ORIGINAL ARTICLE

Frequency of Pulmonary Arterial Hypertension among patients of liver cirrhosis presenting with Acute Respiratory Failure

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ABSTRACT

Background: liver cirrhosis with respiratory failure is frequent cause of admission in critical care unit. Sometime no etiological factor other than hepatopulmonary syndrome is labelled. Does pulmonary arterial hypertension matters in hepatopulmonary syndrome?
Aim: To assess the frequency of pulmonary hypertension among liver cirrhosis patients presenting with respiratory failure at Critical care unit Ittefaq Hospital Model Town Lahore Pakistan.
Methods: Doppler echocardiography was performed for assessments of pulmonary- arterial systolic pressure (PASP) on 80 consecutive patients who were known case of liver cirrhosis (48) men and 32 women) aged > 20 years, admitted to critical care unit at Ittefaq Hospital Model Town Lahore with respiratory failure. Pulmonary hypertension was prospectively defined as a tricuspid regurgitant jet velocity (TRJV) of at least 2.5 m per second which can be estimate pulmonary artery systolic pressure (PASP) equal or more than 25mmHg on transthoracic echocardiograpgy
Results: Doppler-defined pulmonary arterial hypertension was diagnosed in 8.75% among 80 patients included in study using a cutoff of PASP ≥25 mmHg.
Conclusion: The prevalence of PAH among adults liver cirrhotic patient is higher than that reported from the developed countries. Further assessment using invasive techniques is required coupled with analytical study design to predict the factors that favor the development of PAH among liver cirrhotic patients is required. Early detection of hepatopulmonary HPT may help in management plan in the form of liver transplant.
Keywords: Liver cirrhosis, Pulmonary arterial hypertension, Acute respiratory failure, PASP

INTRODUCTION

Viral hepatitis is the leading cause of cirrhosis in developing countries like Pakistan .Hepatitis -C virus (HCV) infection is frequent cause of chronic liver disease which is a slowly progressive disease and ultimately leads to liver cirrhosis which is characterized by replacement of healthy liver parenchyma by scar and fibrotic tissue. Sometime this infection goes on unnoticed till the patients presents with complication of liver cirrhosis, The economic burden due to cirrhosis is high in Pakistan. About 163 million people being chronically infected with Hepatitis C (HCV). This is leading cause of deaths in Medical Wards. There are about 366000 hepatitis C related deaths annually in Pakistan[3].

The direct effects of HCV on the lung may present as worsening of lung function in some patients with preexisting asthma or COPD is well established. In other patients, HCV may present with an interstitial pneumonitis and/or pulmonary fibrosis[6].

There is wide range of chest complications in chronic liver disease in the form of pleural effusion, Hepatopulmonary syndrome (HPS), Porto pulmonary hypertension (PPH),respiratory muscle wasting, Tubercles and fungal infections. Patient may develop acute respiratory distress syndrome with hepatic failure.

Hepatopulmonary syndrome: It is now recognized to develop in 15%–20% of patients with liver cirrhosis[5] but the exact role of HCV in the pathogenesis of declining pulmonary function is not well understood. Several mechanisms could be hypothesized (Fig 1), but the chronic immune activation and inflammation induced by HCV infection may play an important role.

In advance liver failure, many patients presents with progressive shortness of breath. They may be having clubbing and cyanosis. If there is no obvious any cause of hypoxia detected by investigations, then this may be due increased alveolar arterial oxygen gradient while breathing room air and due to pulmonary vascular dilatation. The presence of intrapulmonary vascular dilatations and arteriovenous shunting can be confirmed with contrastenhanced echocardiography, technetium 99m (99mTc)–labeled macro aggregated albumin scanning, or pulmonary

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arteriography[9,10]. Or vascular dilatation on contrast enhanced High Resolution C.T. scan of chest.

Pulmonary arterial hypertension (PAH), is a syndrome characterized by increased pulmonary vascular resistance and remodeling, and is associated with significant morbidity and mortality, which is directly related to cardiac function (Fisher et al., 2009).

Long term prognosis of this clinical condition is not good especially if on presentation PO2 is low on arterial blood gases. If hypoxia is evident on arterial blood gases, then it is indication for liver transplantation.

Pathophysiology underlying this pulmonary vasodilatation is excessive production of vasodilators, particularly nitric oxide, tumor necrosis factor alpha and heme oxygenase-derived carbon monoxide [9] In the presence of portal hypertension, hepatic production of endothelin-1 and expression of endothelial type B receptors occur, but n type A receptors increase in pulmonary vasculature. This leads to increased signaling and production of nitric oxide with the overall effect of pulmonary vascular dilatation, which is pathognomonic of hepatopulmonary syndrome.

PAH affects approximately 6%-15% of adults with liver cirrhosis[1,,2,3]. In liver cirrhosis, PAH has been defined by an elevated tricuspid regurgitant jet velocity (TRJV) on trans-thoracic echocardiography (TTE). However, subsequent studies using direct measurement of PASP by right heart catheterization indicate an overestimation of PAH by Trans-thoracic echocardiography (TTE) (Parent et al., 2011).(3) PAH is associated with markedly increased mortality[4]. Some individuals are relatively asymptomatic in the early stages of PAH.

The prevalence of pulmonary arterial hypertension (PAH) in advance liver cirrhosis is associated with hepatopulmonary syndrome and respiratory failure. with earlydetection of pulmonary hypertension by using non-invasive investigation like echocardiography, patient may be referred for liver transplant.

METHODS & MATERIALS

This study included 80 patients with known cases of liver cirrhosis due to hepatitis C admitted to Medical Intensive Care Unit at Ittefaq Hospital Model Town Lahore Pakistan with acute respiratory failure Respiratory failure was defined as acute respiratory failure was characterized by arterial PaO<60mmhg, or $PaCO_2$ values >55 mm Hg. The diagnosis of liver cirrhosis was based on clinical, biochemical and ultrasound criteria with positive viral marker. These patient were classified in to A,B,C category according to Child-Pugh classification criteria.

Exclusion criteria: All cases with secondary cause of pulmonary hypertension including: Liver cirrhosis patients with lung disease including; chronic obstructive lung disease (COPD), sleep apnea, pulmonary fibrosis and living at high elevation and pulmonary embolism.congenital heart disease or any obstructive heart lesions, collagen vascular disease, HIV, Schistosomiasis

All patients underwent comprehensive physical examination and thorough history taking followed by Echocardiography to determine TRJV and to calculate PASP. Contrast enhanced High resolution C.T scan of chest was also done to detect various risk factors possible for the development of PAH and extent of vascular dilatation that occurs in liver cirrhosis.

Data Management and Statistical Analysis: Data entered and analyzed using SPSS version 16.0 for categorical data, proportions, frequency and percentage will be used for expression; Chi square and Z test for proportions were used for comparison. Continuous data were expressed using median, mean and standard deviation. P value <0.05 considered statistically significant.

RESULTS

Table 1 displays the demographic and clinical characteristics of the included patients with liver cirrhosis. A total of 80patients were included, females constituted 32(33.3%). The age range for the whole sample was 15-64 years. Dyspnea was frequent symptoms (100%) as all patients were in respiratory failure. In our study most common cause (35%) of respiratory failure was infection. 28(35%)patients were having infection in the form of pneumonia , spontaneous bacterial peritonitis and urosepsis which was leading cause of decompensation of live cirrhosis. Septicemia was seen in 83% patients with infection. Other frequent (27.5%) cause of respiratory failure was advance liver failure leading to multi-organ failure in the form of metabolic acidosis, Acute respiratory distress syndrome, acute renal failure and hepatic encephalopathy. Portopulmonary hypertension leading to respiratory failure was diagnosed in 11 patients (13.75%)

Restrictive pattern of respiratory failure was seen in 15 patients (18.75%) in the form of massive ascites and massive pleural effusion leading to tamponade effect. Hepatorenal syndrome was seen in 6 patients (7.5%) and hepatocellular carcinoma in 5 cases (6.25%)

The most common cause of portopulmonary hypertension was in patients with unknown etiology

of respiratory failure. These patients were labelled as a hepatopulmonary syndrome. High resolution C.T scan of chest showed statistically significant increase in diameter of peripheral pulmonary arteries as well as the arteriole/bronchiole ratio in respiratory failure patients with HPS in comparison to HPS negative respiratory failure patients as shown in table. Hepatopulmonary syndrome was diagnosed in 11 patients. Eight patients were child C, two patients was child B and one patient was child A.

There was a statistically significant decrease in oxygen saturation as well as PaO2 in patients with hepatopulmonary syndrome in comparison to HPS negative patients.

Table1: Demographic and clinical features of 80 study patients

Variables	**Clinical Features**
Age (Mean and SD in years)	35.32± 15.3
Sex	48 M /32 F
Dyspnea	80(100%)
Central cyanosis	45 (56%)
Spider naevi	34 (42%)
Cough	63 (78.5%)
Clubbing of fingers	8 (10%)
Orthodeoxia	30(37.5%)

Table 2: Laboratory features of 80 study patients

Variables	**Liver cirrhosis due to Hepatitis C**	**Liver cirrhosis due to Hepatitis B**
AST (U/L)	56.6±10.2	37.42± 14.3
ALT (U/L)	66.6±11.3	27male/7 female
Albumin (g/L)	2.17±1.2	58.42± 12.5
Prothrombin Time (%)	37.18±14.2	64.6± 14.7
Gamma Globulin (g/L)	1.1±.7	2.31± 1.5
Platelets count (10^3/ml)	165± 44.7	174± 44.7
Liver cirrhosis classification		
Child-Pugh Stage A	7.5%	1.66%
B	15.83%	4.16%
C	60%	10.83%
Etiology of liver cirrhosis	86.6%	13.3%

Table 3: Etiology of Respiratory Failure

	Child-Pugh Stage A	**Child-Pugh Stage B**	**Child-Pugh Stage C**
Heparorenal syndrome	1.1%	1.3%	5.1%
Infections and sepsis	5.7%	8.3%	21%
Hepatohydrothorax/Ascites	3.15%	4.4%	11.2%
Advance liver failure	4.5%	8.5%	14.5%
Metabolic acidosis	2.7%	3.2%	8.05%
ARDS	1.1%	2.1%	3.05%
ARF			
Hepatic Encephalopathy			
Hepatopulmonary syndrome			
Hepatocellular Carcinoma			

Table 4: Frequency of Hepatopulmonary HTN in relation to Etiology of Respiratory Failure

Etiology of Respiratory Failure	**Hepatopulmonary HTN Yes (PASP ≥25 mmHg)**	**Portopulmonary HTN No (PASP < 25 mmHg)**
Heparorenal syndrome	1(1.2%)	5(7.5%)
Infections and sepsis	0	28(35%)
Advance liver failure	2(2.4%)	20(27.5%)
Hepatohydrothorax/Ascites	1(1.2%)	14(18.75%)
Hepatopulmonary syndrome	3(3.6%)	8(13.75%)
Hepatocellular Carcinoma	0	5(6.25%)

Table 5: Statistical study of severity of cirrhosis among patients Hepatopulmonary syndrome

Child Pugh Score	Parameter Mean± SD	P value
Class A and B	6.71±.53	0.001(s)
Class C	10.21±22	

Table 4: Statistical study of chest HRCT findings among respiratory failure patients in liver cirrhosis

Variable	Parameter (mean±SD)	
	HPS patients (PASP ≥25 mmHg)	Non HPS patients ((PASP <25mmHg)
Arteriole/Bronchiole (A/B ratio)	1.7±0.1	1.3±0.2
Diameter of peripheral pulmonary artery	5.7±1.1	3.5±0.4

P value <0.001

Table statistical study of PaO2 ,O2 saturation and PO2 (A-a) among patients with Hepatopulmonary syndrome

Variable	Parameter (mean±SD)
PaO2 HPS	55.11±5.23
PaO2 Non HPS	65.3±4.55
O2 Saturation% - HPS	85.4**±6.5**
O2 Saturation% -Non HPS	92.6**±5.54**
P (A-a)O2 mmhg - HPS	22.7**±3.12**
P (A-a)O2 mmhg – Non HPS	14.3**±3.5**

P value <0.01(s)

DISCUSSION

Viral hepatitis is the leading cause of cirrhosis in developing countries like Pakistan .Hepatitis -C virus (HCV) infection is frequent cause of chronic liver disease which is a slowly progressive disease and ultimately leads to liver cirrhosisLiver cirrhosis is often accompanied by arterial hypoxemia in the absence of cardiopulmonary disease[11]. In addition, abnormalities in pulmonary function and impaired gas exchange may occur in as many as 45–50% of patients[12]. Although mechanisms of hypoxemia include an intra or extrapulmonary shunt, ventilation–perfusion inequality, and alveolar capillary diffusion limitation, there is a lack of agreement on which factors are the most important[13]. Hepatopulmonary syndrome (HPS) is a serious vascular complication of liver cirrhosis disease that occurs in 5–32% of patients with cirrhosis[14]. Portopulmonary hypertension is best defined as: A condition characterized by increased mean pulmonary arterial pressure (mPAP) and pulmonary vascular resistance (PVR), resulting in pulmonary arterial hypertension (PAH) in association with portal hypertension, whether or not portal hypertension is related to underlying chronic liver disease[15].

In our study prevalence of pulmonary arterial hypertension was found in 8.4% patients of liver cirrhosis presenting with respiratory failure in Medical ICU whatever the etiology of respiratory failure was determined. In all literature review we could not find any study which similar to our study, In one study conducted by Peter Deiber,H.P.Allgaie et[17] in their study they showed the prevalence of arterial hypoxemia in 5.4% among patient of liver cirrhosis.In their studythey included the patients which were having unknown cause of hypoxia in liver cirrhosis . In our study the prevalence of respiratory failure was 13.5% if etiology was unknown leading to respiratory failure and in these patient pulmonary arterial hypertension was noted in 3.6% patients . In their study they included all etiological factors leading to cirrhosis but in our study hepatitis-C was the leading cause of cirrhosis. this difference may be due to direct effect of Hepatitis C virus on lungs parenchyma. Second factor may be that in our study patient presentation was very late as all patient were in respiratory failure. In all these patients although the pulmonary arterial hypertension was in 3.6% patients but pulmonary vascular dilatation was noted in 100% patients.

In one similar article published by Y. K.Kim, S.S.S Shim[18], they reported pulmonary vascular dilatation and hepatopulmonary syndrome in 15-20% patients of liver cirrhosis. Results of our study were almost close to their results in patients with unknown etiology of respiratory failure.

S. Ahmed A-bary, Maha[19] conducted in Egypt found an 18% prevalence of arterial hypoxemia in patients with liver cirrhosis. This prevalence is different from those reported by Hakan et al[20] Rao et al [5] and Florence et al[21]who showed a prevalence of 43.8%, 13.9% and 14% respectively. Most study are showing almost similar results if the etiology of respiratory failure is unknown in liver cirrhosis

This our study showed a positive correlation between the presence of arterial hypoxemia and the severity of liver disease assessed by the Child-Pugh score and showed that the severity of hypoxemia is positively correlated with the severity of liver disease. These findings agree with those done by Florence et al [21]who showed that, cirrhotic patients with hypoxemia have a higher Child Pugh score than non-hypoxemic patients and the severity of hypoxemia is positively correlated with the Child Pugh score and he stated that, the role of decompensated cirrhosis in the development of hypoxemia explains the improvement in cirrhosis-associated hypoxemia following liver transplantation.

The present study showed that the severity of hypoxemia assessed by PaO2 and SaO2 is positively correlated with the presence of intrapulmonary shunt in HPS. These results agree with the study done by Suceveanu et al[21] who showed a positive correlation between decreased SaO2 detected by pulse oximetry and the presence intrapulmonary vasodilatation characteristic of HPS.

In our study there we included all other etiological factor leading to respiratory failure in liver cirrhosis. And we also measured the pulmonary artery pressure in these patients. What was prevalence of pulmonary artey hypertension (PAH) and all other patient if etiology was well known. Was PAH is contributing factor to respiratory failure in these patients. 28 (35%) patient were in respiratory failure due to infection and sepsis in the form of pneumonia, spontaneous bacterial peritonitis and urosepis. None of these patient was having PAH. This may due to underlying septic shock which can drop the systemic and pulmonary vascular pressures. article published by Y. K. Kim, S.S.S Shim[18] they reported infection in the form of pneumonia and spontaneous bacterial peritonitis up to 21%. There is little difference in our study as his may due to personal hygiene of patient. In developed country the hygienic conditions are much better than developing country . As cirrhosis is immunocompromised state so infection rate is very high if hygienic conditions are not good.

Other etiological factor leading to respiratory failure was Hepatic failure, As liver plays a central role in regulating cytokine kinetics relevant to acute lung injury[28]. If the filtering mechanism of liver is compromised then proinflammatory substances are major risk factor for acute lung injury and ARDS. When acute lung injury occurs under these circumstances, the subsequent clinical course might be unusually severe . In a recent study of 29 patients with end-stage liver failure, the prevalence of ARDS was higher (79%) than in a random control group of intensive care unit patients (6.8%) [23]Doyle et al[24] reported a higher mortality rate from acute lung injury in 76%associated with chronic liver disease.

In our study hepatic failure leading to respiratory failure was noted in 22(29.9%) of patient, and in these controlled patient ARDS was up to 72%. Other factors leading to respiratory failure were severe metabolic acidosis, hepatic encepahalopathy, bleeding diathesis in these patients

Restrictive pattern of respiratory failure in the form of massive ascites and hepatohydrothorax was observed in 15 (19.95%). These patients showed excellent response to treatment by fluid tape. A variety of respiratory symptoms may occur, including dyspnea, nonproductive cough, pleural chest pain, and fatigue due to hypoxemia; patients rarely present with respiratory failure due to an acute tension hydrothorax [24] Diagnostic thoracentesis should be performed in all patients suspected to have hepatic hydrothorax. A recent study showed that analysis of pleural fluid from the first diagnostic procedure yielded a diagnosis other than hepatic hydrothorax in 30% of patients with cirrhosis [24].The pressure gradient favors movement of fluid from the peritoneal cavity to the pleural space; for this reason, it is well known that hepatic hydrothorax may occasionally occur in the absence of ascites [25]. Hepatic hydrothorax develops on the right side in most cases (85%), with 13% of cases occurring on the left side and 2% being bilateral[26]. In our study pulmonary arterial hypertension was noted in 1.2% of these patients. This result was almost very near to studied conducted by Lazaridis KN, Frank JW, Krowka[26.]

Liver cirrhosis from any chronic liver disease predisposes to HCC. The prevalence of HCC in patients with underlying cirrhosis is highest in those with hepatitis C virus infection (17%–30% prevalence of HCC), followed by hereditary hemochromatosis (21%), hepatitis B virus infection (10%–15%), alcoholic cirrhosis (8%), and advanced biliary cirrhosis (4%)[27]. Intrathoracic manifestations of HCC vary. The most common thoracic metastatic manifestation of HCC is multiple pulmonary nodules due to hematogenous metastases .Less common forms include mediastinal lymphadenopathy pulmonary tumor emboli, and tumor extension into the IVC or right atrium[28,29]. In our study we noted hepatocellur carcinoma leading to respiratory failure was observed 5(6.5%) patients in the form of malignant pleural effusion, metastasis to lungs and hepatic failure.

Pulmonary arterial hypertension was noted in these patients. Hepatorenal syndrome leading to respiratory failure was noted in six (9.7%) patient. The cause of respiratory failure was fluid over load (85%) anf metabolic acidosis (67%) of these patients. The pulmonary arterial hypertension was noted in

1.2% of these patients. Not a single study for comparison is available which shows direct relation of hepatorenal syndrome and pulmonary hypertension.

CONCLUSION

Patients with cirrhosis and portal hypertension may present with respiratory failure in variety of ways. One of the important etiology is hepatopulmonary syndrome which is characterized by intrapulmonary vascular dilatations and arteriovenous shunting. Pulmonary arterial hypertension (PAH) is noted in 3-5% of these patients. Early detection of PAH by non-invasive investigation echocardiography will be helpful in assessing the severity of cirrhosis and referral for liver transplant.

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