Hepatopulmonary Syndrome Evaluation in Egyptian Patients with Portal Hypertension and Hepatitis C Virus Cirrhosis

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Abstract: Background: Hepatopulmonary syndrome HPS was defined as a triad of portal hypertension with or without hepatic dysfunction, intrapulmonary vascular dilatation or shunting, and hypoxemia. HPS was known as an independent predictor of survival in end-stage liver disease patients after hepatic transplantation. Egypt ranked among the highest countries in prevalence and incidence of portal hypertension caused by bilharizial peri-portal fibrosis and/or post- hepatitis HCV induced liver cirrhosis, or both. The frequency of occurrence of HPS clinical and laboratory criteria showed wide variability in the different studies. Therefore detection of clinical and laboratory criteria of HPS in a sample of Egyptian patients was of utmost importance. Design and participants: In a cross-sectional comparative observational hospital based study sixty Egyptian patients with portal hypertension in comparison with age matched control group were subjected to: (1) History taking and physical examination to detect manifestations of portal hypertension, hepatopulmonary syndrome and liver cirrhosis. (2) Laboratory investigations including estimation of 1- liver functions including alanine aminotransferase [ALT], aspartate aminotrasferase [AST], alkaline phosphatase, serum albumin, total and direct bilirubin, and prothrombin time and concentration, and international normalized ratio [INR].2- chronic hepatitis viral markers: anti-hepatitis C virus antibodies, hepatitis B surface antigen, hepatitis B surface antibodies, and hepatitis B core antibodies. 3- HCV RNA- PCR qualitative assessment. (3) Arterial blood gases ABG determination in the recumbent and standing position. (4) Chest x-ray. (5) Abdominal ultrasound to detect splenomegaly, ascites, liver cirrhosis, or portal vein dilatation or abnormal flow. (6) Upper endoscopy UE to detect evidence of portal hypertension. (7) Upright trans-thoracic contrast enhanced echocardiography UTCEE to detect intrapulmonary right to left shunting. Objective of the current study was to determine the percentage of occurrence of HPS in a sample of Egyptian patients [with a mean age of 50 ± 4 years] with portal hypertension and HCV induced cirrhosis based on clinical, ultrasound, and laboratory findings, ABG abnormalities, UE and UTCEE. Results: In a total of 60 Egyptian patients with portal hypertension and HCV induced cirrhosis clinical and laboratory evidence of HPS was positive in 6 patients [10%]. All of them belonged to Child-Pugh C class with serum albumin level below 3 mg/dl and prothrombin concentration of less than 50%. Among clinical features dyspnea showed the maximum sensitivity (100%), followed by cyanosis (83.33 %), spider naevi (83.33 %) and palmer erythema (83.33 %), while platypnea (100 %) and clubbing (94.4 %) were the most specific. Partial pressure of oxygen PO2 was less than 70 mmHg in (100%) of HPS cases and was less than 60 mmHg in (50%) of them. Orthodeoxia was present in (66.66 %) of HPS versus (0 %) of non HPS patients with 66.66 % sensitivity and 100% specificity. All Child C patients, who were all HPS positive, showed oesophageal varices and congestive gastropathy, denoting severe portal hypertension. UTCEE was a useful non-invasive diagnostic tool for detection of trans-pulmonary abnormal blood shunting characteristic for HPS. Conclusion: The severity of HPS was clearly correlated with the degree of portal hypertension and liver dysfunction. Dyspnea had the maximum sensitivity followed by cyanosis, spider naevi and palmer erythema. Platypnea and clubbing were the most specific clinical features. Orthodeoxia strongly suggested the diagnosis of HPS with 100% specificity. Trans-thoracic contrast enhanced echocardiography in the upright position was a safe, useful semi-quantitative bed-side tool for assessment of shunting evidence to select cases for further quantitative lung scintigraphy based evaluation.
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Key Words: portal hypertension, liver cirrhosis, hepatopulmonary syndrome, upright trans-thoracic contrast-enhanced echocardiography, hypoxia, dyspnea, platypnea, clubbing, orthodeoxia.

1. Introduction:

Cirrhotic or non-cirrhotic portal hypertension may be associated with arterial hypoxemia caused by pulmonary vascular changes referred to as hepatopulmonary syndrome HPS [1, 2]. This arterial hypoxemia may be due to one or more of the following pathologic mechanisms pre-capillary dilatation, capillary dilatation, or arterio-venous communication [3, 4]. Either due to ventilation perfusion mismatch or due to anatomic shunts bypassing the gas exchange units, these patients have a wide range of presentation ranging from

asymptomatic increase in alveolo-arterial oxygen pressure difference(P[A-a]O2) to severe breathlessness due to hypoxia detected by arterial blood gases [ABG]. Worsening of dyspnea in standing position compared to supine position [platypnea] with associated deterioration of hypoxia [orthodeoxia] may be explained by reduced cardiac output in standing position as well as increased perfusion of middle and lower lung zones by gravitational effects due to associated predilection of arteriovenous shunts to these zones[5,6].

Egypt has the highest countrywide prevalence of hepatitis C virus infection in the world [7]. The majority of cases develop chronic hepatitis that is usually asymptomatic for years. Twenty percent of those with HCV caused chronic hepatitis progress to cirrhosis and a proportion of these die as a result of liver cirrhosis complications [8]. Liver transplantation is a treatment option for end stage liver cirrhosis. HPS with obvious hypoxia was found to be an independent predictor of survival after liver transplantation [9, 10]. Our objectives in the current study were to assess a sample of Egyptian patients with portal hypertension and HCV induced cirrhosis for the percentage of occurrence of HPS clinical and laboratory features in correlation with their Child Pugh classification to determine their prognosis after transplantation. Using a bed side diagnostic UTCEE to screen those patients was suggested to be better than exposing all patients to radio-isotopic lung scanning [11].

2. Participants and Methods:

After informed consents 60 portal hypertension and HCV induced cirrhosis Egyptian patients with a mean age of 50± 4 years and 20 age matched control subjects participated in this observational comparative cross-sectional hospital based study. Patients and control group were subjected to:

- *Medical history taking and physical examination* with special attention to evidence of portal hypertension, Child Pugh classification, and clinical features suggested being HPS related. Excluded from the current study were those who suffer from cardiopulmonary diseases that may overlap in their symptoms or laboratory data with HPS.
- *Liver function tests and liver enzymes were determined:* Alanine aminotransferase(ALT), aspartate aminotransferase(AST), alkaline phosphatase, serum albumin ,total bilirubin, direct bilirubin , prothrombin time, concentration and INR.
- *Chronic hepatitis viral markers were assessed:* anti-hepatitis C virus antibodies HCV Ab, hepatitis B surface antigen HBsAg, hepatitis B surface antibodies HBsAb, and hepatitis B core antibodies HBcore Ab.
- *Qualitative HCV RNA-PCR was done for all cases.*
- *Child Pugh classification for liver disease severity assessment was used:* One to three points were given for each of the following items from least to worst affection: 1-history of encephalopathy, 2-detection of ascites clinically or by ultrasound, 3-serum bilirubin, 4-serum albumin, 5-prothrombin time, concentration, and international normalized ratio INR.
    - Child A: till 7
    - Child B: 8- 10
    - Child C: > 10
- *Arterial blood gases [ABG]*: Samples were obtained by radial arterial puncture in recumbent position to determine PO2, PCO2, and pH, and after standing for 20 minutes to detect orthodeoxia.
- *Chest x-ray* was performed complementary to clinical data to exclude those with any cardiac or pulmonary abnormalities.
- *Abdominal ultrasound was done.*
- *Upper endoscopy was done:* The presence of oesophageal varices and congestive gastropathy confirmed portal hypertension.
- *Contrast-enhanced Trans-thoracic Echocardiography CEE in the upright position UTCEE:* 10 ml of hand agitated normal saline were injected in an upper limb peripheral vein with the patient in the upright position. Positivity was defined as late opacification of the left cardiac chambers after more than five cardiac cycles following appearance of microbubbles in the right side of the heart. This finding suggested passage of these microbubbles through dilated pre-capillary or capillary pulmonary vessels or pulmonary arteriovenous shunts. Those with CEE evidence of inter-atrial shunts [early opacification of the left side before five cardiac cycles], valvular heart disease, dilated right side of the heart, or pulmonary hypertension were excluded.
- *HPS was suggested in patients with evidence of portal hypertension, with hypoxia [with a recumbent PO2 cutoff level of 80 mmHg in an arterial blood sample], and positive UTCEE.*

Statistical Analysis:

Clinical data were presented in a descriptive manner. Numerical laboratory data were presented as mean ± standard deviation. Sensitivity, specificity, and frequency of occurrence of clinical, imaging, and laboratory features were evaluated. One way analysis

of variance [ANOVA] was used to compare patients' groups and control group. P-value < 0.05 was considered statistically significant.

3. Result*s*

Sixty portal hypertension cirrhotic patients were included in this study. Their age ranged from 35 to 60 years, 24 male and 36 female patients. Portal hypertension was proved by physical examination, upper endoscopy, and abdominal ultrasound. According to Child-Pugh classification patients were subdivided into 3 groups:

- Child Pugh A: 10 patients with mean age (39±3), 4 males and 6 females.
- Child Pugh B: 15 patients with mean age(45±7), 6 males and 9 females.
- Child Pugh C: 35 patients with mean age (51±6), 14 males and 21 females.

20 sex and age matched healthy subjects were taken as a control group.

Table (1) showed that in Child-Pugh A group dyspnea was present in 1 patient (10%), spider naevi in 1 patient (10%), palmer erythema in 1 patient (10%), collaterals in 1 patient (10%); while platypnea, clubbing and cyanosis were not present in any patient. In Child-Pugh B group dyspnea, clubbing, cyanosis, spider naevi, palmer erythema and subcutaneous collaterals were present in 3 (20%), 1 (6.66%), 2 (13.3%), 3 (20%), 3 (20%), 1 (6.66%) of patients respectively, while platypnea was not present in any patient (0%). In Child-Pugh C group dyspnea, platypnea, clubbing, cyanosis, spider naevi, palmer erythema and subcutaneous collaterals were present in 14 (40%), 2 (5.71%), 6 (17.1%), 9 (25.7%), 15 (42.9%), 16 (45.7%), 11 (31.4%) of patients; respectively.

Palmer erythema was the most common finding among all cirrhotic patients. It was detected in 20 cases, who represented 33.3 % of cirrhotic patients. It was found in five cases out of the six HPS cases, so represented 83.3 % of HPS patients.

Spider naevi were the next common clinical finding among all cirrhotic patients (31.66 %) with incidence of 83.3 % in HPS cases. Dyspnea was found in 30 % of all cirrhotic patients. It was evident in (100%) of HPS cases, with a sensitivity of 100%.

In our study 6 patients met the suggested diagnostic criteria for HPS, while 54 patients had no evidence of HPS.

Table (2) showed that among patients who met the suggested criteria of HPS, dyspnea was present in 6 patients (100%), platypnea in 2 patients (33.33%), clubbing in 4 patients (66.66%), cyanosis in 5 patients (83.33%), spider naevi in 5 patients (83.33%), palmer erythema in 5 patients (83.33%), and subcutaneous collaterals were present in 1 patient (16.66%). However, in patients who had no evidence of HPS dyspnea was present in 12 patients(22.22%), platypnea was not present in any patient(0%) clubbing was present in 3 patients(5.55%), cyanosis in 6 patients(11.11%), spider naevi in 14 patients (25.9%), palmer erythema in 15 patients(27.77%), and subcutaneous collaterals were present in 12 patients(22.22%).

Table (3) showed that dyspnea had a sensitivity and a specificity of 100%, and 77.78% respectively with p-value < 0.0001 (i.e. highly significant statistical difference). Platypnea had a sensitivity and specificity of 33.33%, and 100%, respectively with p-value < 0.0001. Clubbing had sensitivity and a specificity of 66.66%, and 94.4% respectively with p-value < 0.001. Cyanosis had sensitivity and a specificity of 83.33%, and 88.88% respectively with p-value < 0.0001. Spider naevi had sensitivity and a specificity of 83.33%, and 74.07%, respectively [p-value < 0.05]. Palmer erythema had sensitivity and a specificity of 83.33%, and 72.23% respectively [p-value < 0.05]. Subcutaneous collaterals had sensitivity and a specificity of 16.66%, and 77.78%, respectively [p-value > 0.05 (i.e. no significant statistical difference)].

Dyspnea had the highest sensitivity (100%) in HPS cases followed by cyanosis (83.33 %), spider naevi (83.33 %) and palmer erythema(83.33%).

Dyspnea (100 %), platypnea (100 %), and clubbing (94.4 %) were the most specific clinical features, respectively.

Table (4) showed that PO_2 in the supine position was 59.83 mmHg ±3.488 in HPS patients compared to 81.35 mmHg ± 9.853 in non HPS patients with highly significant statistical difference [p-value < 0.001]. Also PO_2 in the standing position was 55.166 mmHg ± 5.382 in HPS patients compared to 82.56 mm Hg ± 9.484 in non HPS patients [p-value < 0.001].

Table (5) showed that patients belonging to Child Pugh A and B groups had recumbent PO2 values exceeding 70 mmHg without significant decline in the standing position i.e. no orthodeoxia. On the other hand out of 35 patients belonging to Child Pugh C group five patients (14%) had recumbent P02 readings between 60 and 70 mmHg without significant decline after standing, and four patients (11%) showed readings below 60 mmHg in the recumbent position with significant decline after standing i.e. orthodeoxia.

Table (6) showed that 3 out of 6 HPS patients (50%) had recumbent PO2 readings between 60 and 70 mmHg and another 3 (50%) had recumbent PO2 readings below 60 mmHg. The later 3 patients [PO2 <60 mmHg] plus one from the former group [PO2

between 60 and 70 mmHg] representing together 66.66% out of HPS patients showed orthodeoxia after standing.

Table 7 showed that all cases who belonged to Child Pugh A class had cords of grade I to II oesophageal varices, but nor had fundal varices or congestive gastropathy. In Child Pugh B class upper endoscopy revealed grade II oesophageal varices in 7 patients, and grade III in 17 patients. Fundal varices were found in 2 patients and congestive gastropathy in 7 patients. All cases positive for HPS manifestations belonged to Child Pugh group C, who showed grade II oesophageal varices in 7 patients, grade III in 17, and grade IV in 9 patients by upper endoscopy. From these fundal varices were detected in 6 and congestive gastropathy in all 26 cases; respectively.

As shown by table 8 UTCEE study was positive in 6 out of 60 cirrhotic patients (10%). All CEE positive patients belonged to Child Pugh C group only. All patients with positive CEE had recumbent PO_2 readings below 70 mmHg.

Table (1): The number and the percentage of HPS related symptoms and signs in the three groups of patients:

	Dyspnea	Platypnea	Clubbing	Cyanosis	Spiders	Palmer erythema	Collaterals
Child Pugh A	1(10%)	0(0%)	0(0%)	0(0%)	1(10%)	1(10%)	1(10%)
Child Pugh B	3(20%)	0(0%)	1(6.66%)	2(13.3%)	3(20%)	3(20%)	1(6.66%)
Child Pugh C	14(40%)	2(5.71%)	6(17.1%)	9(25.7%)	15(42.9%)	16(45.7%)	11(31.4%)
Control	_	_	_	_	_	_	_

Table (2): Characteristics and diagnostic values of signs and symptoms suggestive of hepatopulmonary syndrome

	Dyspnea	Platypnea	Clubbing	Cyanosis	Spider naevi	Palmer erythema	Collaterals
Cases HPS	6	2	4	5	5	5	1
Non HPS Cases	12	0	3	6	14	15	12
	100%	33.33%	66.66%	83.33%	83.33%	83.33%	16.66%
% HPS	22.22%	0%	5.55%	11.11%	25.9%	27.77%	22.22%

Table (3): Comparison between symptoms and signs related to HPS as regards their frequency, sensitivity, and specificity.

Symptoms and signs	Frequency in HPS (%)		Sensitivity (%)	Specificity (%)	P-value
	Pos	Neg			
Dyspnea	100	22.22	100	77.78	< 0.0001
Platypnea	33.33	0	33.33	100	<0.0001
Clubbing	66.66	5.55	66.66	94.4	< 0.001
Cyanosis	83.33	11.11	83.33	88.88	< 0.0001
Spider naevi	83.33	25.92	83.33	74.07	< 0.05
Palmer erythema	83.33	27.77	83.33	72.23	< 0.05
Subcutaneous Collaterals	16.66	22.22	16.66	77.78	>0.05

Table (4): PO_2 in the recumbent and standing positions in HPS and non HPS patients:

	HPS [n = 6]	Non HPS [n = 54]	p-value
PO_2 [recumbent] in mmHg	59.83 ± 3.488	81.35 ± 9.853	< 0.001
PO_2 [standing] in mmHg	55.166 ± 5.382	82.56 ± 9.484	<0.001

Table (5): Distribution of PO_2 values in the patients' groups and control subjects:

_	PO_2>70 mmHg	60<PO_2<70 mmHg	PO_2<60 mmHg	Orthodeoxia
Child Pugh A	10	0	0	0
Child Pugh B	15	0	0	0
Child Pugh C	26	5	4	4
Control	20	0	0	0
Total	71	5	4	4

Table (6): Distribution of PO_2 values within HPS and non HPS cases:

	PO_2>70	60<PO_2<70	PO_2<60	orthodeoxia
HPS	0(0%)	3(50%)	3(50%)	4(66.66%)
Non HPS	51(94%)	2(4%)	1(2%)	0(0%)
Total	51	5	4	4

Table (7): Upper Endoscopy data of studied cases: *OV: oesophageal varices;* FV: fundal varices

	Upper endoscopy		
Child Pugh A	*OV* *10 grade I and II*	*FV* *1*	*Congestive Gastropathy* *0*
Child Pugh B	*OV* *6 grade I and II*	*FV*	*Congestive Gastropathy*
	7 grade III	*2*	*7*
Child Pugh C	*OV* *7 grade II*	*FV*	*Congestive Gastropathy*
	17 grade III	*6*	*26*
	9 grade IV		
Control group	*0*	*0*	*0*

Table (8): Upright Trans-thoracic Contrast-enhanced Echocardiography [UTCEE] findings in HPS and non HPS cases:

	UTCEE positive	UTCEE negative
HPS	6	0
Non HPS	0	54
Total	6	54

4. Discussion:

Hepatopulmonary syndrome HPS was defined as a triad of portal hypertension with or without hepatic dysfunction [12], intrapulmonary vascular dilatation or shunting, and hypoxemia [13].

Bilharzial periportal fibrosis of the liver was one of the oldest parasitic infections in Egypt [14]. Serological and epidemiological studies showed a high prevalence and incidence of HCV among families from Egyptian areas known previously to be endemic for schistosomiasis. Co-infection with schistosomiasis and HCV was found to cause more severe disease due to resultant imbalance in HCV-specific T-cell responses leading to increased viral load, chronicity, and faster progression of complication and end stage liver disease [15]. Therefore Egypt was considered to have the highest countrywide prevalence of hepatitis C virus in the world nowadays [7]. Twenty percent of those with HCV caused chronic hepatitis progressed to cirrhosis [8]. HPS was an independent predictor of mortality and morbidity after hepatic transplantation [10]. Therefore studying the frequency of clinical features of HPS among Egyptian patients with portal hypertension and/or liver cirrhosis was suggested to be of utmost importance, especially when we found a wide variability of prevalence of HPS among end-stage liver disease patients in relation to etiological, racial and geographical factors [16].

In our study we suggested HPS in patients with evidence of portal hypertension, hypoxia and positive UTCEE showing delayed right to left shunting. Portal hypertension was detected by physical examination or ultrasound evidence of splenomegaly, ascites, shrunken cirrhotic liver and portal vein dilatation ± abnormal portal hepatofugal flow. Upper endoscopy was used for detection of oesophageal and/or fundal varices and congestive gastropathy. Hypoxemia was defined by a recumbent PO2 cutoff level of 80 mmHg in an arterial blood sample to pick up these patients for further evaluation by UTCEE.

This arterial PO2 cutoff level was suggested by previous researchers [17], who found that patients with PO2 of more than 80mmHg were unlikely to have HPS. Others defined hypoxia by arterial recumbent PO2 level of less than 70 mmHg [13]. A PO2 value of > 80 mmHg was considered mild, <80 and ≥ 60 mmHg moderate, <60 and ≥ 50 mmHg severe, and < 50 mmHg very severe HPS by other researchers [21]. Hypoxemia in HPS was explained by intrapulmonary dilatation or shunting through direct arterio-venous communications [24]. As vascular abnormalities were suggested to predominate in the middle and lower lung fields, gravitational effect was expected to increase the blood flow to worsen the ventilation-perfusion mismatch and finally resulted in deterioration of arterial oxygenation when the upright position was attained by the patient (orthodeoxia), hence

worsening of dyspnea in the upright position (platypnea) [25]. The intrapulmonary vascular dilatation or shunting was confirmed by different tools in the various studies interested in this syndrome as Technetium 99m macro-aggregated albumin lung scintigraphy [26], pulmonary angiography [27], and contrast enhanced trans-thoracic echocardiography CEE [28].

In the current study, among the 60 Egyptian patients with portal hypertension and HCV induced cirrhosis, 6 patients (10 %) met the clinical, laboratory and radiological criteria of HPS. This agreed in prevalence with previous studies [28, 33]. However HPS showed a wide variability in prevalence in the different studies, ranging from 4 to 47% among cirrhotic patients [34], depending on the diagnostic criteria and the cutoff levels used for hypoxia. Moreover etiological, racial and geographical factors were suggested to explain this variability by some investigators [16].

All our HPS patients belonged to Child-Pugh C group classification, which suggested a correlation between the severity of liver affection and possibility of development of HPS. This agreed with other studies [35]. It was explained by increased release of endothelin-1 and tumor necrosis factor alpha [TNF-α] together with increased vascular shear stress with high levels of nitric oxide [18, 36], and carbon monoxide secondary to liver injury and/or portal hypertension. These mediators resulted in intrapulmonary pre-capillary or capillary vasodilatation considered the main pathogenic mechanism of HPS [34, 36]. As all this cascade was dependent on liver injury, it was suggested to be positively correlated with the degree of liver function deterioration as assessed by Child Pugh classification. On the contrary other studies [13, 37, 38] showed that Child Pugh grade didn't influence the prevalence of intrapulmonary vascular dilatation or HPS among cirrhosis patients.

In our study dyspnea was the most prevalent clinical feature in HPS patients. It was present in 100% of HPS patients. This agreed with other investigators [13, 35]. However ascites by elevating the diaphragm and impairing the ventilation/perfusion match might lead to mild hypoxemia and dyspnea in cirrhotic patients without HPS [35].

In our study platypnea was the most specific clinical feature. These results were closely similar to other investigators [35]. Platypnea and orthodeoxia were explained in HPS by the preferential circulation to the basal areas of the lungs in the upright position, as these areas were assumed to be more affected by intrapulmonary dilatation and/or shunting [39]. However in our study just two out of four HPS patients with orthodeoxia had platypnea, suggesting that these two conditions did not necessarily go together. Gomez and co-investigators [25] found that HPS patients with orthodeoxia had lower cardiac output in both supine and standing positions in comparison to HPS patients without orthodeoxia [25]. Attaining the upright position was associated with increased minute ventilation with deterioration of ventilation perfusion [V/Q] in orthodeoxia group versus improvement of V/Q in non-orthodeoxia group in their study due to altered pulmonary vascular tone [25]. Platypnea on the other hand is a symptom i.e. more subjective, as dyspnea may be perceived by the HPS patient without special attention to worsening of the condition while standing.

In our study dyspnea (100 %) , platypnea (100 %), clubbing (94.4 %), and spider naevi (74%) were the most specific clinical features; respectively. This is closely similar to Alizadeh et al [35]. It was also in agreement with Anand et al [41] and Varghese et al [36] who detected that patients with HPS had significantly higher incidence of dyspnea, platypnea, clubbing and spider naevi.

Moreover cyanosis showed in the current study high sensitivity and specificity. This was consistent with previous researchers [13, 16, 35]. Lee and co-workers [16] concluded that only cyanosis could reliably distinguish between shunt positive and shunt negative patients.

Spider naevi showed high sensitivity and specificity. This agreed with Hira and co-workers [13], who concluded that the presence of spider naevi was significantly correlated with intra-pulmonary vascular dilatation. In agreement with Alizadeh et al [35] our study showed a significant specificity of subcutaneous collaterals in relation to HPS.

Dyspnea had the highest sensitivity (100%) in HPS cases followed by cyanosis (83.33%), spider naevi (83.33 %) and palmar erythema (83.33 %). On the other hand platypnea had the highest specificity (100%) in HPS cases followed by clubbing (94.4 %), and cyanosis (88.88 %). These results were similar to Alizadeh and co-workers [35].

In our study all HPS patients had albumin level below 3 and PC less than 50% suggesting that HPS development was related to liver synthetic dysfunction. This agreed with Alizadeh et al [35], but disagreed with Kim et al [42].

In our study recumbent PO_2 was less than 70 mmHg in 100% of HPS patients versus 3.7% of non HPS patients. It was less than 60 mmHg in 50% of HPS patients versus 1.9% of non HPS patients. These results were closely similar to Alizadeh et al [35] and Krowka et al [12]. Moreover in their research on HPS patients Pastor and Schiffer [17] recommended that

patients with PO2 between 50-60 mmHg should have the priority for orthotropic liver transplantation. On the other hand 3 months follow up was their recommendation for those with PO2 levels between 60-80 mmHg for early detection of deterioration. PO2 of less than 50 mmHg might preclude liver transplantation [17].

In the current study there was a highly significant statistical difference in PO_2 both in recumbent and standing positions between HPS and non-HPS patients. These results were similar to Hira et al [13]. Orthodeoxia was defined by some authors as PO2 reduction by 5% in the standing position as compared to recumbence [25]. Nevertheless the pathophysiology of orthodeoxia in HPS patients was not fully understood [21, 40]. High progesterone level was suggested as an explanation by some authors [30]. We found orthodeoxia in HPS patients with 66.66% sensitivity and 100% specificity. This agreed with Alizadeh et al [35], Hira et al [13], as well as Wang and Lin [30] who considered orthodeoxia a suggestive indicator of HPS.

In our study all patients with positive UTCEE had arterial $PO_2 < 70$ mmHg and were qualified for the diagnosis of HPS. Among investigators who used CEE for diagnosis of pulmonary shunting some used it in the recumbent and other used it in the upright position. The later method, which was used in our study, was proved by previous investigators to be more yielding as regards diagnosis of HPS than that performed to patients in the recumbent position [32]. They explained this finding similar to platypnea and orthodeoxia, by gravitational effect of the upright position in shifting blood to areas of pulmonary vascular dilatation and/or shunting in HPS. CEE was proved by previous investigators to be useful sensitive and specific screening test for HPS even in early stages of liver dysfunction even in whom the lung scintigraphy was still negative [30,31]. On the other hand no patient had positive lung scintigraphy and negative CEE results [29]. The only privilege of lung scintigraphy over CEE was quantitation of the degree of shunting in relation to cardiac output [31, 32]. Some authors suggested transoesophageal CEE as a goldstandard [44, 45]. However others claimed that transthoracic CEE was as accurate as transoesophageal CEE in determining the presence of right to left shunt. Proper timing of left atrial opacification by microbubbles during the cardiac cycle was considered a distinguishing step in the transthoracic CEE between intracardiac and intrapulmonary shunting by Viles-Gonzalez and Rodriguez-Roisin [47]. Only in rare cases when timing of microbubbles was not clear cut, visualization of the microbubbles traveling through the pulmonary veins using transoesophageal CEE was suggested by both authors [47].

Study Limitations:

In the current study we didn't confirm liver cirrhosis by biopsy. This was not necessary as HPS was described in portal hypertension patients without or with cirrhosis. Portal hypertension was suggested by other investigators [2, 38, 42] as the determining factor for HPS.

Conclusions and recommendations:

The occurrence of HPS among Egyptian patients suffering from portal hypertension and liver cirrhosis was not uncommon. Diagnostic criteria were found in 10% of our studied sample in a small hospital based study. This suggested a mandatory wider scale research of cases with HPS especially after availability of liver transplantation as a treatment option for end stage liver disease Egyptian patients. Severity of HPS correlated with liver synthetic dysfunction evidenced by its positive correlation with Child Pugh class of the patients. Dyspnea had the maximum sensitivity followed by cyanosis, spider naevi and palmer erythema. Platypnea and clubbing were the most specific clinical features. So detection of these clinical manifestations mandated further evaluation of any portal hypertension patient by other investigations to confirm diagnosis of HPS. Arterial blood gases evaluation in the recumbent followed by re-sampling in the upright position should be the next step, as orthodeoxia in the current study strongly suggested the diagnosis of HPS with 100% specificity. Imaging confirmation of transpulmonary right to left shunting using upright trans-thoracic CEE was proved by our study to be an accurate, safe, and useful semi-quantitative bed-side tool for assessment of shunting evidence to select cases for further quantitative lung scintigraphy based evaluation.

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