ORIGINAL ARTICLE

CORRELATION OF DEVIANCE IN ARTERIAL OXYGENATION WITH SEVERITY OF CHRONIC LIVER DISEASE

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Background: Hepatitis B and C related chronic liver diseases have led to development of a serious threat to the people of South Asia. The main aim of this study was to evaluate the correlation of magnitude of arterial deoxygention to the severity of liver disease. **Methods:** It was a hospital based cross-sectional descriptive study, carried out in the Medical Department of Khyber Teaching Hospital Peshawar. All in all 115 patients were assessed for the severity of the liver diseases and were correlated with arterial deoxygenation using linear regression models. **Results:** Male to female ratio was 1.5:1. Males infected with hepatitis B, hepatitis C and both were 9, 60 and 1, while females suffered from hepatitis B, Hepatitis C and both were 2, 42 and 1 respectively. The linear relationship between A-a DO2 with severity of liver disease showed positive correlation while PO2 showed negative correlation with severity of liver disease. **Conclusion:** There was a positive correlation between A-a DO2 and severity of liver diseases while PO2 and severity of liver diseases showed negative correlation

Keywords: Chronic liver disease, severity, arterial oxygenation, deviance, correlation

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INTRODUCTION

Hepatitis B and C induced chronic liver diseases have taken epidemic proportions in South Asia. The prevalence of HBsAg and Anti-HCV antibodies among high-risk candidates like I/V drug abusers, unscreened blood or serum transfusion recipients is anywhere between 10-28%.[1,2] The over-all prevalence of chronic hepatitis is 4–6% among the general population of Khyber Pukhtoonkhwa.[3]

Chronic liver disease culminates clinically into multi-organ dysfunction with often complex presentations. Hepatic decompensation is a combination of histological changes resulting in clinically visible stigmata like ascites, variceal bleed and functional changes like detoxification reactions and/or synthesis. The latter for instance, can manifest as bleeding diathesis due to clotting factors deficiency amongst other functional derangements.[4]

Cardiopulmonary symptoms are not a rare finding in a patient of CLD. For example, a physician in a tertiary care setting would frequently encounter cases of respiratory compromise secondary to hydrothorax or tense ascites.[5] Often however, the presenting signs and symptoms mask a more complex pathophysiology intrinsically affecting the cardiopulmonary system, which we usually fail to recognize. Overlooking the presence of such complications, result in significant morbidity and mortality. These include Hepato-Pulmonary Syndrome, Hepatic-Cardiac Syndrome (Cirrhotic-Cardiomyopathy) and Porto-pulmonary Hypertension.

These complex pathophysiological developments have been poorly studied and there has been no universally accepted screening test or standardized diagnostic criteria so far. Despite variable clinical presentation, they can be detected biochemically with a traceable effect on the arterial oxygen saturation.

This study was carried out to correlate the magnitude of arterial deoxygenation expressed as a drop in PO2 and increased (Alveolar- arterial) Difference in Oxygen, i.e., (A-a) DO2 to the severity of liver disease, suggestive of latter's effect on the cardiopulmonary system.

MATERIAL AND METHODS

This cross-sectional descriptive study was carried out in the Department of Medicine, Khyber Teaching Hospital Peshawar from Oct 1, 2013 to April 1, 2014, and a period of 6 months. A total of 115 cases were considered for the study with Non-Probability Convenient Sampling.

The patients were screened for HBV and HCV positivity by ELISA based technique, i.e., anti-HBsAg and Anti-HCV in case of no previous record of CLD aetiology. The decompensated status of the liver in previously undiagnosed patients was assessed with an ultra-sonogram providing evidence of serrated liver margins, portal vein dilatation >1.5 cm, ascites and splenomegaly. The functional status of the liver was accessed through venous blood sampling for serum albumin and bilirubin concentration and Prothrombin Time.

Meticulous care was taken to exclude all possible confounding factors primary or secondary to cirrhosis liver but not under our observational aspect of study. Such factors included co-

morbidities that directly or indirectly affected the patient's arterial oxygen saturation mimicking the disease processes being studied. These included:

- Congestive Cardiac Failure: patients with recorded history of congestive cardiac failure prior to diagnosis with CLD, or with a history of Coronary Artery Disease.
- Anaemia or Massive Blood Loss: All prospective patients were screened with a standard peripheral blood smear and tested for mean corpuscular volume, Hb and Retic Count. Patients with an Hb <10 g/dl were de-considered for analysis.
- Chronic Obstructive/Restrictive Lung Disease/ Asthma:Standard Roentgenograms and Pulmonary Function Tests were utilized for excluding suspected cases from the study.
- Hydrothorax/ Peumothorax: Standard roentgenograms and ultrasonography was utilized for excluding patients from study with clinical evidence of either.
- Acute/ Chronic Renal Failure: It is well considered that Hepato-Renal Syndrome is not uncommonly observed with advanced liver disease. Therefore all patients were screened with renal function tests for derangement of urea and creatinine.
- Long Term Oxygen Therapy:

The required data was collected with a standardized *pro forma* after informed consent of the patients and approval of the hospital's ethics committee. The variables included preliminary information like age and gender, Hep B or C infection, severity of liver disease classified with the Child-Pugh Score chart (see figure) and correlated with data acquired through arterial blood sampling for arterial blood gas analysis that included observed variation in arterial oxygen tension (PO2) and Alveolar-arterial O2 difference (A-a) O2. The data was analysed through SPSS ver. 16.020.

Results were obtained as mean, SD, frequency and linear regression of variables to obtain correlation. These results are presented as tables and charts.

RESULTS

The study was carried out on 115 patients both male and female, of different racial and economic backgrounds, included on the basis of consecutive non-probability sampling. The number of male and female patients was 70 and 45 constituting 60.9 and 39.1 % respectively (Table-1). The ratio of male patients diagnosed with Hep B and Hep C was 9 and 60 respectively and one patient being diagnosed with both Hep B and C co-infection. The ratio for female patients was 2 and 42 for Hep B and C respectively with 1 patient co-infected with B and C (Table-2). Most of the patients under study were observed in the 41–60 years age group (Table-3). The patients cumulative Child-Pugh Score is correspondingly categorized as Child-Pugh Class A, B or C, reflecting more advanced liver disease in ascending alphabetical order. The highest frequency was observed in Category C, with 39 and 32 patients for male and female category respectively (Table-4).

The values obtained for the A-a DO2 were observed for their linear relationship to the severity of chronic liver disease or Child-Pugh Score (Figure-1).The circles in the graphical depiction or figures represent individual patients. In perspective, figure-1 is a linear regression depicting a positive correlation (calculated Pearson's R=0.598) between Alveolar-arterial O2 difference (A-a) DO2 and increasing severity of liver disease (CP Score).

Vice Versa there is a negative correlation (calculated Pearson's R=-0.468) between Pressure of arterial O2 (PO2) and severity of liver disease (CP Score) (Figure-2).

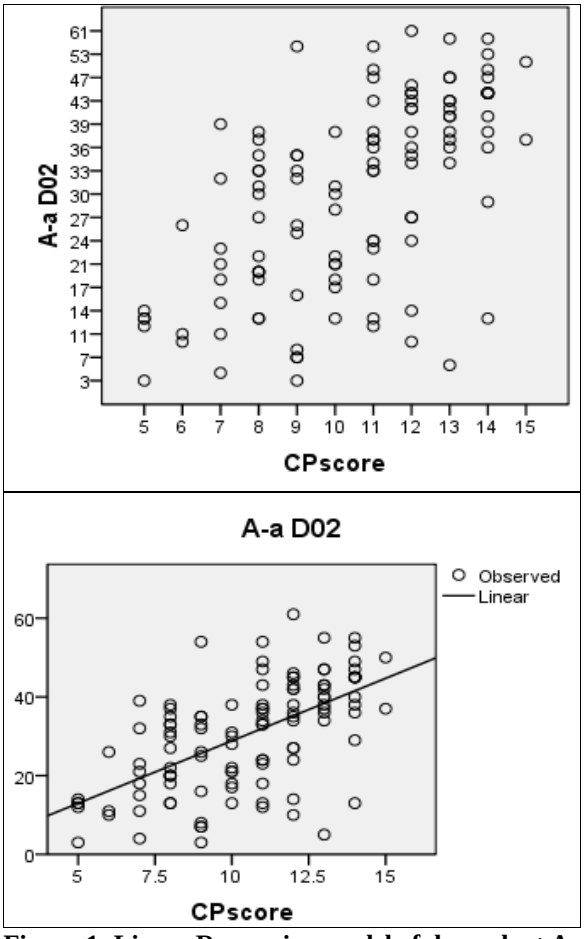

Figure-1: Linear Regression model of dependant A-a DO2over CP Score

Higher C-P Score values correspond to a widened A-a DO2 and a lower PO2 in all the graphical outcomes.

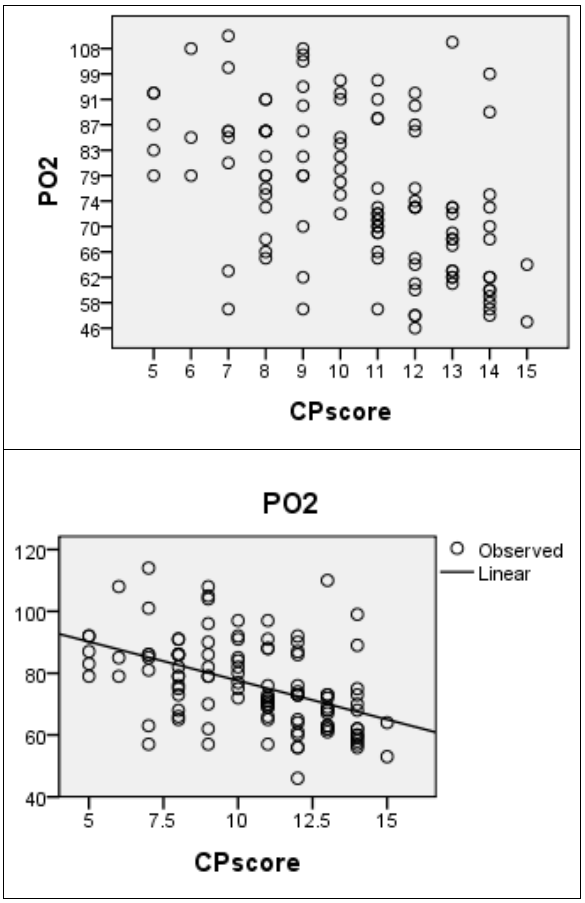

Figure-2: Linear Regression model of dependant PO2 over CP Score

Table-1: Gender Distribution Frequency

		Frequency	%	Valid %	Cumulative %
Valid	F	45	39.1	39.1	39.1
	M	70	60.9	60.9	100.0
	Total	115	100.0	100.0	

Table-2: Gender-Infection distribution

	Hep B or C			
Gender	B	B & C	C	**Total**
Male	9	1	60	70
Female	2	1	42	45
Total	11	2	102	115

Table-3: Age Group Stratification

Age Group (years)	**Gender**	
	Male	**Female**
20–40	17	5
41–60	42	28
61–70	6	10
>71	5	2
Total	70	45

Table-4: C-P Class Stratification

	C-P Class			**Total**
Gender	A	B	C	
Male	7	24	39	70
Female	2	11	32	45
	9	35	71	115

Table-5: Diagnostic Criteria for Cirrhotic cardiomyopathy (Moller and Hendrickson, 2008)[32]

Systolic Dysfunction	**Diastolic Dysfunction**	**Supportive Criteria**
Blunted increase in cardiac output with stress (exercise, volume and pharmacological EF < 55%	E/A Ratio <1.0 (age corrected) Prolonged deceleration time (>200 ms) Prolonged isovolumetric relaxation time (>80ms)	Electrophysiological Abnormalities Abnormal chronotropic response Electromechanical uncoupling Prolonged QTc Interval Enlarged left atrium Increased myocardial mass Increased cardiac enzymes

DISCUSSION

Our study visualizes a linear correlation between severity of chronic liver disease and hypoxemia, depicted as a drop in arterial oxygen saturation evident through a widened A-a DO2 and lower PO2.

We observed the end variable, i.e., hypoxemia as a consequential function of latent cardiopulmonary complications of chronic liver disease with application of exclusion criteria. There is no way in which we can establish a 'cause and effect' or the presence or absence of Hepato-pulmonary, Cirrhotic Cardiomyopathy or Porto-Pulmonary Hypertension. Nonetheless, we have a valuable insight into potential resulting outcomes with research while utilizing more advanced diagnostic and therapeutic techniques. Studies have provided a higher prevalence of cardiopulmonary complications with worsening liver disease. For instance, P Schenck *et al* observed a higher prevalence of Hepato-Pulmonary Syndrome in hypoxemic patients with lower PaO2 and wider (A-a)DO2 values.[6] All three complications have different pathophysiological basis and require advance techniques for definitive diagnosis.

Hepato-pulmonary Syndrome is a triad of cirrhosis, hypoxemia and pulmonary arterial shunting secondary to pre- and post-capillary intra-pulmonary micro-vascular dilatation (IPVD) leading to alveolar-capillary disequilibrium. IPVD shunts nearly 20% of the cardiac output without adequate oxygenation.[5,7] Exercise will further worsen this shunted fraction. Less common causes of HPS include portal hypertension sine cirrhosis for-instance, budd-chiari, idiopathic/non-cirrhotic portal hypertension, NASH and reportedly some cases of compensated cirrhosis.[8–13]

The mechanism for IPVD is postulated to be a combination of increased vasodilators or cytokine production like Nitric Oxide, endothelin1 & 3 and TNFα as well as decreased hepatic clearance of the same.[5,13] A newer insight suggests possible angiogenesis co-existing with the primary pathophysiology.[13] Consequently angiogenesis inhibitors discussed later may prove useful in future as non-surgical ways of care. The presence of HPS is

independently associated with increased mortality, morbidity and thus a shortened life span in a cirrhotic patient.[14–17]

Clinical presentation of IPVD is with worsening dyspnea and hypoxia, mimicking a cardiac or primary pulmonary pathology. Digital clubbing, cyanosis, platypnea and orthodeoxia are other associated pulmonary signs. 'Platypnea' refers to shortness of breath precipitated by a change in position from recumbency to standing or sitting. This symptom is induced by a paradoxical pooling of blood in the dilated vasculature of lungs resulting in a state of hypoxia. 'Orthodeoxia' is oxygen de-saturation of blood or a widened A-a (Alveolar-arterial) gradient as shown by Arterial Blood Gases (ABGs) with change to upright posture.[5,7] The mechanism is an increased perfusion of the lung bases thus exaggerating the physiological shunt.[7] 'Orthodeoxia' has a relatively high specificity for HPS with the appropriate application of exclusion criteria.[18]

Certain studies have also advocated the utilization of ABGs as a screening tool for HPS. It is possible to check for O2 desaturation in a patient with orthostatic positional change.[5,20–22]

The prevalence of Hepato-Pulmonary Syndrome is between 15 and 30%.[23] The presence of intra-pulmonary micro vascular dilatation can be reliably confirmed with the presence of double-contrast echocardiography and Computed Pulmonary Angiography (CT Angiography). In the formal case for instance agitated saline bubbles should not normally be detected in the left ventricle unless there is significant dilatation of pulmonary vascular bed facilitating the bypass from systemic venous return. Angiography has a high sensitivity and specificity for detection of these vascular malformations.

Porto-pulmonary hypertension (PoPH) to be considered as a sequel of chronic liver disease needs a careful exclusion of readily identifiable differentials like congestive cardiac failure, COPD, interstitial lung diseases amongst others. The European Respiratory Society Pulmonary Hepatic Vascular Disorder Task Force 2004 Consensus Report has provided diagnostic criteria for PoPH.[24] PoPH is defined as an elevation of mean right ventricular systolic pressure above 25mmHg with pulmonary capillary wedge pressure of less than 15mmHg and pulmonary vascular resistance greater than 240 dynes-sec-cm.[4,5,25] Porto-Pulmonary Artery Hypertension is therefore a combination of portal and pulmonary hypertension as a consequence of liver disease. Microscopic evaluation of lung biopsy specimen in defined cases of PoPH has revealed capillary lumen narrowing with medial hypertrophy [4]. Therefore from the histological perspective, PoPH can be considered the opposite of HPS. Survivability is considered to be very low; at around 6 months with development of this complication.[26] This clinical entity was first defined by Mantz and Craig in 1951.

The prevalence of Porto-Pulmonary Hypertension (PoPH) is estimated in the range of 2–10%.[27,28] Transthoracic, Trans-Oesophageal and Doppler Echocardiography can detect dynamic evidence of pulmonary artery hypertension with fair accuracy. According to literature, the development of porto-pulmonary hypertension can ameliorate the effects of Hepato-pulmonary syndrome making a distinction between the two quite a challenging task.

There is no standardized definition of Cirrhotic Cardiomyopathy. Nonetheless, Cirrhotic decompensation is associated with a hyper dynamic circulatory state, decreased vascular resistance, vasodilatation and low cardiac output.[4] The resultant diastolic and latter systolic dysfunction of the heart is therefore deceptively latent and observed as gradual deterioration in cardiac function precipitated with stress.

The patho-physiology is both intriguing and multifactorial. As cited forehand, hepatic decompensation includes a drop in hepatic clearance/ detoxification reactions, as such an increase in circulation of vaso-active peptides like NO, TNF factors, Vaso-active Intestinal Peptides, prostacyclins, endothelin 1 and 3 amongst others.[4] These cause through complex mechanisms a poor adrenergic response to stress and cardiac myocyte dysfunction. Newer insights include high circulating levels of carbon mono-oxide and endocannibinoids. The latter acts through CB1 receptor causing vasodilatation and has intrinsic cardiotoxic effects.

The cardiologic dysfunction is thus manifested 3-fold. These include Electro-physiological, structural/anatomical abnormalities and poor physiological response to stress.

Electro-physiological changes are noted in electrocardiograms as prolongation of QT-interval and/or Brady/ tachy-arrythmias. The frequency of interval prolongation is directly correlated with increasing hepatic dysfunction.[4,19,26]

Structural changes can be observed as atrio-ventricular chamber hypertrophy and in latter stages dilatation with reduced Fractional shortening/ Ejection Fraction on echocardiograms.[19,26]

Early recognition of Hepatic-cardiac syndrome is important as pertinent clinical measures for co-morbidities like hypotension, Hepato-renal syndrome or portal hypertension for instance, TIPSS (Trans-jugular Intra-hepatic Porto-Systemic Shunting) can potentially precipitate congestive cardiac failure.[29,30]

Diastolic dysfunction is observed before systolic dysfunction. The syndrome will mimic congestive cardiac failure in long term, presenting with

an increased frequency of hypoxemia, decreased exercise tolerance and a detectable drop in arterial saturation.

The exact prevalence of Cirrhotic cardiomyopathy is currently unknown due to its confounding and latent presentation.[31] The diagnostic criteria however were laid out at the 2005World Congress of Gastroenterology at Montreal (Table-5).[32] Cirrhotic cardiomyopathy can thus be accurately diagnosed with multiple diagnostic modalities applied altogether like ECG, echocardiography and imaging techniques like nuclear scans to observe functional and structural deterioration. It is possible to utilize Pulmonary Capillary Wedge Pressure (PCWP) to exclude systolic dysfunction from PoPH, as higher values would be recorded in the former case; however the procedure is invasive, carrying a fairly high risk for cirrhotic patients.

CONCLUSION

This study established that there was a positive correlation between Alveolar-arterial oxygen difference and severity of chronic liver disease, i.e., A-a DO2 increases with the increasing severity of liver disease, whereas there is negative correlation between PO2 and severity of chronic liver disease. These findings suggest a possible higher prevalence of primary cirrhosis related cardiopulmonary complications when confounding secondary contributing factors like anemia, pleural effusion, atelectasis etc. were ruled out. A case in point, PO2 decreases with the increase in severity of liver diseases and vice versa.

AUTHOR'S CONTRIBUTION

AAS envisaged the study, collected the data designed and edited the manuscript and takes the liability and is answerable for all aspects of the work in certifying that questions related to precision and accuracy of any part of the work are appropriately scrutinised and resolved AZ did data collection and manuscript writing. MZ did statistical analysis, review, editing and finalising the manuscript. SSA did data collection, statistical analysis and manuscript editing.

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