Detection Of Hepatopulmonary Syndrome in Patients With Liver Cirrhosis

Adel Hearum El-Ghamrawy[1], Saad Rabie Samra[1], Alaa Elsayed Salama [2],Mustafa Samy Negm [1]

(1) Chest Diseases Department Faculty of Medicine - Zagazig University, Egypt
(2) Cardiology Department Faculty of Medicine - Zagazig University, Egypt
Corresponding author: Mustafa Samy Negm , Mail: mustafasamynegm558@gmail.com

Received: 1 October 2024, **Accepted:** 25 October 2024, **Published:** 30 October 2024

Abstract

Background: Hepatopulmonary syndrome (HPS) is characterized as a triad: liver disease, intrapulmonary vascular dilatation and arterial hypoxemia. HPS is reported to be present in 4% to 32% of adult patients with end-stage liver disease. The pathogenesis of HPS has not been clearly identified. **Aim of work:** To study frequency as well as clinical, laboratory and imaging characteristic of hepatopulmonary syndrome in dyspneic cirrhotic hepatic patients admitted in zagazig university hospitals. **Patients and methods:** This study include 60 patients with cirrhotic liver disease as 38 males (63.3%)of the studied group and 22 females (36.7%) admitted in (Zagazig University Hospitals) during period of 1 year from May 2022 to May 2023 . The diagnosis of cirrhosis is based on clinical, serological workup and imaging. Full history taking with special attention to dyspnea according to dyspnea score of Modified Medical Research Council (mMRC) and analysis of its onset, course, duration, precipitating and relieving factors. Full abdominal examination Full cardiac and chest examination Chest imaging was done for all patients. Pelvi-abdominal ultrasonography .Contrast enhanced echocardiography. Results: Twenty-six patients(43.3) out of the studied 60 patients were found to have HPS and seven patients (11.7) were having subclinical HPS**. Conclusion:** HPS is detected frequently in dyspneic patients with liver cirrhosis (43.3% in the present study). Moreover,grade of dyspnea and extent of alveolar arterial oxygen gradient are directly proportional to echbubbling findings

Keywords: *Hepatopulmonary Syndrome, Liver Cirrhosis, Detection*

Introduction

Cirrhosis of liver is a very common disease which clinicians encounter both at primary and tertiary care. Cirrhosis is associated with several complications and overall carries a poor prognosis. The management of cirrhosis includes early detection and treatment of various complications like hepatic encephalopathy, coagulopathy, ascites, hepatorenal syndrome etc(1)

Recently there has been an increased interest in literature about pulmonary manifestations of cirrhosis of liver which are equally important and has been relegated to background both in the world. Development of pulmonary manifestations of cirrhosis has several clinical implications with regard to their management, since they carry a poor prognosis. Cirrhosis and portal hypertension are associated with pulmonary manifestations that affect the pleura, lung parenchyma, and pulmonary vasculature. Dyspnea and hypoxemia are the predominant presentations(2)

Aim:

To study frequency as well as clinical,laboratory and imaging characteristics of hepatopulmonary syndrome in dyspnic cirrhotic hepatic patients admitted in zagazig university hospitals

Patients and methods: This study include 60 patients with cirrhotic liver disease as males were 38 patients considering 63.3% of the studied group while females were 36.7% admitted in (**Zagazig University Hospitals**) **during period of 1 year from May 2022 to May 2023** . The diagnosis of cirrhosis based on clinical,serological workup and imaging.

Inclusion criteria: patients with chronic liver disease with dyspnea

Exclusion criteria:

1- Patients having chronic liver disease with dyspnea attributable to another known cause
2- End stage systemic disease other than hepatic cirrhosis.
3- Poor echocardiographic image

All patients in this study were submitted to the following :

1- **FuII history taking** with special attention to dyspnea according to dyspnea score of (mMRC) and analysis of its onset, course, duration, precipitating and relieving factors. Also special consideration to any coexistint cardiopulmonary

problems . Age, gender, and special habits of medical importance as smoking and . Patients were asked about history of liver disease, chronic HCV or HBV infection , history of Bilharsiasis and HCC . The history taking included also history of other medical diseases as diabetes and hypertension. Patients were also asked about

history of attack of haematemesis, presence of melena and blood transfusion due to anemia and band ligation

2- **Thorough general examination** with stress on general aspects related to chest and liver diseases e.g. degree of clubbing and spider navi(a vascular lesion characterized by anomalous dilatation of end vasculature found just beneath the skin surface).

3- **FuII abdominal examination** searching for signs of chronic liver disease, liver cell failure such as: Ascites (diffuse abdominal enlargement with fullness and dullness in flanks, mild: detected only by ultrasonography, moderate: detected by positive bilateral shifting dullness, tense: positive transmitted thrill). Organomegally enlarged liver and spleen.

4- **Full cardiac and chest examination** searching for signs respiratory failure as tachycardia,tachypnea,working accessory muscles,patient position and cyanosis.

5- Laboratory investigation :

A-CBC,ALT, AST, fasting and 2 hours postprandial blood glucose level, bilirubin (total & direct), serum albumin, PT, PC, INR ,alpha fetoprotein and autoimmune markers.

B-Also 1 ml arterial blood was taken from radial artery, after disinfecting the site of sampling with alcohol swap, for arterial blood gases analysis while the patient is in supine position and another sample while the patient is in standing (upright) position with interval 10 minutes.

6- Electrocardiography: was done for all patients to assess pulmonary artery hypertension,Right heart diseases and valvular heart diseases to exclude theses cases

7- Chest imaging :CT chest without contrast was done for all patients to assess findings in CT chest in all groups as congestion ,interstitial nodules,pleural or pericardial effusion

8- Pelvi-abdominal ultrasongraphy.

9- Alveolar-arterial oxygen tension difference P(A-a)O2: was calculated as follow:

= (FIO2 x713 - 5/4 Pa C02)-(PaO2) (Paul Marino ,1991).

where FIO2 fraction of inspired oxygen, Pa C02 arterial CO2 tension, PaO2 arterial oxygen tension.

10- Child-Pugh Classification of hepatocellular function in Cirrhosis

Child-Turcotte-Pugh Classification for Severity of Cirrhosis			
Clinical and Lab Criteria	Points*		
	1	2	3
Encephalopathy	None	Mild to moderate (grade 1 or 2)	Severe (grade 3 or 4)
Ascites	None	Mild to moderate (diuretic responsive)	Severe (diuretic refractory)
Bilirubin (mg/dL)	< 2	2-3	>3
Albumin (g/dL)	> 3.5	2.8-3.5	<2.8
Prothrombin time Seconds prolonged International normalized ratio	 <4 <1.7	 4-6 1.7-2.3	 >6 >2.3
*Child-Turcotte-Pugh Class obtained by adding score for each parameter (total points) Class A = 5 to 6 points (least severe liver disease) Class B = 7 to 9 points (moderately severe liver disease) Class C = 10 to 15 points (most severe liver disease)			

Figure (1) : Child-Pugh Classification for severity of cirrhosis

(Chung RT and Podolsky .,(2001)

11- Contrast enhanced echocardiography;

Ten ml of agitated saline were used which provides a stream of microbubbles 60 to 90 microns in diameter that usually opacify only the right heart chambers, it will be injected slowly into a venous peripheral line (cannula) in patient's upper limbs either right or left ,then observing if it will appear in the left side of the heart and after how many beats after its appearance in 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 .

The patients will be investigated also for the rest of cardiac parameters as ejection fraction, chambers size ,valves, systolic dysfunction and diastolic dysfunction .

Echo grading of shunt: relative pacification of the LA was assessed semiquantitatively as follows**: Grade 0**, no microbubble in LA; **grade I**, a few bubbles in LA indicating small 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) **EL-Maraghy et al ., (2018).(3)**

Patients were classified in 3 groups:

1st group had no pulmonary shunts in dyspnic patients(control group)

2nd group was patients had pulmonary shunt without hypoxemia(subclinical syndrome) in dyspnic patients

3rd group was hepatopulmonary syndrome :that had pulmonary shunt with hypoxemia in dyspnic patients

Statistical analysis:

The collected data were coded, processed and analyzed using the SPSS (Statistical Package for Social Sciences) version 22 for Windows® (IBM SPSS Inc. (Chicago,

IL, USA). Qualitative and quantitative data were described using number and

percent as Chi-Square test ,median, range & inter quartile range for non-parametric data and mean and standard deviation , paired or independent Student's t-test.

Pearson's correlation coefficient (r) was used to calculate correlations between different variables . Significance of the obtained results was judged at the (0.05) level.

Results:

Table1: demographic data distribution among studied group (N=60)

Age **(years)**	Mean± SD	62.43±7.66	
	Median (Range)	**62.0 (42-83)**	
Duration of disease **(years)**	**Mean± SD**	**9.96±3.99**	
	Median (Range)	**10.0**	
		N	**%**
Sex	**Female**	**22**	**36.7**
	Male	**38**	**63.3**
	Total	**60**	**100.0**

Table 2: Prevalence HPS patients among studied group

		N	%
HPS	**Control**	**27**	**45**
	Subclinical HPS	**7**	**11.7**

	HPS	26	43.3
	Total	60	100.0

Table (3): Presentation of associated symptoms and signs between studied groups

Associated medical conditions	HPS n=26		Subclinical n=7		Controlled n=27		Chi-square	
	n	%*	n	%*	n	%*	x^2	p
Cough Expectoration	17	65.4	5	71.4	17	63	0.178	0.915
Hemoptysis	6	23.1	3	42.9	3	11.1	3.77	0.152
Spider Angioma	26	100	4	57.1	6	22.2	22.4	<0.001
Palmer erythema	22	84.6	3	42.9	13	48.1	5.01	<0.001
Cyanosis	26	100	4	57.1	2	7.4	36.36	<0.001
* Within HPS groups								

Table (4): Presentation of clinical characteristics between studied groups

			HPS	Subclinical	Control	Test	P value
Dyspnea	I	n	2	3	13	X^2 23.9	0.001*
		%	7.7	42.9	48.1		
	II	n	7	4	10		
		%	26.5	57.1	40.7		
	III	n	10	0	1		
		%	38.5	0	3.7		
	IV	n	7	0	2		
		%	26.5	0	7.4		
Degree of Ascites	No	n	6	2	9	X^2 3.047	0.803
		%	23.1	28.6	35.3		
	Mild	n	5	2	8		
		%	19.2	28.6	29.6		
	Moderate	n	7	1	6		
		%	26.9	14.3	22.2		
	Tense	n	8	2	4		
		%	30.8	28.6	14.8		
CHILD score	A	n	3	0	10	X^2	0.001*
		%	11.3	0	37		

	B	n	8	2	10	10.1	
		%	30.8	28.6	37		
	C	n	15	5	7		
		%	57.9	71.4	26		

Table (5): Presentation of Echocardiographic findings between studied groups :

	HPS n=26		Subclinical n=7		Controlled n=27		Chi-square	
	n	%*	n	%*	n	%*	X^2	p
Echocardiographic Grading								
I	0	0	1	14.3	0	0	94.05	<0.001
II	2	7.7	1	14.3	0	0		
III	8	30.7	5	71.4	0	0		
IV	16	61.6	0	0	0	0		

Table (6): correlation of Echocardiography grade with dyspnea:

n(%)*Percentage within Echo grouping		Echocardiography grade					X^2	p
		Norm al	I	II	III	IV		
dyspnea	1	14(50)	0(0)	3(42.9)	1(12.54)	0(0)	32.8	0.001
	2	11(39.3)	1(100)	4(57.1)	3(37.5)	3(18.8)	rs*	p
	3	1(3.6)	0(0)	0(0)	2(25)	8(50)		
	4	2(7.1)	0(0)	0(0)	2(25)	5(31.3)	.6	<0.001

X^2 chi-square s spearman correlation*

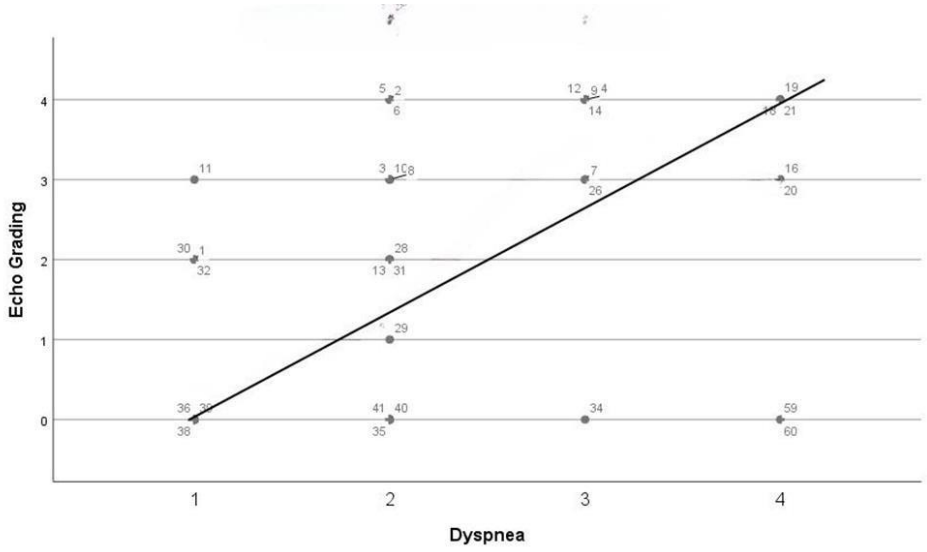

Figure 2: showed positive correlation between Echo grade groups and dyspnea degree .

Table (7): Presentation of clinical P(A-a)O2 gradient mmHg between studied groups.

n(%)*Percentage within Echo grouping		Echocardiography grade					X^2	p
		Normal	I	II	III	IV		
A-a gr	>30	0(0)	0(0)	1(14.3)	2(25)	14(87.5)	79.1	<0.001
	20-30	0(0)	0(0)	5(71.4)	5(62.5)	2(12.5)	rs*	p
	15-20	15(53.6)	1(100)	1(14.3)	1(12.5)	0(0)		
	<15	13(46.4)	0(0)	0(0)	0(0)	0(0)	0.89	<0.001
*X^2 chi-square * spearman correlation*								

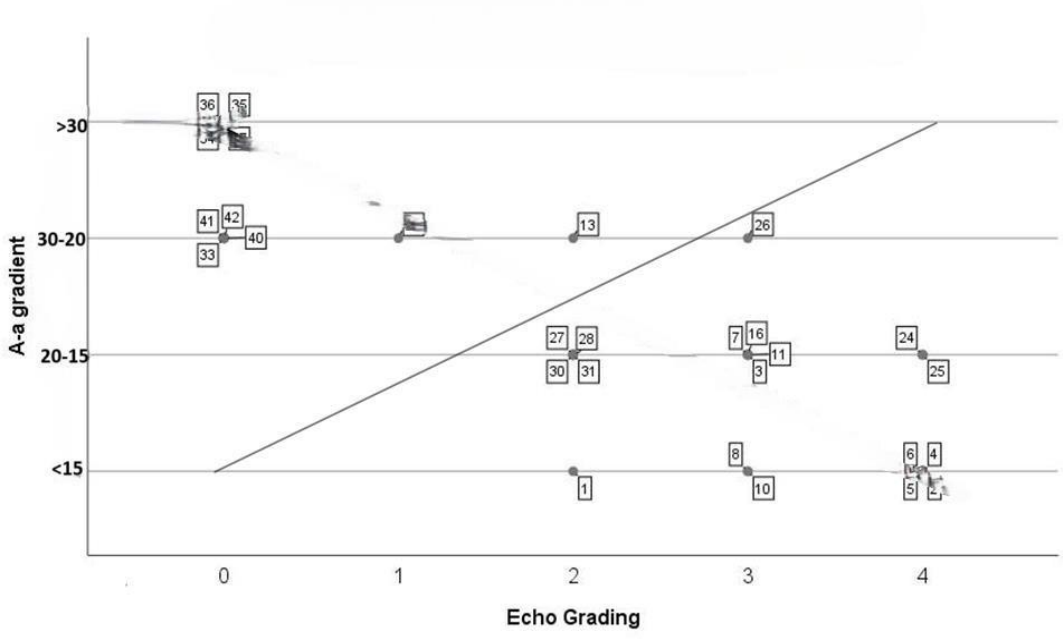

Figure (3): showed positive correlation between Echocardiography grade and A-a gradient.

Table 1: Age was distributed as 62.43±7.66 with minimum 42 and maximum 83 years, duration of disease 9.96±3.99, sex was distributed as38 males (63.3%) of the studied group while 22 females (36.7%.)

Table 2: This table showed 45% were control 11.7% were sub-clinical and 43.3% were HPS

Table 3 showed that there was significant difference between different groups and spider angioma , cyanosis and palmer erythema

table 4 There was no statistically significant difference regarding degree of ascites among HPS subgroups. While there was statistically significant difference between subgroups regarding degree of child Pugh which 15 cases tended to be group c and dyspnea in which most of controlled cases tended to be in grade I while full picture HPS tended to be within grades III and IV

table 5: This table showed that there was a significant difference between different groups as regard Echocardiographic degree , all patient-controlled group was in zero Echocardiograph, while most of HPS group 61% tended to be in grade IV.

Table 6 The study observed that there was a significant positive correlation between degree of dyspnea and echocardiography grading with spearman

correlation and p value <0.001. Most of subjects with normal echo finding (50%) were with 1st degree dyspnea while patients with grade 4 echo 50% were with score 3 dyspnea and 31.3% of them with score 4 dyspnea

Table 7 The study observed that there was positive correlation between Echocardiography grade and A-a gradient with p value below 0.001.

87.5% of grade IV had A-a gradient above 30, while all normal echocardiography had A-a gradient lower than 20

Discussion

In our study 60 cases were studied **(table 1)**. There were 38 male (63,3%) and 22(36,7%) females. Their age ranged 62.43±7.66 with

minimum 42 and maximum 83 years. They divided into 3 groups **(table 2),** 1st group included 27 patients with dyspnea only, Second group

included 7 patients with dyspnea and subclinical HPS, third group included 26 patients with dyspnea and HPS

Prevalence of hepatopulmonary syndrome in our study **(table 2)** was 43.3% higher in males 19 cases **(table 1)** and in comparison to 7 cases were females. The mean age at diagnosis was 61.5±6.8 **(table1).**which was relative higher prevalence than **Faissal et al., (2007),**[3] study

which the prevalence of HPS was 5% (less than our study),and was

higher in males rather than females (ratio 4: 1),it was higher as in our study and **In Wang et al., (2009),**[4] their study on 279 cirrhotic patients, HPS was found in 9.3%, also in the study conducted by **Gupta et al., (2001)** [5]on 54 patients, 11.1% of the patients had

hepatopulmonary syndrome. **Also In Ansari (2015),** [6]study on 40 cirrhotic patients conducted that hepatopulmonary syndrome was present in 4 patients (10%) **and in Mohammad et al., (2010)** ,[7]the

incidence of HPS was 33, 3% in a great with our study. Post bilharzial cirrhosis was found to be higher than in those of post hepatitis C cirrhosis

In El-Maraghy et al.,(2018) study[8],HPS was found that the prevalence of HPS was 25.28% which is lower than our study

results,Also **Pascasio et al.,(2016)** study,[9]the prevalence of HPS was 81 patients of total 316 patients in percentage of 25,6% **and Chandra et al.,(2019)** study ,[10] The frequency of HPS among the studied group of Indian patients with chronic liver disease was 14% was lower than our prevalence. **Other studies as**

Mokhtarifar et al .,(2016)[11] study

,HPS was found to be 15,8% in total of his study and **Younis et al.,(2015)** study ,[12] The frequency of HPS among the studied group of Indian patients with chronic liver disease was 26% and Also in the study

conducted by **Schenk et al., (2000)** [13]on 98 patients using PaO2 <80 mmHg as the cut off value (not using PaO2 <70 mmHg as in this study), HPS was found in 19%. This proved that using various cut off values for

arterial oxygenations led to wide variation in the prevalence of hepatopulmonary syndrome

The difference in prevalence was mostly due to highly selection of our cases as cases not all dypsnic patients taken as there were many causes of dyspnea in hepatic patients as pleural effusion to a limit that

cause dyspnea,muscle weakness and also associated diseases as chronic chest diseases as COPD and also due to difference in geographical

causes of liver cirrhosis as alcohol in some countries is more than Egypt and using various cut off values for arterial oxygenations led to wide variation in the prevalence of hepatopulmonary syndrome .The

hypothesis that HCV association in Egyptian may be related to genetic susceptibility or to different HCV sub-types. Much was known about the heterogenicity of HCV genome, as there are at present 6 known major geno-types and over 90 sub-types assumed to be prevalent in different parts of the world.21-23 The HCV genotype 4a is the most common genotype in Egyptian population,20 that may be responsible for predilection of Egyptian population for HCV infection

In current study, cyanosis was present in 26 patients(100%) of HPS and in 4 patients in subclinical HPS (57,1%) and 2 cases in non HPS cases (7,1%)**(table 3). Alizadeh et al., (2006)** [13]found cyanosis in 90% of HPS patients and 15% of non HPS patients and **Hira et al.,**

(2003),[14]found cyanosis in 100% of HPS patients and none of the non HPS patients had cyanosis. **DE et al., (2000)**[15] found that cyanosis might be the only reliable indicator of HPS. **El-Maraghy et al.,(2018)** found that cyanotic patients in HPS was (81,2%) in his study.

In current study spiders was present in 100 % of HPS patients and in 22% of non HPS **(table 3).** These results were nearly in agreement with

Alizadeh et al., (2006) who found spiders in (80% of HPS patients and 29.5% of non HPS patients) and were closely similar to **El-Maraghy et al.,(2018)** who found that spiders present 90,9% of his study,also **Hira et al., (2003)study** found spiders in 7 of 10 patients of HPS (70%) compared with 5 of 20 cirrhotic patients without HPS (25%) and

Mohammad et al., (2010) study, there were 6 patients of non-HPS showing spider angiomata (30%) and 7 patients of HPS with those angiomata (70%), showing that there was a significant correlation between cutaneous spider nevi and the severity of HPS

Stoller et al., (2017)and Jensen et al., (2008) studies [16] supported these previous reports and showed that there was a significant correlation between cutaneous spider nevi and the severity of HPS

In current study dyspnea was the most prevalent clinical feature in HPS patients (100% of HPS patients **(tables 4,6)** and there was significant positive correlation between Echo and degree of dyspnea(figure 2) **.**This was in agreement with **El-Maraghy et al.,(2018)** and **Alizadeh et al., (2006)** who found dyspnea in 100% of HPS patients and 25% of non HPS patients with sensitivity and specificity (100%, 75%) also **Hira et al., (2003) study** found 100% of HPS patients and 45% of non HPS patients. However **in disagreement with Schenk et al., (2000)** study found that dyspnea was more often present in patients with "clinically significant" HPS (57%) compared with "subclinical HPS" (8%), and patients without HPS (6%) and **Aboussouan et al., (2000)** [17]who found only 18% of HPS group were dyspnic

There was a highly significant between echo grading and each of Child's score **(table 4)** and degree of ascites **(table 4),** like **Younis et al.,2015 study** who stated the same significance . this was mostly due to more severe Child's score-figure1-(which contained Child's one of its items) leads to more toxic substances which leads to intrapulmonary dilatation

This study revealed that**(table 5)** 2 cases with echo grade II +ve bubble test and 8 cases echo grade III+ve bubble test and 16 cases grade IV bubble test, only 26 cases correlated with criteria of HPS and 7 cases with +ve contrast echo but not fulfilled criteria of HPS and diagnosed as subclinical HPS.

In **Bakir and El shahed.,(2010) study** [18] 31 patients (51.67%) showed positive echo findings, reflecting the presence of IPS. Twelve patients (20%) had grade II echo findings, 7 (11.67%) had grade III, and 12 (20%) had grade IV echo findings. Sixteen patients (26.67%) showed the clinical picture and criteria of HPS, while 15 patients (25%) had positive echo findings without the clinical picture(subclinical).

El-Maraghy et al.,(2018), 3 cases with echo grade 1 +ve bubble test and 5 cases echo grade II+ve bubble test and 7 cases grade III and 12 cases grade IV only 22 cases of 27 cases correlated with criteria of HPS and 5 cases with +ve contrast echo but not fulfilled criteria of HPS 9 (subclinical).

Also there was significant positive correlation between echo grading and dyspnea **(table 6)(figure 2),** and positive correlation between echo and A-a gradient ratio**(table 7)(figure 3)** in totally agree with **El-Maraghy et al.,(2018) study** who revealed that there was the the same correlation to dyspnea and A-a gradient ratio **.** Also these correlations were in parallel with **R Gaber et al.,(2012)[19] , Alipour et al.,(2020)[20] Beatriz et al.,(2004)[21] and Qasim A et al.,(2024)[22]** who detected significant positive correlation between echo and A-a gradient ratio and dyspnea.there was due to highly selection of our cases of dyspnea that has no other suggestion cause of HPS and explanation of more dyspnea and wide A-a gradient and more decrease in PaO2 which associated echo grades3,4 due to more deterioration of liver which can not remove vaso dilator substances and leads to more dilatation of pulmonary vasculaure

Conclusion

HPS is detected frequently in dyspnic patients with liver cirrhosis (43.3% in the present study) .Moreover,grade of dyspnea and extent of alveolar arterial oxygen gradient are directly proportional to echbubbling findings

Recommendation

Studying the clinical as well as the radiological features of HPS in patients undergo liver transplantation before and after transplantation to detect if HPS is reversible or not.

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