)]	χ^2	*P*-value
Diastolic dysfunction	10 (16.67)	6 (27.27)	0 (0.00)	16 (18.39)	3.195	0.202
positive Contrast echo (bubble test)	5 (8.33)	22 (100.00)	0 (0.00)	27 (31.03)	73.351	0.000
Pulmonary hypertension	0 (0.00)	0 (0.00)	5 (100.00)	5 (5.75)	38.272	0.000

Table 11 Echocardiographic grading of shunt in the studied groups

Echocardiographic grades	Grade I	Grade II	Grade III	Grade IV	Total
Group 1	2	3	0	0	5
Group 2	1	2	7	12	22
Total	3	5	7	12	27

Group 1 included 60 patients as controls who had neither hepatopulmonary syndrome (HPS) nor PPHTN but five patients with intrapulmonary vascular dilatation. Group 2 included 22 patients with HPS.

Pulmonary artery catheterization was performed for all patients of group 3 (patients with PPHTN) (Table 12). For the purpose of comparison and correlation, the echocardiographic findings of patients of group 3 (patients with PPHTN) are presented (Table 13).

By comparing estimated PASP by echocardiography (86.00±18.16 mmHg) and measured PASP by pulmonary artery catheterization (78.00±16.04 mmHg), we found a statistically significant difference (*P*=0.003) (Table 14).

By comparing mean PAP by echocardiography (59.00 ±15.57 mmHg) and mean PAP by pulmonary artery catheterization (51.00±8.94 mmHg), there was a small difference that did not reach statistical significance (*P*=0.140) (Table 15).

In this study, there was a positive correlation between DE and pulmonary artery catheterization, but this correlation was only statistically significant in diagnosing PASP (*r*=0.995, *P*=0.000). However, the mean PAP measured by DE was higher compared with pulmonary artery catheterization, but without statistical significance (*r*=0.817, *P*=0.092) (Table 16).

Table 12 Pulmonary artery catheterization findings in group 3

	PASP (mmHg)	Mean PAP (mmHg)	PCWP (mmHg)	HVPG	RAP (mmHg)
Case 1	65	45	8	12	8
Case 2	70	50	10	14	8
Case 3	90	60	12	12	6
Case 4	65	40	10	11	4
Case 5	100	60	8	12	9

HVPG, hepatic venous pressure gradient; PAP, pulmonary artery pressure; PASP, pulmonary artery systolic pressure; PCWP, pulmonary capillary wedge pressure; RAP, right atrial pressure.

Table 13 Echocardiographic findings in group 3

	ESPAP (mmHg)	Mean PAP (mmHg)	IVC diameter (cm)
Case 1	70	50	2.6
Case 2	80	55	3.1
Case 3	100	60	2.87
Case 4	70	45	3.1
Case 5	110	85	3.2

ESPAP, estimated systolic pulmonary artery pressure; IVC, inferior vena cava; PAP, pulmonary artery pressure.

Discussion

In this study, 87 patients [48 (55.17%) males and 39 (44.83%) females) aged 37–66 years were studied. They were divided into three groups:

Group 1 included 60 patients with dyspnea only.
Group 2 included 22 patients with dyspnea and HPS.
Group 3 included five patients with dyspnea and PPHTN.

HPS, a liver-induced lung vascular disorder, consists of a triad of hepatic dysfunction, IPVD, and hypoxemia

Table 14 Comparison between pulmonary artery catheterization and echocardiographic findings in group 3 regarding pulmonary artery systolic pressure (mmHg)

	PASP (mean±SD) (mmHg)	Difference of mean		Paired *t*-test	*P*-value
		Mean	SD		
Echocardiography	86.0000±18.16590	8.00000	2.73861	6.532	0.003
Catheterization	78.0000±16.04681				

PASP, pulmonary artery systolic pressure.

Table 15 Comparison between pulmonary artery catheterization and echocardiography findings in group 3 regarding mean pulmonary artery pressure (mmHg)

	PAP (mean±SD) (mmHg)	Difference of mean		Paired *t*-test	*P*-value
		Mean	SD		
Echocardiography	59.0000±15.57241	8.000	9.747	1.835	0.140
Catheterization	51.0000±8.94427				

PASP, pulmonary artery systolic pressure.

Table 16 Correlation between pulmonary artery catheterization and echocardiographic findings in group 3

Correlations	*r*	*P*-value
ESPAP (echocardiography) and PASP (catheterization)	0.995	0.000
Mean PAP (echocardiography) and mean PAP (catheterization)	0.817	0.092

ESPAP, estimated systolic pulmonary artery pressure; PAP, pulmonary artery pressure; PASP, pulmonary artery systolic pressure.

(PO_2<70 mmHg) [4]. Hepatic patients with IPVD who are normoxemic are found to have subclinical HPS or IPVD syndrome in contrast to overt or clinically significant HPS patients who fulfill all three criteria of the triad [9].

Prevalence

The present study showed that the prevalence of PPHTN was 5.7% (five cases), and the prevalence of HPS was 25.28% (22 cases), which was slightly higher in females (12 cases) than in males (10 cases). The mean age at diagnosis was the fifth decade of life.

Kuo *et al.* [10] reported that the mean age at diagnosis was the fifth decade. Regarding sex, they found a similar distribution of both sexes. Ferreira *et al.* [11] reported that the prevalence of HPS was 16% and PPHTN was 2% and was higher in males than in females.

The prevalence of HPS in the study by Yi *et al.* [12] on 279 cirrhotic patients was 9.3%. In the study conducted by Gupta *et al.* [13], on 54 cirrhotic patients, 11.1% of patients had HPS.

Vedrinne *et al.* [7] studied 37 cirrhotic patients, and they found that 8 and 13% of patients had HPS when using transthoracic contrast echocardiography (TTCE) and transesophageal contrast echocardiography (TECE), respectively. They concluded that TECE has a higher detection rate of intrapulmonary shunting compared with TTCE.

In addition, in the study conducted by Schenk *et al.* [14], on 98 patients using PaO_2 less than 80 mmHg as the cutoff value (not using PaO_2<70 mmHg as in the present study), HPS was found in 19% of patients. This implies that using various cutoff values for arterial oxygenations may lead to a wide variation in the prevalence of HPS.

In the study conducted by Krowka *et al.* [15], on 38 cirrhotic patients, HPS was found in 5%. In addition, Stoller *et al.* [16] studied 98 cirrhotic patients, and they found that 4% had HPS. In this study, the higher prevalence of HPS than that recorded by Krowka *et al.* [15] and by Stoller *et al.* [16] could be attributed to their use of lung perfusion scan (^{99m}Tc-labeled macroaggregated albumin) with contrast echocardiography in detecting intrapulmonary shunts. Therefore, different contrast agents used during echocardiography may have contributed to different prevalence data. In addition, they used indocyanine green dye solution, which provides microbubbles with different diameters, in contrast to saline solution in the present study, which creates microbubbles of 15–180-μm in diameter. Therefore, the prevalence may be affected by different contrast material used in echocardiography to detect IPVDs.

Krowka *et al.* [15] used indocyanine green dye solution, which provides microbubble diameters of up to 90 μm, whereas Vedrinne *et al.* [7] used a modified fluid gelatin solution, which creates microbubbles of 10±2-μm diameter. In addition, the prevalence may be affected by the route of contrast-enhanced echocardiography.

According to Vedrinne *et al.* [7], when the transesophageal approach was used, the prevalence of HPS increased by 19%. In addition, Aller *et al.* [17], who used the transesophageal approach, found an increase in prevalence of HPS by 6%. The usefulness of the transesophageal approach was limited because of the imposed risk as an invasive procedure in patients who had a history of variceal bleeding.

Therefore, variation in prevalence of HPS among studies can be attributed to various factors including patient criteria (e.g. etiology, severity, and duration of the underlying liver disease), cutoff value for PaO_2, contrast material used in echocardiography, and the route of contrast-enhanced echocardiography.

Dyspnea

In this study, according to the MMRC dyspnea scale, 30 (50%) patients of group 1 (n=60) were of grade I, 20 (33.33%) patients were of grade II, eight (13.33%) patients were of grade III, and two (3.33%) patients were of grade IV. In group 2 (n=22), four (18.18%) patients were of grade II, 11 (50%) patients were of grade III, and seven (31.82%) patients were of grade IV. In group 3 (n=5), two (40%) patients were of grade II and three (60%) patients were of grade III. This is in agreement with Alizadeh *et al.* [18] who found dyspnea in 100% of HPS patients and 25% of non-HPS patients with sensitivity and specificity of 100 and 75%, respectively. This study is also in agreement with Hira *et al.* [19], who found dyspnea in 100% of HPS patients and in 45% of non-HPS patients.

The most common symptom of PPHTN is dyspnea on exertion; the present study showed that 100% of patients with PPHTN had dyspnea. This is in agreement with Hoeper *et al.* [20], who found that almost all cases diagnosed as PPHTN were dyspneic.

In this study, there was a statistically highly significant correlation (P<0.001) between dyspnea grading and echocardiographic grading of shunt.

This is in agreement with Schenk *et al.* [14], who found that dyspnea was more often present in patients with 'clinically significant' HPS (57%) compared with 'subclinical HPS' (8%) and in patients without HPS (6%).

Orthodeoxia

Orthodeoxia is considered when there is a decrease in SaO_2 of more than 4% after change from the supine to the upright position [21].

In this study, 17 (77.27%) patients with orthodeoxia had HPS. Regarding arterial blood gases, the mean value of PaO_2 in group 1 was 92.54±8.54 mmHg in the supine position and 94.21±10.58 mmHg in the standing position. On the other hand, the mean value of PaO_2 in group 2 was 65.45±9.05 mmHg in the supine position and 59.3±8.11 mmHg in the standing position. In group 3, the mean value of PaO_2 was 87.85±7.55 mmHg in the supine position and 89.7±10.77 mmHg in the standing position. These results are in agreement with Alizadeh *et al.* [18], who found orthodeoxia in 66% of patients with HPS and in 0% of patients with no HPS. In addition, Krowka *et al.* [22] found orthodeoxia in 14 out of 16 (88%) patients with HPS.

However, these results are inconsistent with Younis *et al.* [23] and Lima *et al.* [24], where all patients with HPS developed orthodoxia, as well as with the study by Ferreira *et al.* [11], who found orthodeoxia in all HPS patients.

Although orthodeoxia is not pathognomonic of HPS, it strongly suggests this diagnosis in the setting of liver dysfunction.

As patients with advanced liver disease typically have a rapid respiratory rate that results in hypocapnia, the alveolar–arterial oxygen gradient $P(A–a)O_2$ (which incorporates the partial pressure of $CO_2$and the inspired O_2 concentration) is a more accurate clinical measure of impaired gas transfer.

Oxygenation

In the present study, we utilized the PaO_2 and $P(A–a)O_2$ gradients for detecting hypoxia using PaO_2 less than 70 mmHg and $P(A–a)O_2$ more than 15 mmHg as cutoff values. Therefore, in patients with HPS, three cases out of 22 (13.64%) had a $P(A–a)O_2$ gradient of 15–20 mmHg, nine cases out of 22 (40.91%) had a $P(A–a)O_2$ gradient of 20–30 mmHg, and 10 cases out of 22 (45.45%) had a $P(A–a)O_2$ gradient of more than 30 mmHg, with all cases having PaO_2 less than 70 mmHg.

In patients with PPHTN, two cases out of five (40.00%) had a $P(A–a)O_2$ gradient of 15–20 mmHg, one case out of five (20.00%) had a $P(A–a)O_2$ gradient of 20–30 mmHg, and two cases out of five (40.00%) had a $P(A–a)O_2$ gradient of more than 30 mmHg, with all cases having PaO_2 less than 70 mmHg. Therefore, the increase in the $P(A–a)O_2$ gradient may suggest HPS. This is in agreement with Schenk *et al.* [14], who stated that the prevalence of HPS increased with increased $P(A–a)O_2$ gradient.

This is also in agreement with Beatriz *et al.* [25], who studied the $P(A–a)O_2$ gradient (alveolar–arterial oxygen gradient) and also considered $PaCO_2$, which allows a more accurate assessment of abnormal arterial oxygenation. This was because the use of PaO_2 alone may underestimate the degree of hypoxemia, which may be masked by hyperventilation and hyperdynamic circulation that occurs in such patients.

The European Respiratory Society had proposed a classification system that uses PaO_2 to classify the severity of HPS. According to this system, HPS was considered very severe when PaO_2 was less than 50 mmHg, severe when PaO_2 was between 50 and 60 mmHg, moderate when PaO_2 was between 60 and70 mmHg, and mild when PaO_2 was 70 mmHg or more [26].

Accordingly, in this study, 17 out of 22 (77.27%) patients had very severe and severe HPS ($PaO_2<60$ mmHg), and 5 out of 22 (22.73%) patients had moderate HPS ($PaO_2=60–70$ mmHg).

Schenk *et al.* [14] recommended using various cutoff values for arterial oxygenation, which led to a wide variation in the prevalence of HPS in the same sample of cirrhotic patients. They also found that PaO_2 less than 65 mmHg could be used as a rough predictive value for HPS with accuracy up to 100%.

Echocardiography

Most studies investigating HPS had used TTCE for the detection of IPVDs and all reviews on HPS described TTCE as the method of choice for assessing IPVDs. Transthoracic echocardiography is available, noninvasive, easier, and cheaper compared with the transoesophageal technique [27].

TECE has a higher detection rate of intrapulmonary shunting than TTCE. However, given the higher expense, required procedure time, and complication rate associated with TECE, especially possible variceal bleeding, TTCE is more widely used as the primary diagnostic test [6].

In this study, in group 1, diastolic dysfunction was reported in 10 cases and positive contrast echocardiography (bubble test) was detected in five cases (subclinical HPS). In group 2, diastolic dysfunction was reported in six cases and positive contrast echocardiography (bubble test) in 22 cases (overt HPS), whereas in group 3 all cases had pulmonary hypertension.

All patients with positive contrast echocardiography (22 patients) had PaO_2 less than 70 mmHg and were qualified for the diagnosis of HPS, whereas patients with PaO_2 of 60–70 mmHg and having intrapulmonary vascular shunts proved by positive contrast echocardiography (five patients) constituted a group of patients having IPVD syndrome. This group may present a category of patients who need further assessment and future studies.

DE is relatively sensitive in detecting increased right ventricular systolic pressure as an estimate of PASP, as long as the pulmonary valve is normal [28].

DE is the current screening procedure of choice if PPHTN is suspected, but RHC is mandatory for the definitive diagnosis.

Transthoracic DE should be the screening test of choice for orthotopic liver transplantation candidates, as recommended by the Third World Symposium on Pulmonary Arterial Hypertension. Patients who are listed for orthotopic liver transplantation without evidence of PPHTN on initial evaluation should undergo echocardiography annually, and those with PPHTN may have to be followed-up more frequently, at least twice or three times every year [29].

Echocardiographic grading of hepatopulmonary syndrome

This study revealed that 27 cases had positive contrast echocardiography on bubble test, and among them three cases were of echocardiographic grade 1 (positive bubble test), five cases were of echocardiographic grade II (positive bubble test), seven cases were of echocardiographic grade III positive, and 12 cases were echocardiographic grade IV positive. Only 22 out of 27 cases correlate with criteria for HPS and five cases with positive contrast echocardiographic did not fulfill criteria of HPS and were diagnosed as subclinical HPS.

Bakir and Elshahed [30], reported that 31 out of 60 (51.67%) patients had positive contrast echocardiographic (bubble test). Twelve (20%) patients were of echocardiographic grade II (positive bubble test), seven (11.67%) patients were of echocardiographic grade III (positive bubble test), and 12 (20%) patients were of echocardiographic grade IV (positive bubble test). Sixteen (26.67%) patients showed clinical symptoms and met criteria for HPS, whereas 15 (25%) patients had positive echocardiographic findings without the clinical picture. They reported PaO_2 of 60 mmHg as the

best cutoff point of hypoxia in predicting HPS with sensitivity and specificity of 100 and 93.1%, respectively.

Pulmonary artery catheterization

Pulmonary artery catheterization was performed for all patients in group 3 (patients with PPHTN). The recorded parameters included PASP, mean PAP, pulmonary capillary wedge pressure, hepatic vein pressure gradient, and RAP. For the purpose of comparison and correlation, the echocardiographic findings of patients of group 3 (patients with PPHTN) were presented. The recorded parameters included estimated systolic pulmonary artery pressure, mean PAP, and inferior vena cava diameter.

There was a statistically significant difference (P=0.003) when comparing estimated PASP by echocardiography (86.00±18.16 mmHg) and measured PASP by pulmonary artery catheterization (78.00±16.04 mmHg).

When comparing mean PAP by echocardiography (59.00±15.57 mmHg) and mean PAP by pulmonary artery catheterization (51.00±8.94 mmHg), there was a difference, but it was not statistically significant (P=0.140).

In this study, there was a positive correlation between DE and pulmonary artery catheterization, but this correlation only had statistical significance in diagnosing PASP (r=0.995, P=0.000), but the mean PAP measured by DE was higher compared with pulmonary artery catheterization, but with no statistical significance (r=0.817, P=0.092).

There was a positive correlation between estimated PASP by echocardiography and measured PASP by pulmonary artery catheterization. Usually DE overestimates or underestimates directly measured PASP by more than 10 mmHg in about 50% of patients without pulmonary hypertension and by 30% if patients have pulmonary hypertension. As DE is a useful screening test but not for individual diagnosis of pulmonary hypertension, definitive diagnosis and follow-up of hemodynamic assessments should be performed with RHC. Many causes make echocardiography a less accurate diagnostic technique as it is operator dependent, and tricuspid regurge prevalence in patients with PASP more than 35 mmHg is 80% and increases to 95% in patients with PASP more than 50% [31]. Tricuspid regurge, a common finding in patients with pulmonary hypertension, decreases the gradient as blood passes to the atrium during systole and may result in underestimation of estimated pulmonary artery systolic pressure (EPASP).

Despite the unreliability of DE to accurately determine PASP, echocardiography remains a critically important tool to determine pulmonary hypertension (PHT) by providing an assessment of various indices of right ventricular size and function. Many causes of secondary PH can also be diagnosed by echocardiography, and therefore it is a complementary tool for RHC [31].

Conclusion

In conclusion, HPS and PPHTN are not uncommon in patients with hypoxemia and chronic hepatic disease, and detecting the presence of such disorders is essential, especially in patients who are listed for liver transplantation.

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Conflicts of interest

There are no conflicts of interest.

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