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CARDIAC & PULMONARY COMPLICATIONS SEEN IN LIVER CIRRHOSIS-AN OBSERVATIONAL STUDY AT A TERTIARY CARE HOSPITAL

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Abstract

Introduction: *Cirrhosis is a condition that is defined histopathologically and has a variety of clinical manifestations and complications, some of which can be life-threatening. Patients with cirrhosis and portal hypertension exhibit characteristic cardiovascular & pulmonary hemodynamic changes. The cardiovascular complications include systolic dysfunction, diastolic dysfunction & electrochemical abnormalities like prolonged QT interval in Electrocardiogram (ECG), and Respiratory complications include Consolidation, Pleural Effusion & Pulmonary Arterial Hypertension, which may be due to Hepatopulmonary or Portopulmonary syndrome.* ***Study Design:*** *A two-year prospective observational study was conducted from July,2014 to June 2016.* ***Aim:*** *To study the different cardiac and pulmonary complications in the patients of Liver Cirrhosis.* ***Materials & Methods:*** *A two-year prospective observational study was conducted from July,2014 to June 2016 at a tertiary care hospital in Ahmedabad, Gujarat, India, including 30 patients (>12 years old), who were known cases of cirrhosis of liver as well as those newly diagnosed with it, with cardiopulmonary complications, developed after liver cirrhosis, in the absence of other etiological factors. Clinical profile with laboratory studies and diagnostic tests were studied.* ***Results:*** *This study showed that cardiopulmonary complications in cirrhotic patients are more frequently seen in males than females, which commonly manifest during third & fourth decade. Dyspnoea is the most common symptom seen in the study. Among the pulmonary complications, Pneumonia & Hydrothorax are more common compared to hepatopulmonary & portopulmonary syndromes, and among cardiac complications, Diastolic dysfunction is a major complication in such patients, which increases with increasing severity of cirrhosis, as indicated by CP score.* ***Conclusion:*** *Among these patients, Cardiac and pulmonary complications have nearly the same incidences.*

Keyword: *Cardiac, Pulmonary, Liver Cirrhosis, Tertiary Care Hospital*

INTRODUCTION

Cirrhosis is a condition that is defined histopathologically and has a variety of clinical manifestations and complications, some of which can be life-threatening [1]. It is most commonly caused by Alcohol, Hepatitis B, Hepatitis C and Non-Alcoholic Fatty Liver Disease[1,2]. Regardless of the cause of cirrhosis, the pathologic features consist of the development of fibrosis to the point that there is architectural distortion with the formation of regenerative nodules. This results in a decrease in hepatocellular mass, and thus function, and an alteration of blood flow. The induction of fibrosis occurs with activation of hepatic stellate cells, resulting in the formation of increased amounts of collagen and other components of the extracellular matrix[1]. This fibrosis & nodules leads to increased intrahepatic resistance to the passage of blood flow and higher pressure in the portal venous system, resulting in Portal Hypertension[1]. Clinically significant portal hypertension is present in >60% of patients with cirrhosis[1].

Patients with cirrhosis exhibit characteristic cardiovascular & pulmonary hemodynamic changes. In cirrhosis, there is overproduction of the vasodilators of systemic or intestinal origin, & these circulating vasodilators escape degradation in the damaged liver or bypass the liver through portosystemic collaterals. [3] This leads to widespread peripheral arterial vasodilation. And according to Schrier's "peripheral arterial vasodilation" hypothesis[4], there is primarily splanchnic arteriolar vasodilation, which eventually decreases blood volume & blood pressure in the areas where baroreceptors are located in the body, leading to activation of these receptors & vasoconstrictor systems (SNS, RAAS) & secondary sodium retention. [4,5]

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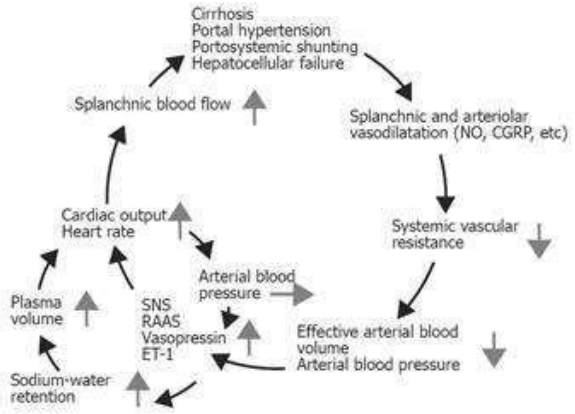

Figure 1: HEMODYNAMIC CHANGES IN CIRRHOSIS
The hemodynamic consequences are increase in cardiac output, heart rate and blood volume, and decrease in renal blood flow, low arterial blood pressure & fluid and water retention. This development of hyperdynamic circulation may, in turn, increase splanchnic blood flow & further aggravates the portal hypertension in a vicious cycle.

CARDIOVASCULAR MANIFESTATIONS
The hyperdynamic circulation, as described above, increases cardiac output, heart rate & blood volume, which eventually increases heart's work & oxygen demand [6,7]. In patients without cirrhosis, this would cause cardiac failure, but because of the decreased afterload as reflected by decreased systemic vascular resistance & increased arterial compliance, a left ventricular failure may be latent in cirrhosis. [7,8] Such Heart failure may manifest during physical stress (exercise), or pharmacological stress (treatment with vasoconstrictors) [9]. This type of cardiac dysfunction is knows as cirrhotic cardiomyopathy and includes systolic dysfunction, diastolic dysfunction & electrochemical abnormalities like prolonged QT interval in Electrocardiogram (ECG).[10] Various electrophysiological mechanisms for the conductance abnormalities and impaired cardiac contractility have been put forward, including reduced beta-adrenoreceptor density, post-receptor signal defects, abnormal excitation-contraction coupling, and metabolic abnormalities.(11)

A) Systolic Dysfunction:
The Left Ventricular Ejection Fraction (LVEF) i.e. the stroke volume relative to the left ventricular end-diastolic volume, is an often-used measure of systolic function. At rest, LVEF has been normal in some studies (12-14) and reduced in one study in a subgroup of patients with ascites. (15) The functional capacity of heart decreases in cirrhosis, as reflected by some studies, in which the maximum aerobic exercise capacity and maximum heart rate are lower in most of the patients with cirrhosis (9,13,16). Also, after exercise, the increase in LVEF is significantly less in cirrhotic patients than in controls. (9,16,17) The reduced functional capacity may be attributed to a combination of factors such as blunted heart rate response to exercise, reduced myocardial reserve, & profound skeletal muscle wasting with impaired oxygen extraction.(13)
Also as described above, multiple studies have proved that physical or pharmacological stress usually unmasks the latent, underlying systolic dysfunction in cirrhotic patients(9,16,18).

B) Diastolic Dysfunction:
In multiple studies, the cardiac hypertrophy, patchy fibrosis & subendothelial edema of cirrhotic patient's heart has been reported, all of which eventually lead to diastolic dysfunction .(11,17) In decompensated cirrhotic patients with ascites, diastolic dysfunction is aggravated after TIPS (19,20), and while Liver transplantation reverse all the cardiac abnormalities to normal, including diastolic dysfunction (17), paracentesis seems to reverse only diastolic dysfunction and not systolic dysfunction (15). Many studies have reported of unexpected death from heart failure following surgical procedures like portocaval shunts & TIPS (21). These procedures involve a rapid increase in cardiac preload in a less compliant heart, during which the diastolic dysfunction is enough to cause pulmonary edema and heart failure. This is consistent with the findings of Hounker et al (20), who reported an increase in pulmonary artery pressure, pre-load, and diastolic dysfunction after TIPS. Diastolic dysfunction could thus account for part of the cardiac dysfunction in cirrhotic cardiomyopathy. This is further proven by multiple studies that have reported much increased A-wave (reflecting the late atrial contraction) & E-wave velocities(reflecting the early rapid trans mitral flow) and isovolumetric relaxation & deceleration times with decreased E/A ratio in Doppler-echocardiogram during diastole, in cirrhotic patients with ascites, which indicates diastolic dysfunction(15,19).

C) Autonomic Dysfunction:

Most studies have found a high prevalence of autonomic dysfunction in cirrhosis with associations to liver dysfunction & survival [22,23]. The results of Mohamed et al[24] suggest that the autonomic dysfunction is temporary, arises as a result of liver dysfunction, and may be reversible after liver transplantation. Whereas most of the studies have focused on the sympathetic system dysfunction, recent papers have emphasized the importance of defects in parasympathetic system & vagal nerve conduction leading to sodium & fluid retention [23,25]. Sympathetic responses to dynamic exercise seem to be normal in patients with cirrhosis, but those to isometric exercise are clearly impaired [26,27]. Similarly, blood pressure responses to orthostasis are impaired, probably because of a blunted baroreflex function [28,29].

PULMONARY MANIFESTATIONS

Patients with cirrhosis often have complaint of breathlessness and decreased arterial oxygenation, which typically occurs while sitting up [platypnea] [30,31]. The etiology of abnormal lung function and ventilation in cirrhosis may be multifactorial and is often a combination of cardiac dysfunction, heavy smoking and Chronic obstructive pulmonary Disease (COPD), which is common in the patients with alcoholic cirrhosis [32]. But independent of smoking status, patients with cirrhosis have a compromised lung function with a reduced transfer factor and ventilation/perfusion abnormalities [32-35], and arterial hypoxemia is seen in 30-70% of the patients with chronic liver disease, depending on the severity [36].

A) HEPATOPULMONARY SYNDROME:

HPS is defined as the triad of liver disease, pulmonary gas exchange abnormalities leading to arterial deoxygenation, and evidence of intrapulmonary dilatations, in the absence of detectable primary cardiopulmonary disease[35]. According to the hypothesis "peripheral arterial vasodilation", as described above, Primary vascular resistance of pulmonary circulation is also decreased in cirrhosis[37] which ultimately leads to increased perfusion as compared to alveolar ventilation in many areas, leading to perfusion/ventilation mismatch[33]. Besides the abnormal ventilation/perfusion ratio and the presence of regular pulmonary arteriovenous shunts, intrapulmonary vascular dilatations have also been described [34,37] .Pulmonary angiography of these patients has revealed two types of patterns with a spongiform appearance of the vessels & small arteriovenous communications [34]. Fallon et al [38] have recently reported increased pulmonary vascular endothelial NOS to be the major cause. The diagnosis of the hepatopulmonary syndrome is based on arterial hypoxemia (PaO_2<9.31 kPa), an age-adjusted increased alveolar-arterial oxygen gradient (>2.66 kPa) and intrapulmonary vasodilatation [39]. A 100% oxygen shunt study with the patient breathing 100% oxygen may discriminate between functional & anatomic shunts [34]. Contrast enhanced echocardiography is considered as the method of choice in the diagnosis of the HPS [40].

B) PORTOPULMONARY SYNDROME:

Portopulmonary hypertension is defined as pulmonary arterial hypertension (PAH) associated with portal hypertension, in the absence or presence of underlying liver disease[41-43] and is diagnosed as a mean pulmonary artery pressure > 3.325 kPa and pulmonary vascular resistance >120dyn.s/cm^5, and normal left atrial pressure (<1.995 kPa) [37]. It is rare in cirrhosis with an average prevalence from 1% to 4% [44]. Symptoms are typically progressive and include fatigue, dyspnea & edema [34] The histologic appearance of pulmonary vessels is similar to that seen in primary pulmonary hypertension and includes smooth muscle proliferation & hypertrophy [39]. Local vasoconstrictor systems, like the endothelin system, may play a role and recently the administration of a mixed ET-antagonist has showed beneficial effects in portopulmonary hypertension[45,46].

MATERIAL AND METHODS

A two-year prospective observational study was conducted from July,2014 to June 2016 at a tertiary care hospital in Ahmedabad, Gujarat, India. The study included 30 patients (>12 years old), who were known cases of cirrhosis of liver as well as those newly diagnosed with it (fibronodular chronic changes with altered echotexture & irregular margins with decreased size in ultrasonography), with cardiopulmonary complications, developed after liver cirrhosis, in the absence of other etiological factors. Their detailed history was taken, and complete general, physical and systemic examination was done. The following haematological investigations were carried out for all the patients – Arterial Blood Gas Analysis (ABGA), Haemoglobin (Hb), Total Leucocyte Count (TLC), Platelet Count, Erythrocyte Sedimentation Rate (ESR), total & direct bilirubin, total proteins, serum albumin, prothrombin time (PT) & INR, serum urea & creatinine, serum sodium & potassium, Viral markers: HIV, HBsAg, HCV. Other investigations included: Ultrasonography (USG), Electrocardiogram (ECG), Echocardiography (2D ECHO), Chest Xray (PA), HRCT thorax, Coronary Angiography (CAG) & Pulmonary Function Test (PFT) were carried out according to availability & indications. Patients were

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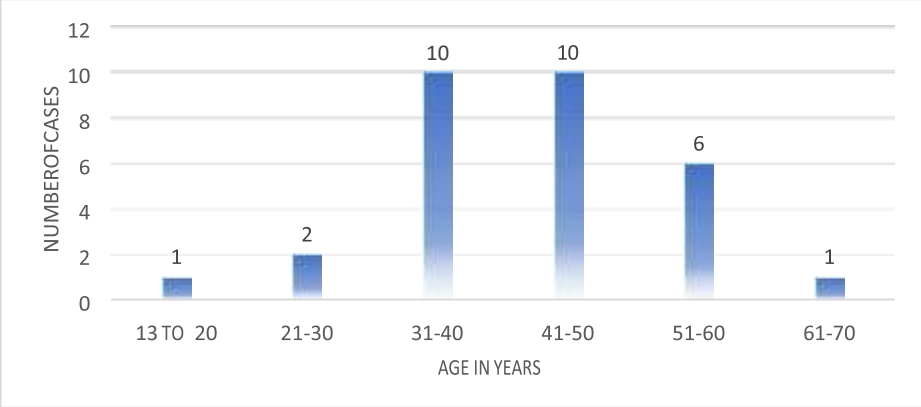
categorised according to Child Pugh Score (CPS). Patients <12 years old, with pre-existing cardiopulmonary diseases, active smokers & known case of Hypertension & Diabetes Mellitus were excluded from the study.

TABLE 1: THE AGE DISTRIBUTION

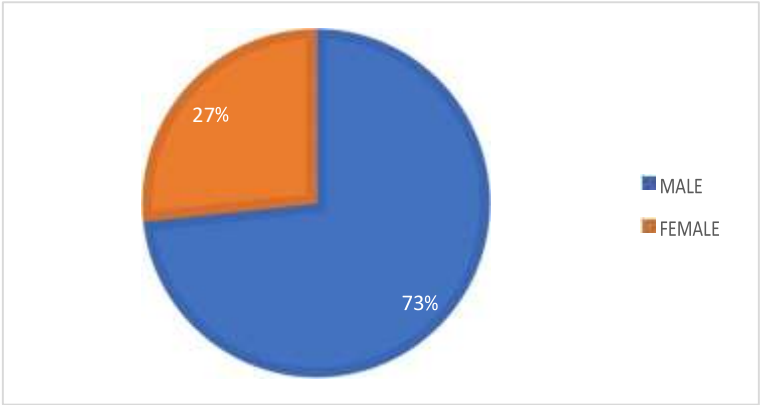
AGE IN YEARS	NUMBER OF CASES	PERCENTAGE (%)
13 TO 20	1	3.33
21-30	2	6.67
31-40	10	33.33
41-50	10	33.33
51-60	6	20
61-70	1	3.33
MEAN=43		
STANDARD DEVIATION=10.2		



Among 30 cases studies, maximum incidence was in 4th & 5th decade, of around 67%. The youngest patient was 18 years old, while the oldest was 65 years old.

TABLE 2: SEX DISTRIBUTION

SEX	NO. OF CASES	PERCENTAGE (%)
MALE	22	73
FEMALE	8	27



The above table & pie chart show that in liver cirrhosis, cardiopulmonary complications are more common in the males than females.

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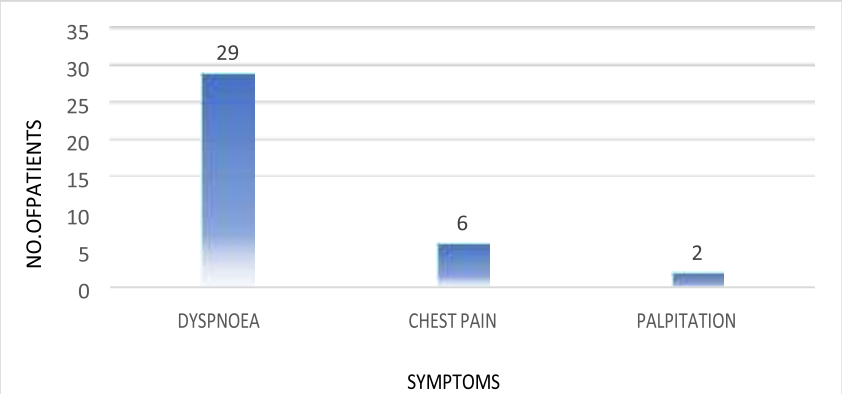
TABLE 3: INCIDENCE OF THE PRESENTING SYMPTOMS.

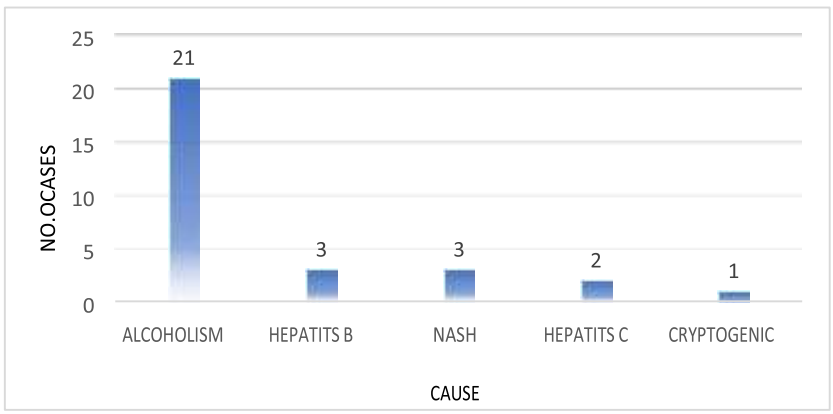
SYMPTOMS	NO. OF PATIENTS	PERCENTAGE (%)
DYSPNOEA	29	96.66
CHEST PAIN	6	20
PALPITATION	2	6.67



In this study, most of the patients, i.e. 96.6% presented with complaint of dyspnea.

TABLE 4: CAUSES OF CIRRHOSIS IN THIS STUDY

CAUSE	NO. OF CASES	PERCENTAGE (%)
ALCOHOLISM	21	70
HEPATITS B	3	10
NASH	3	10
HEPATITS C	2	6.67
CRYPTOGENIC	1	3.33



In this study, most of the patients had cirrhosis due to chronic alcoholism (70%).

TABLE 5: INCIDENCE OF VARIOUS CARDIAC & PULMONARY COMPLICATIONS IN LIVER CIRRHOSIS PATIENTS.

COMPLICATIONS	NO. OF PATIENTS	PERCENTAGE (%)
CARDIAC	15	50
PULMONARY	14	46.6
CARDIAC & PULMONARY BOTH	1	3.33

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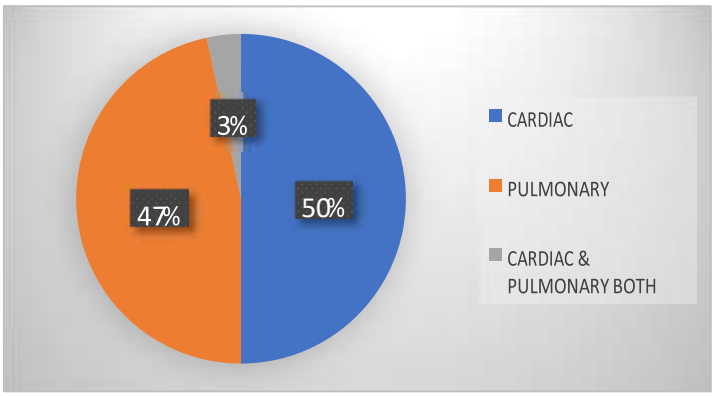

In this study, 50 % of the patients had cardiac complication and around 46% had pulmonary complications, while only 1 patient had both cardiac as well as pulmonary complications.

TABLE 6: INCIDENCE OF VARIOUS CARDIAC & PULMONARY COMPLICATIONS COMPARE TO TOTAL PATIENTS INCLUDED IN THE STUDY.

COMPLICATIONS	NO. OF PATIENTS	PERCENTAGE (%)
CARDIAC		
DIASTOLIC DYSFUNCTION	9	30
LONG QT INTERVAL	8	26.66
CARDIOMEGALY	8	26.99
SYSTOLIC DYSFUNCTION	1	3.33
PULMONARY		
CONSOLIDATION	8	26.66
PLEURAL EFFUSION	7	23.33
PULMONARY HYPERTENSION*	7	23.33

*Includes moderate to severe pulmonary hypertension with RVSP>40 mmHg.

The table shows that among cardiac complications, diastolic dysfunction (30%) is more common than systolic dysfunction (3.33%), & among pulmonary complications, consolidation (26.66%) is more common than pulmonary hypertension (23.33%) & pleural effusion (23.33%).

TABLE 7: RVSP (RIGHT VENSTRICULAR SYTOLIC PRESSURE) OF THE PATIENTS INCLUDED IN THE STUDY, ON 2D ECHO.

RVSP (mmHg)	NO. OF PATIENTS	PERCENTAGE (%)
<25 (NO PH)	4	13.33
25-40 (MILD PH)	19	63.33
>40 (MODERATE-SEVERE PH)	7	23.33
MEAN=33.8		
STANDARD DEVIATION=6.7		

According to the analysis, most of the patients (63.33%) in our study had mild Pulmonary Hypertension (PH), while only 23% had moderate to severe PH, due to any cause including Hepato-pulmonary & Porto-pulmonary syndromes.

TABLE 8: HYPOXEMIA IN THE PATIENTS INCLUDED IN OUR STUDY.

ARTERIAL PARTIAL PRESSURE OF OXYGEN=PaO_2 (mmHg)	NO. OF PATIENTS	PERCENTAGE (%)
>80 [NORMAL]	3	10

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60-79 [MILD]	23	76.6
40-59 [MODERATE]	4	13.33
<40 [SEVERE]	0	0

In our study, most of the patients (76%) had mild hypoxemia, while only 13% had moderate hypoxemia & 10 % had no hypoxemia.

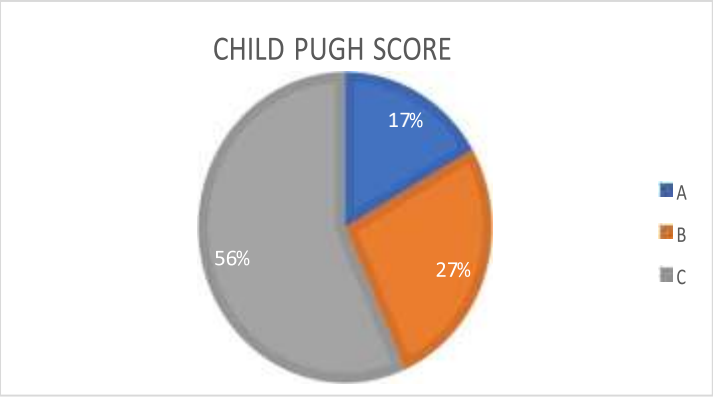
CHILD PUGH SCORE: CPS, initially termed as Child-Turcotte score, was proposed more than 30 years ago. It was originally designed for predicting the outcome after surgery for portal hypertension (portocaval shunting and transection of the esophagus) in patients with cirrhosis. Child-Turcotte score included two continuous variables: Bilirubin & Albumin, and three discrete variables: Ascites, Encephalopathy & nutritional status, which were empirically selected because they were felt to have their own influence on the prognosis in the context.

TABLE 9: INTERPRETATION OF CPS.

CPS CLASS	SEVERITY	ABDOMINAL SURGERY PERI-OPERATIVE MORTALITY	1 YEAR SURVIVAL	LIFE EXPECTANCY
A (5 to 6 points)	LEAST SEVERE	10%	100%	15-20 years
B (7 to 9 points)	MODERATELY SEVERE	30%	80%	candidate for liver transplant
C (10 to 15 points)	MOST SEVERE	82%	45%	1-3 months

TABLE 10: DISTRIBUTION OF OUR PATIENTS ACCORDING TO CPS.

CHILD PUGH SCORE (CPS)	NO. OF PATIENTS	PERCENTAGE (%)
A	5	17
B	8	27
C	17	56



DISCUSSION

The two-year prospective observational study was conducted from July 2014 to June 2016 at a tertiary care hospital; total of 30 cirrhotic patients with cardio-pulmonary complications were studied.

TABLE 11: INCIDENCE OF PNEUMONIA [CONSOLIDATION]

	Present Study	Tsung-Hsing Hung et al.47
Incidence of Pneumonia	26%	21.40%

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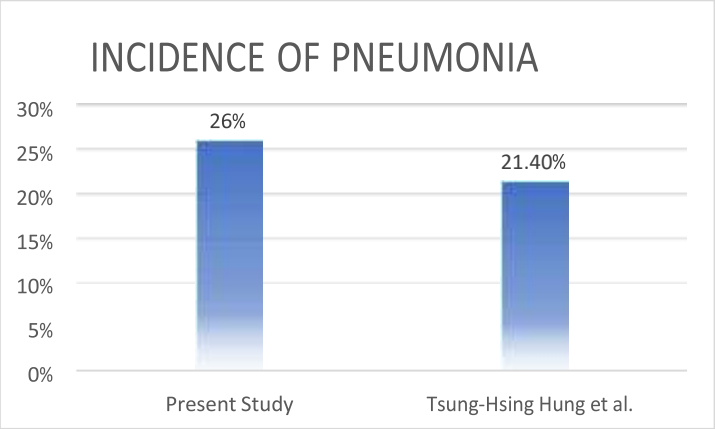

According to this study, 26% of the cirrhotic patients developed pneumonia in the form of consolidation, which included community, hospital-acquired & Aspiration Pneumonia. These findings are comparable with the Tsung-Hsing Hung[47], in which 21% of the patients had pneumonia. Cirrhotic patients are more prone to develop infectious diseases because of their underlying immunocompromised status. Also, Hepatic Encephalopathy & tracheal intubations are usually considered to be the risk factors for the development of Pneumonia in cirrhotic patients. In addition, plasma-based blood products transfusion increases the risk acute lung injury & pneumonia. In order to prevent cirrhotic patients from developing pneumonia, it is critical to avoid needless transfusions & influenza infections [(47)].

TABLE 12: INCIDENCE OF HEPATIC HYDROTHORAX.

	Present Study	Amr M. Helmy et al.[48]
Hepatic Hydrothorax	23%	23.34%

Our study showed that around 23% developed hydrothorax, which is comparable to Amr M.Helmy study[48], which also shows that 23% developed hydrothorax.
Hepatic hydrothorax or Pleural Effusion due to Cirrhosis is typically right sided, which usually coexists with ascites, although it can also be present without significant ascites. The mechanism of hydrothorax is thought to be due to diaphragmatic defects, which allow the seepage of ascitic fluid from abdomen, through hepatic surface, into the pleural space. The negative intrathoracic pressure draws the fluid into the pleural space. Consequently, Pleural Fluid analysis shows similar characteristics to that of ascitic fluid.

TABLE 13: INCIDENCE OF PULMONARY HYPERTENSION.

STUDY	INCIDENCE OF PULMONARY HYPERTENSION
AMR M. HELMY[48]	12%
THEVENOT ET AL[49]	20%
KARI ET AL[50]	24%
PRESENT STUDY	23.33%

In our study, we have taken the RVSP as a marker of pulmonary hypertension, and patients with RVSP>40 mmHg, are included in this table. In our study, 23% of the patients developed Pulmonary Hypertension, which is comparable to the studies like Thevenot et al[49], in which 20% of the patients & Kari et al[50], in which 24% of the patients developed pulmonary hypertension.
This pulmonary hypertension in liver cirrhosis can be due to hepatopulmonary syndrome, portopulmonary syndrome, due to long standing respiratory infections, secondary to cardiac involvement or may be primary.

TABLE 14: INCIDENCE OF PROLONGED QT INTERVAL.

STUDY	INCIDENCE OF PROLONGED QT INTERVAL
S. PATIL ET AL[51]	33.33%
KOSER ET AL[52]	32%

PRESENT STUDY	27%

In our study, ECG showed QT prolongation in 27% of the patients, while in other studies like S.Patil et al[51] & Koser et al[52], it was present in 33% & 32%, respectively.

This ECG finding was unrelated to the etiology of cirrhosis but was positively related to the severity of disease. It may reflect electrolyte abnormalities, especially those of calcium, hyperbilirubinemia, myocardial ischemia, drugs & alcohol toxicity, and hypersensitivity of autonomic nervous system.

TABLE 15: PERCENTAGE OF MALE & FEMALE PATIENTS COMPLICATED BY CARDIOPULMONARY SYMPTOMS IN LIVER CIRRHOSIS.

SEX	PRESENT STUDY	S. PATIL ET AL[51]
MALES	73%	68.33%
FEMALES	27%	32%

This table concludes that, in our study, the cardiopulmonary complications in liver cirrhosis is more common in males (73%) than in females (27%), which is comparable to the study S. Patil et al[(51)], mentioned in the table. In our country, males are more commonly alcoholic than females, which could be the reason for same[(51)].

TABLE 16: RELATION OF CPS & DIASTOLIC DYSFUNCTION.

CHILD PUGH SCORE (CPS)	PRESENT STUDY	SALARI ET AL52
A	22.22%	18.20%
B	33.30%	47.40%
C	44.50%	55%

This table suggests the significant correlation between severity of cirrhosis, in the form of Child Pugh Score (CPS), and diastolic dysfunction in our study. As the severity increases from score A to C, normal diastolic function decreases. The same has been proved by Salari et al study[(52)]. This diastolic dysfunction can be due to stiffened ventricular wall as a result of cardiac hypertrophy described in cirrhotic cardiomyopathy.

LIMITATIONS OF THE STUDY

Ideally, hepatopulmonary and portopulmonary syndromes are diagnosed based on contrast echocardiography & other investigations, but we had no facility for such investigations, so we have not included such patients separately in the study. Instead, we have studied them commonly as pulmonary hypertension based on RVSP.

CONCLUSION

The study showed that cardiopulmonary complications in cirrhotic patients are more frequently seen in males than females, which commonly manifest during third & fourth decade. Dyspnoea is the most common symptom seen in the study. Alcohol is a major risk factor for liver cirrhosis as well as for high incidence of cardiopulmonary complications in cirrhotic patients, followed by viral hepatitis.

Cardiac and pulmonary complications have nearly the same incidences. Among the pulmonary complications, Pneumonia & Hydrothorax are more common compared to hepatopulmonary & portopulmonary syndromes.

Diastolic dysfunction is a major cardiac complication in such patients, which increases with increasing severity of cirrhosis, as indicated by CP score. Electrophysiologic abnormalities are also seen in many patients compared to other cardiac complications, seen in the form of prolonged QT interval in ECG. Most cirrhotic patients have mild pulmonary hypertension with dyspnoea as a major symptom.

NOTE: No Conflict of Interest

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