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11

Prevalence of Hepatopulmonary Syndrome in Cirrhotic Patients without Intrinsic Cardiopulmonary Disease

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ABSTRACT

Background: The hepatopulmonary syndrome (HPS) is defined as the triad of liver disease, hypoxemia or increased Alveolar-arterial oxygen gradient, and intrapulmonary vasodilatation. The presence of HPS independently worsens prognosis of patients with cirrhosis. Mortality of cirrhotic patients with HPS is higher than cirrhosis without HPS.

Objective: To determine the prevalence of HPS in cirrhotic patients that has still not been reported in Thailand.

Patients and Methods: One hundred and fifty cirrhotic patients (103 males, 47 females) were enrolled in this study .These patients underwent history taking, physical examination, laboratory data, pulse oximetry (upright position) chest radiograph, imaging study, arterial blood gas analysis, pulmonary function test and transthoracic contrast echocardrogram. Diagnosis of HPS will be fulfilled and established with : 1) The presence of chronic liver disease. 2) Hypoxemia PaO_2 (70 mmHg or an upper limit-widened age-corrected alveolar-arterial gradient greater than normal. 3) Intrapulmonary vascular dilatation, detected by transthoracic contrast echocardiography, and 4) absence of intrinsic cardiopulmonary disesse.

Results: Total numbers of the 150 consecutive cirrhotic patients were enrolled. Only three cases were compatible with HPS. These 3 cases were distributed in all Child -Pugh classification. There was no significant difference in history, physical examination, laboratory tests to determine the predictor of HPS presentation.

Conclusion: In our study, prevalence of HPS in cirrhotic patients without intrinsic cardiopulmonary disease is 2 percent.

Key words : Hepatopulmonary syndrome, HPS, cirrhosis

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BACKGROUND

Pulmonary manifestations of liver disease are pulmonary hypertension, acute lung injury, restrictive , obstructive pulmonary disease, interstitial fibrosis, pleural effusion, and various impairments of pulmonary gas exchange. Hepatopulmonary syndrome is the one of the major important entity. Clinical manifestations of Hepatopulmonary syndrome (HPS) are progressive dyspnea, orthodeoxia, platypnea, cyanosis, and with clubbing of finger in long standing of chronic liver disease[1].

HPS is defined as the triad of liver disease, impaired arterial oxygenation and widespread pulmonary vascular dilatation[2,3]. The hallmarks of pulmonary vascular changes in HPS are both direct arteriovenous communications and dilated vessels of precapillary and capillary level[2]. The results of the inability of oxygen to diffuse to the center of these abnormal dilated vessels and couple with hemoglobin are an apparent right-to-left intrapulmonary shunt..

Although, both acute and chronic liver disease can be associated with HPS, but in cirrhosis, it is more common. The mortality in cirrhotic patients with HPS is high. In retrospective analysis[4], the mortality rate was 41% over 2.5 year in 22 patients with HPS. In one prospective study, the mortality was significantly higher (median survival, 10.6 months) when compared with patients without HPS (40.8 months, $p < 0.05$) . In multivariate analysis, HPS was an independent predictor of survival[5]. In the literature, the prevalence of HPS varies between 4% and 32% in cirrhotic patients[6-13]. The objective of this study is to determine the prevalence of HPS in cirrhotic patients without intrinsic cardiopulmonary disease. Which data is not available in Thailand.

PATIENTS AND METHODS

Consecutive patients with cirrhosis due to any cause attending the liver clinic of Bhumibol Adulyadej Hospital were included in the study. All cases will be screened by history taking, physical examination, especially cutaneous signs of chronic liver disease, blood test, imaging study and liver histology in some cases. The cases were enrolled between March 2005 and November 2005.

All subjects underwent history taking, physical examination, and pulse oxymeter measurement in upright position with room air. Blood chemistry and laboratory data are complete blood count (CBC), liver test (albumin, globulin, aminotransferase, total bilirubin and direct bilirubin), prothrombin time, INR, fasting blood sugar, blood urea nitrogen (BUN) and serum creatinine. Exclusion of intrinsic pulmonary disease is whether abnormal pulmonary function test or abnormal chest radiograph was found except the presence of minimal basilar interstitial infiltration and minimal effusion with ascitis, which could be found in HPS[17]. Ultrasonogram, CT scan, or MRI of the abdomen may be indicated in some patients to evaluate the liver morphology. Esophagogastroduodenoscopy was done to evaluate portal hypertension. Description of esophageal varices is classified by the Italian Liver Cirrhosis Project (ILCP) group. Gastric varices, and portal hypertensive gastropathy are classified by the New Italian Endoscopic (NIEC)[15]. Child-Pugh scores were defined and calculated in all patients. The one with pulse oxymeter measured below or equal 97% oxygen saturation in upright position with room air will have arterial blood gas analysis. Pulmonary function test (PFT) will be done if PaO_2 is less than 70 mmHg or an upper limit-widened age corrected alveolar-arterial gradient greater than normal [10 + 0.43 (age in years)] to rule out the intrinsic pulmonary disease[16]. Patients with normal PFT will be interviewed and ruled out intrinsic cardiovascular disease with contrast echocardiograph by cardiologist. Cirrhotic patients with severe hepatic encephlopathy, unable to co-operate or status intubation are excluded from this study. Diagnosis of HPS was established with:1) The presence of cirrhosis in all causes. 2) Hypoxemia results from a partial pressure of oxygen below or equal 70 mmHg or an upper limit widened age corrected alveolar arterial gradient greater than normal. 3) Intrapulmonary vascular dilatation, detected by transthoracic two dimension contrast echocardiography. 4) Absence of intrinsic cardiopulmonary disease, according to history, electrocardiogram, echocardiography, chest radiography (normal results or basilar increased interstitral markings,minimal pleural effusion are typical for HPS[17]. [and lung function test (forced expiratory volume at the first second (FEV1)] or total lung capacity >66% predicted[6,18].

Methods

1. **Pulse Oximetry**

   Pulse oxymeter is a noninvasive modality that

indirectly measures oxygen saturation and provides a screening test for hypoxemia. Oxygen saturation less than the level of 97% in upright position provided a sensitivity of 96% and specificity of 76% in detection of mild hypoxemia (PO_2 <70 mmHg)[16]. Instruments of hypoxemia screening test are oxygen saturation measurement with pulse oxymeter (Hanaulife® pulsoximeter that calibrated every 6 months)

2. Arterial Blood Gas Analysis

Arterial blood gas samples were obtained by percutaneous radial artery puncture in sitting position with room air breathing, and were analyzed with a standard blood gas analyzer (Osmetech OPTI™ CCA Blood Gas Analyzer). A-aDO_2 was calculated by using the alveolar gas equation.

3. Contrast Echocardiography

Two-dimensional transthoracic contrast echocardiography is the best technique used to detect intrapulmonary vasodilatation. Typically, agitated saline, which creates micro bubbles visible on echocardiography, was used as a contrast agent. A positive test for intrapulmonary vasodilation occurred when delayed visualization of intravenously administered microbubbles were observed in the left cardiac chamber after the third heart beat post injection as illustrated in Figure 1, 2 and 3[8,9]. Immediate visualization of the injected contrast in left cardiac chamber before the third heart beat indicates intracardiac shunting.

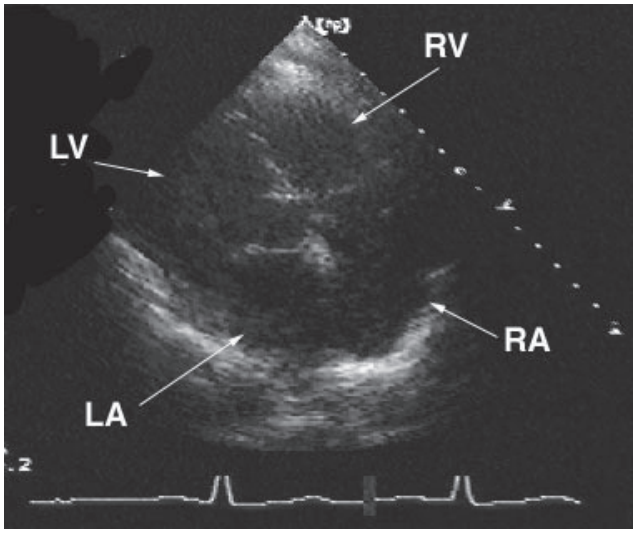

Figure 1 Four chamber view of the Echocardiogram showed normal chamber size and good function. Chambers are labeled in the lower picture and orientation is the same in subsequent images.

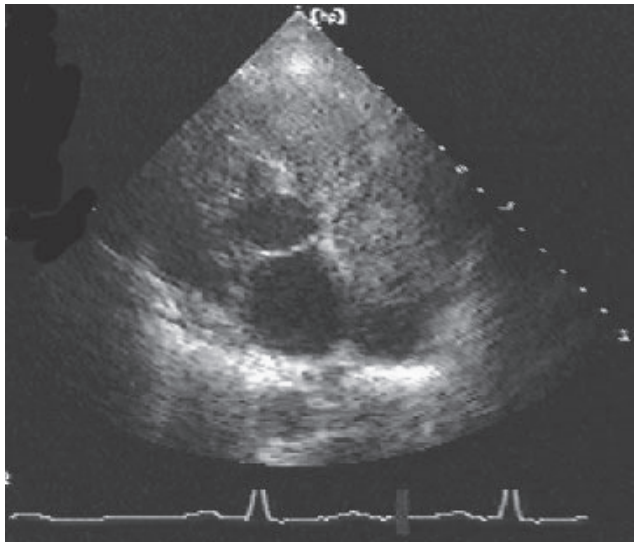

Figure 2 Right atrium and right ventricle are filled with air bubbles (bright white speckled pattern) immediately after intravenous injection of frothy saline.

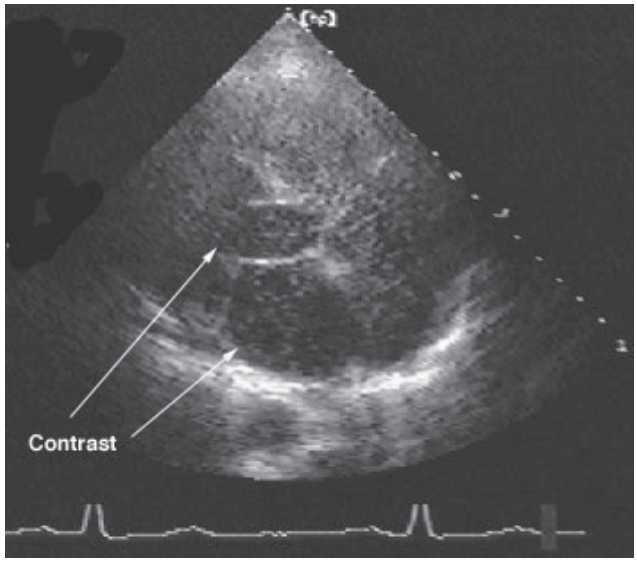

Figure 3 After 3 heart beats air contrast appears in the left atrium and left ventricle as bright speckles.

4. Pulmonary Function Test

Vital capacity and FEV1 were obtained by a computerized spirometer (Vmax Series 22, Sensor Medics corporation. Made in U.S.A.), according to standard procedures and reported with reference to standard predicted percentages[19].

Data Analysis

Data were analyzed, using SPSS version 11.0 soft

ware programs, and expressed as percentage, mean values and standard deviation.

RESULTS

Of the 150 from 162 cirrhotic patients with eligibility criteria were enrolled , 103 patients (68.7%) were men and 47 patients (31.3%) were women. The causes of cirrhosis were alcohol related in about 89 patients (59.3%), hepatitis B virus infection in 42 (28%), hepatitis C virus in 23(15.3%), autoimmune hepatitis in 6 (4%) , and cryptogenic cirrhosis in 16 (10.7%) as shown in Table 1,2.

The most common co-morbid diseases of cirrhotic patients were diabetes mellitus in 42 (28.0%), hypertension in 20 (13.3%), which also found in every grade

Table 1 Sex and cirrhotic Child -Pugh classification.

Child Turcotte-Pugh class	Grade A		Grade B		Grade C		Total	
Sex	n	%	n	%	n	%	n	%
Male	69	46.0	22	14.7	12	8.0	103	68.7
Female	28	18.6	16	10.7	3	2.0	47	31.3

Table 2 Etiology of cirrhosis

Child Turcotte-Pugh class	Grade A		Grade B		Grade C		Total	
Etiology	n	%	n	%	n	%	n	%
Alcohol	55	56.7	23	60.5	11	73.3	89	59.3
Hepatitis B virus	31	32.0	7	18.4	4	26.7	42	28.0
Hepatitis C virus	17	17.5	5	13.2	1	6.7	23	15.3
Autoimmune hepatitis	4	4.1	2	5.3	0	0	6	4.0
Crytogenic cirrhosis	9	9.3	6	15.8	1	6.7	16	10.7

Table 3 Distribution of co-morbid disease.

Child Turcotte-Pugh class	Grade A		Grade B		Grade C		Total	
Co-morbid disease	n	%	n	%	n	%	n	%
DM	31	32.0	8	21.1	3	20.0	42	28.0
HT	16	16.5	3	7.9	1	6.7	20	13.3
Hyperthyroidism	1	1.0	0	0	0	0	1	0.7
OA	2	2.1	2	5.3	0	0	4	2.7
Other	0	0	1	2.6	0	0	1	0.7

Table 4 Chronic liver stigmata of patients

Child Turcotte-Pugh class	Grade A		Grade B		Grade C		Total	
Chronic liver stigmata	n	%	n	%	n	%	n	%
Parotid gland enlargement	23	23.7	10	26.3	1	6.7	34	22.7
Spider nevi	45	46.4	24	63.2	8	53.3	77	51.3
Clubbing of fingers	7	7.2	1	2.6	1	6.7	9	6.0
Palmar erythema	68	70.1	23	60.5	8	53.3	99	66.0
Gynecomastia (male = 103)	36	37.1	11	28.9	8	53.3	55	53.4

of Child Turcotte-Pugh class (Table 3)

The classic signs of chronic liver disease were also present such as palmer erythema in 99 (66%), spider nevi in 77 (51.3%), gynecomastia in 55 (53.4%), parotid gland enlargement in 34 (22.7%), and clubbing of fingers in 9 (6.0%).

The endoscopic findings of 134 patients, showed the presence of esophageal varices (EV.) grade I was 30 of 86 (34.9%) in Child-Pugh A patients, 11 of 33 (33.3%) in Child-Pugh B patients and 9 of 14 (60.0%) in Child-Pugh C patients. Esophageal varices with grade II and grade III were shown as in Table 7. Portal hypertensive gastropathy was found with mild grade in 53.5 %in Child-Pugh A patients, 63.6%in Child-Pugh B patients and 80.0%in Child-Pugh C patients. The severe grade was 5.8 %in Child-Pugh A patients, 9.1%in Child- Pugh B patients and no one was found in Child-Pugh C.

There was only 3 cases with evidence of hepatopulmonary syndrome, one of 96 cases (1%) in Child- Pugh A, one of 37 cases (2.6%) in Child-Pugh B patient and one of 14 cases (6.7%) in Child-Pugh C patient. The prevalence of hepatopulmonary syndrome was only 2 % (3 of 150 cases).

Table 5 Splenomegaly in cirrhotic patients

Child Turcotte-Pugh class	Grade A n = 97		Grade B n = 38		Grade C n = 15		Total n = 150	
Splenomegaly	n	%	n	%	n	%	n	%
Absent	40	41.2	12	31.6	4	26.7	56	37.3
Present	57	58.5	26	68.4	11	73.3	94	62.7

Table 6 Demographic and clinical data of patients.

Child Turcotte-Pugh class	Grade A n = 97 (65%)		Grade B n = 38 (25%)		Grade C n = 15 (10%)		Total n = 150	
Data	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.
Age (year)	56.9	10.8	54.9	12.9	55.4	11.4	56.2	11.4
Pulse Rate (/min)	74.2	11.0	73.4	16.3	74.1	15.1	74.1	12.9
SBP. (mmHg)	128.6	18.8	116.2	14.7	119.3	19.5	124.6	18.7
DBP. (mmHg)	76.7	11.3	69.9	10.7	67.6	8.8	74.0	11.5
O_2 sat (%)	97.8	1.1	97.9	1.1	97.8	1.9	97.9	1.2
Hb (gm/dl)	12.8	2.2	11.3	1.7	9.3	2.0	12.5	5.4
Hct (%)	39.0	6.2	34.0	4.8	27.5	5.7	36.6	6.9
White count (/mm^3)	5964.4	2043.2	7082.5	10276.9	6730.0	3521.1	6180.8	5495.9
Platelet count (/mm^3)	123755.1	65513.4	91973.7	78409.3	82333.3	50642.5	110,001.1	69922.6
Total Bilirubin (mg/dl)	1.3	1.4	2.9	1.4	4.4	2.2	2.0	1.8
Direct Bilirubin (mg/dl)	0.5	0.3	2.3	5.3	2.2	1.1	1.1	2.8
AST (U/L)	51.4	32.9	129.3	213.2	72.7	50.8	65.7	62.2
ALT (U/L)	41.5	32.4	52.9	46.5	41.9	16.6	49.1	49.9
Alk.-Phosphatase (U/L)	118.4	60.6	154.3	96.4	165.7	61.8	132.2	73.5
Albumin (gm/dl)	4.0	0.5	3.0	0.5	2.4	0.7	3.6	0.8
Globulin (gm/dl)	3.7	0.7	4.2	0.9	4.9	1.3	3.9	0.9
BUN (mg/dl)	13.2	7.6	11.6	6.1	12.0	5.5	12.7	7.0
Creatinine (mg/dl)	1.1	0.4	0.9	0.3	1.1	0.6	1.0	0.4
FBS (mg/dl)	122.4	42.8	111.7	53.1	128.5	47.9	120.8	45.3
PT (sec.)	12.4	1.3	14.4	1.9	18.1	4.8	13.5	2.7
PTT (sec.)	29.2	5.9	29.5	3.8	32.7	5.7	29.5	6.0
INR	1.1	0.1	1.2	0.2	1.5	0.4	1.1	0.2

Table 7 Endoscopic findings of cirrhotic patients.

Child Turcotte-Pugh class	Grade A n = 86		Grade B n = 33		Grade C n = 15		Total n = 134	
Gastroscopy	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Esophageal varices								
Absent	25	29.1	5	15.2	4	26.7	34	25.4
Grade I	30	34.9	11	33.3	9	60.0	50	37.3
Grade II	29	33.7	15	45.5	2	13.3	46	34.3
Grade III	2	2.3	2	6.1	0	0.0	4	3.0
Gastric Varices								
Absent	79	91.9	30	90.9	12	80.0	121	90.3
Present	7	8.1	3	9.1	3	20.0	13	9.7
PHG								
Absent	35	40.7	9	21.3	3	20.0	47	35.3
Mild grade	46	53.5	21	63.6	12	80.0	79	58.9
Severe grade	5	5.8	3	9.1	0	0.0	8	6.0

Table 8 Hepatopulmonary syndrome in cirrhotic patients

Child Turcotte-Pugh class	Grade A n = 97		Grade B n = 38		Grade C n = 15		Total n = 150	
Splenomegaly	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Absent	96	98.9	37	97.3	14	93.3	147	98.0
Present	1	1.0	1	2.6	1	6.7	3	2.0

Table 9 Characteristics of cirrhotic patients with HPS

Patient number	Age (yr)	Sex	Cause of cirrhosis	Liver stigmata	Child-Pugh Class	Child-Pugh Score	PaO_2 (mmHg)	A-aDo_2 (mmHg)
1	67	F	HBV	spider nevi, palmar erythema	C	11	66	28
2	47	M	Alcohol	spider nevi, clubbing of finger, palmar erythema	A	6	73	39
3	54	M	Alcohol	parotid gland enlargement spider nevi, palmar erythema gynecomastia	B	9	69	35

DISCUSSION

HPS is a syndrome associated with liver disease. The syndrome is one of the extrahepatic manifestations of chronic liver disease. In advanced end-stage hepatic disease the incidence was 13- 47%[9,20]. In all cirrhotic patients, the prevalence of HPS varies between 4% and 32%[13].

The most recent study reported the prevalence of HPS in cirrhosis without intrinsic cardio pulmonary disease was 24% (27 case in 111 cirrhotic patients)[5].

The prevalence of HPS in our study is quite low

(2%) when compared with the recent western study. This may be related to the geographic, ethnicity disparities of study population. Although, in Thailand HBV is more commonly found, but alcohol (59%) is the most common etiology of cirrhosis similar to previous studies. There was no specific etiology of cirrhosis has been found to increase the risk of developing HPS[21]. Many different clinical and laboratory characteristics were noted, none of these data can determine the factors related to the presence of hepatopulmonary syndrome. Major limitations of this study were the low prevalence with a small number of index cases. Until now, it has not been clear whether the severity of the liver disease is related to the presence of HPS or not. Some studies found more prevalence of HPS in Child-Pugh class A than other classes[6], and some studies found more prevalence of HPS in Child-Pugh class C than in other classes[5].

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