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CORRELATION OF SEVERITY OF CHRONIC LIVER DISEASE AND PULMONARY DYSFUNCTION – A BED SIDE ASSESSEMENT

Gastroenterology

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ABSTRACT

Introduction: Chronic liver disease with portal hypertension leads to many deleterious effects on multiple organ systems, including the pulmonary system. Portopulmonary hypertension and hepatopulmonary syndrome are the well recognised complications of chronic liver disease.
These pulmonary manifestations are in general less recognized by attending clinicians and are usually not given due importance in routine management of patients with chronic liver disease .
Objective : This study aimed to investigate the frequency of hypoxemia and impairment of pulmonary function tests in patients with chronic liver disease and to correlate these impairments with the severity of liver cirrhosis as per child pugh score.
Method: Fourty five patients with chronic liver disease without intrinsic cardiopulmonary disease were enrolled in this study. All the patients were subjected to complete clinical examination, Routine laboratory investigations, Pulse oximetry, Arterial blood gas analysis, Pulmonary function tests, Radiological investigations including abdominal ultrasound, chest x ray, Upper GI Endoscopy, ECG. 2D Echo was done in selected patients.
Results: Hypoxia was found in significant number of patients. Among the PFT parameters, FEV1 values were found to be lower in patients with severe liver disease. The presence of hypoxemia is increased in patients with advanced liver disease and its severity is positively correlated with the severity of liver disease. Clubbing, Orthodeoxia and Platypnea are important clinical indicators for hypoxia.
Conclusion: Chronic Liver disease is associated with distinctive pulmonary complications. Hypoxemia is a significant parameter found in considerable number of patients with chronic liver disease. Pulse oximetry is a easy, economical, and commonly available tool which reliably suggests the existence and severity of hypoxemia in patients with advanced liver disease. The timely detection of pulmonary dysfunctions in cirrhotic patients is decisive as it alters prognosis and helps in better management

KEYWORDS

PFTs, Hypoxia

INTRODUCTION

Chronic liver disease carries poor prognosis with various complications like ascites, hepatic encephalopathy, coagulopathy, hepatorenal syndrome. Recently there has been an increased interest in literature about pulmonary manifestations of CLD. Around 70% of CLD patients complain of dyspnea [1] and found to be hypoxemic during work up for liver transplantation. The pathogenesis of hypoxemia in CLD includes ascites, muscle weakness, enlarged liver, hepatopulmonary syndrome, volume overload, Hypoalbuminemia and anemia[2]. The various pulmonary manifestations are Hepatic hydrothorax, Pneumonia, Hepato pulmonary syndrome and Porto pulmonary hypertension.

METHODOLOGY

45 Patients of chronic liver disease hospitalized between May 2016 and April 2017 at the Chettinad Hospital and Research Institute are included in the study. An informed consent was obtained from all the patients.

Inclusion criteria: All patients aged above 18 years diagnosed as CLD based on clinical, laboratory and imaging findings are included in the study.

Exclusion criteria: Patients who were in a poor general performance status and having prior lung, cardiac and pleural diseases are not included. Patients with h/o smoking and the patients having altered sensorium due to hepatic or metabolic encephalopathy were also excluded.

Study Groups: The liver functional reserve was determined according to the Child–Pugh classification in all patients.

All patients were subjected to complete clinical examination, Routine laboratory investigations, Pulse oximetry, Arterial blood gas analysis, Pulmonary function tests, Radiological investigations including abdominal ultrasound, chest x ray, Upper GI Endoscopy, ECG. 2D Echo was done in selected patients.

Arterial oxygen saturation (SaO2) was determined using a pulse oximeter. Patients were labelled hypoxemic when SaO2 ≤ 90 % in supine position and platypnoea was interpreted when SaO2 decrease of ≥4% after change from supine to upright position.

The presence of hypoxemia and orthodeoxia was also detected. Orthodeoxia was defined as a fall in PaO2 levels more than 3mmHg on changing position from supine to standing and hypoxemia if PaO2 was less than 70mmHg breathing room air in any position at rest (supine, sitting or standing).

All patients were subjected to PFT using spirometer according to standard procedures. Forced expiratory volume in one second (FEV1), forced vital capacity (FVC), peak expiratory flow rate (PEFR) were measured. Predicted values for each of the parameters were obtained from standardized references.

Statistical analysis: Pao2, Sao2, FEV1, FVC, PEFR were considered as primary outcome variable. Secondary outcome is variable. CTP class was considered as explanatory variable. Descriptive analysis was carried out by mean and standard deviation for quantitative variables, frequency and proportion for categorical variables. The association between CTP class and Sao2, Pa02, FEV1, FVC, PEFR, was assessed by comparing the mean values. The mean differences along with their 95% CI were presented. Independent sample t-test data was also represented using appropriate diagram like bar diagram. The association between CTP class and Pao2, Sao2 was assessed by cross tabulation and comparison of percentages with 95% CI is presented. Chi square test was used to test statistical significance. P value < 0.05 was considered statistically significant. IBM SPSS version 22 was

used for statistical analysis.

RESULT:

A total of 45 subjects were included among them 37 (82.22%) were male and remaining 8 (17.78%) were female.

Among the study population, 27 (60.00%) had abdominal distension, 21 (46.67%) had jaundice, 21 (46.67%) had fatigue, 12 (26.67%) had abdominal pain, 12 (26.67%) had dyspnoea and 12 (26.67%) had fever. Among the study population, 30 (66.67%) had ascites, 15 (33.33%) had icterus, 9 (20.00%) had pallor, 17 (37.78%) had edema, 5 (11.11%) had clubbing, 4 (8.89%) had spider naevi, 24 (53.33%) had palmar erythema and 23 (51.11%) had parotid swelling.

Among the study population 31 (68.89%) had alcohol as etiology of CLD and remaining 14 (31.11%) had cryptogenic, 8 (17.78%) had hepatitis B, 3 (6.67%) had hepatitis C. Some patients have combined etiology of alcohol and viral infection.

Among the study population, 2(4.44%) had cyanosis, 5 (11.11%) had Orthodeoxia and 5 (11.11%) had Platypnoea.

Among the study population, 12 (26.67%) had hypoxia and remaining 33 (73.33%) had normal ABG.

Considering very small number of subjects (4) in CTP class A, to facilitate comparative analysis CTP A and B categories were combined together.

Among the study population, 36 (80.00%) were in CTP class A+B, and remaining 9 (20.00%) were in CTP class C.

Among the study population PFT was normal in 32 (71.11%) patients, while obstructive and restrictive patterns were seen in 1 (2.22%) and 12 (26.67%) subjects respectively (Table 1).

Table 1: Descriptive analysis of PFT in study population (N=45)

PFT	Frequency	Percentages
Normal	32	71.11%
Obstructive	1	2.22%
Restrictive	12	26.67%

The mean pa02 was 76.82 ± 7.82 in the study population. Minimum level was 60 and maximum level was 96 in the study population (95% CI 74.47 to 79.17). (Table 2)

The mean pco2 was 38.11 ± 3.11 in the study population. Minimum level was 32 and maximum level was 45 in the study population (95% CI 37.18 to 39.05).

The mean sao2 was 90.36 ± 4.61 in the study population. Minimum level was 78 and maximum level was 100 in the study population (95% CI 88.97 to 91.74).

Table 2 : Descriptive analysis of ABG parameters in study population

Parameter	Mean ±STD	Median	Min	Max	95% C.I. for EXP(B)	
					Lower	Upper
paO2	76.82 ± 7.82	78.00	60.00	96.00	74.47	79.17
pcO2	38.11 ± 3.11	38.00	32.00	45.00	37.18	39.05
SaO2	90.36 ± 4.61	90.00	78.00	100.00	88.97	91.74

The mean FEV1 was 80.05 ± 10.78 in the study population. Minimum level was 54 and maximum level was 98 in the study population (95% CI 76.81 to 83.29). (Table 3)

The mean FVC was 81.97 ± 12.75 in the study population. Minimum level was 49.10 and maximum level was 98.20 in the study population (95% CI 78.14 to 85.80).

The mean PEFR was 86.14 ± 11.93 in the study population. Minimum level was 40.80 and maximum level was 100 in the study population (95% CI 82.55 to 89.72).

Table 3: Descriptive analysis of PFT Parameters for in study population

Parameter	Mean ±STD	Median	Min	Max	95% C.I. for EXP(B)	
					Lower	Upper
FEV1	80.05 ± 10.78	80.20	54.00	98.00	76.81	83.29
FVC	81.97 ± 12.75	86.10	49.10	98.20	78.14	85.80
PEFR	86.14 ± 11.93	88.10	40.80	100.00	82.55	89.72

Out of 36 people CTP class A+B, 6 (16.66%) had hypoxemia and remaining 30 (83.33%) are normoxemic. Out of 9 people in CTP class C, 6 (66.66%) had hypoxemia and remaining 3 (33.33%) are normoxemic.(Figure 1) . The difference in the proportion of pao2 between CTP class status was statistically significant (P value 0.002), (Table 4).a

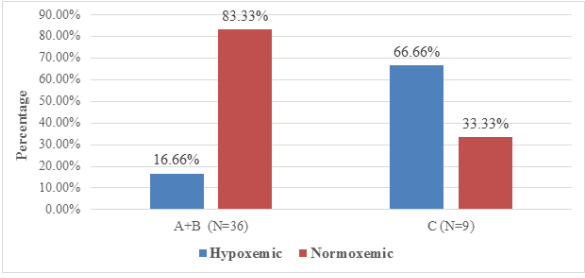

Figure 1: Bar chart of association of Pao2 group with CTP class of study population

Table 4: Association of Pao2 group with CTP class of study population

CTP Class	Pao2 group		Chi square	P-value
	Hypoxemic	Normoxemic		
A+B (N=36)	6 (16.66%)	30 (83.33%)	9.205	0.002
C (N=9)	6 (66.66%)	3 (33.33%)		

Out of 36 people CTP class A+B, 19 (52.77%) had Sao2 up to 90 and another 17 (47.22%) had more than 90. Out of 9 people CTP class C, 8 (88.88%) had up to 90 and another 1 (11.11%) had more than 90(Figure 2). The difference in the proportion of sao2 between CTP class status was statistically significant (P value 0.048). (Table 5)

Table 5: Association of Sao2 group (pulse oximetry) with CTP class of study population

CTP Class	Sao2 group		Chi square	P-value
	Up to 90	More than 90		
A+B (N=36)	19 (52.77%)	17 (47.22%)	3.912	0.048
C (N=9)	8 (88.88%)	1 (11.11%)		

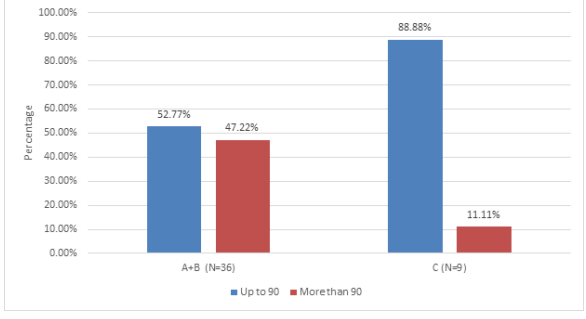

Figure 2: Bar chart of association of Sao2 group with CTP class of study population

The mean FEV1of CTP class A+B was 81.95 ± 11.18 and CTP class C was 72.46 ± 3.36, and the mean difference (9.49) between two groups was statistically significant (P value<0.016).

(Table 6)

The mean FVC of CTP class A+B was 81.55 ± 12.98 and CTP class C was 83.64 ± 12.39, and the mean difference (2.09) between two groups

was statistically not significant (P value 0.665).

The mean PEFR of CTP class A+B was 86.68 ± 11.69 and CTP class C was 83.98 ± 13.37, and the mean difference (2.70) between two groups was statistically not significant (P value 0.550).

Table 6: Comparison of mean FEV1 across study groups

CTP Class	FEV1 Mean± STD	Mean difference	95% CI		P value
			Lower	Upper	
A+B	81.95 ± 11.18	9.49	1.83	17.15	***0.016***
C	72.46 ± 3.36				

Discussion

Hypoxemia

Hypoxemia was seen in 26.67% of patients which was comparable to a study conducted by Yigit etal [3].Studies by Hakan et al [4], Florence et al[5] showed a prevalence of hypoxemia in 43.8% and 14% respectively. This variability in the prevalence can be explained by the dissimilarity in number of patients included in these studies.

The present study reveals a positive correlation among the finding of arterial hypoxemia with the severity of liver disease as per Child-Pugh score and reveals that the severity of hypoxemia and severity of liver disease are positively correlated with each other. This correlation is also seen in a study done by Florence et al. [5] which explains that, cirrhotic patients with hypoxemia have a higher Child Pugh score than non-hypoxemic patients. On the basis of this finding they explained the improvement of hypoxemia in post transplant patients.

The clinical indicators of hypoxemia like cyanosis was seen in 2 patients (4.44%), orthodeoxia in 5 patients (11.11%) and platypnea in 5 patients (11.11%). However studies of Krowka et al[6], Anand AC et al[7], De BK et al[8], Rao MY et al[9] showed around 5% patients have orthodeoxia and platypnea.

Clubbing of fingers, observed in chronic liver disease occurs due to hyperdynamic circulation and arteriole–capillary dilatation. In present study 5 patients (11.11%) had clubbing, while orthodeoxia and platypnoea are noted in 11.11 % of patients [10,11]. The reason this number is high in our study is due to the inclusion of more number of patients in the Child–Pugh B and C groups.

In our study, contrast echocardiography was not included. This can be a limitation in our study. The main objective for which this study was planned is to determine hypoxia and PFT alterations and their relationship with severity of chronic liver disease, rather than proving hepatopulmonary syndrome in these cases.

Pulmonary function tests interpretation:

A restrictive type of pulmonary function tests was expected in 25% of cases and an obstructive abnormality in 3.4% of cases. In this study, 12 patients (26.67%) had restriction & 1 patient (2.22%) had obstructive abnormality and is similar to the study done by Rao MY et al.[9]

In our study correlation between predicted values of Forced Expiratory Volume in One Second (FEV1), Forced Vital Capacity (FVC) and Peak Expiratory Flow Rate (PEFR) with CTP Classes was done.

It was seen that there was progressive decline in predicted values of FEV1 as the chronic liver disease became more advanced as per Child class which was statistically significant and is similar to a study done by Schenk P et al[12]. However the results obtained for predicted values of FVC and PEFR were not statistically significant.

Pulse Oximetry findings:

The present study showed a statistically significant decrease in O2 saturation in patients with child C cirrhosis. These results coincide with findings of studies conducted by Konstantinos et al. [13], and Hakan et al. [4]. These parameters can be explained by the point that patients with intrinsic pulmonary disease and smokers were excluded from our study. Pulse oximetry is a reliable and well known method for noninvasive interpretation of oxygenation[14] in patients without liver disease and a recent study has got similar results even in chronic liver disease patients[14,15]. However in both situations, SpO2 can overvalue oxygen saturation obtained directly by ABG of around 1.5%–3.5%.

Management of Pulmonary Manifestations

I General measures:

Patients having marked dyspnea and proven hypoxemia should be given oxygen supplementation[16] and nutritional care to improve muscle mass.

II Drugs

Diuretics dosage should be optimized in patients with significant edema and ascites,Various studies are done for therapy of HPS with nitric oxide inhalation, decreased consumption of L-arginine by methylene blue, somatostatin, indomethacin, aspirin, gut specific antibiotics for decreasing intestinal bacterial translocation, garlic, and transjugular intrahepatic portosystemic shunt (TIPS), but none among all these are proven for long-term management of HPS [17].

Studies suggested that garlic possibly have some role in the treatment of HPS by altering nitric oxide production [17]. A randomized controlled trial showed garlic supplementation helps in increasing baseline arterial oxygen levels by 24.66% and 28.35% decrease in alveolar-arterial oxygen gradient [18]. It also adds that garlic supplementation benefits in the reversal of intrapulmonary shunts and for reducing hypoxemia and mortality, although study with more patients is required to show proven benefits [18].

III Liver transplantation (LT)

The only effective treatment available for Hepatopulmonary syndrome (HPS) is liver transplantation. HPS patients on waiting list for transplantation should be monitored and managed carefully to prevent further worsening. After LT, 85% recipients had noteworthy improvement in gas exchange parameters, however it can take up to 1 year[19].Occasionally severe hypoxemia occurs in post-operative period with prolonged respiratory weaning that often results in mortality.

IV Other treatment alternatives

One of the recent advances for severe hypoxemia is extracorporeal membrane oxygenation (ECMO) [20]. Monsel et al.explained the use of ECMO before LT in patients with refractory hypoxemia caused by a combination of acute respiratory distress syndrome (ARDS) and HPS [21]. The initial data showed that ECMO aids in controlling gas exchange [22] thus results in successful liver transplantation. It assists in early ventilator weaning, thus prevented the need of prolonged ventilation and sedation [20].

CONCLUSION

Chronic Liver disease is associated with distinctive pulmonary complications. Hypoxemia is a significant parameter found in considerable number of patients with chronic liver disease. Pulse oximetry is a easy, economical, and commonly available tool which reliably suggests the existence and severity of hypoxemia in patients with advanced liver disease. The timely detection of pulmonary dysfunctions in cirrhotic patients is decisive as it alters prognosis and helps in better management.

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