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"Cardiovascular manifestations in alcoholic liver disease"

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Abstract
Background*:*
Alcohol(Ethanol) is known to cause harmful effects to body. According to World Health Organization (WHO), harmful use of alcohol accounts for 5.3% of all deaths worldwide.[1] Excessive consumption of alcohol significantly increases morbidity and mortality from hepatic, cardiovascular, pancreatic, brain, renal and oncological diseases.[2]Of all deaths attributable to alcohol consumption 19% is attributed to cardiovascular diseases.[1] Numerous cardiac diseases are directly or indirectly attributed to alcohol use more so in chronic usage. The amount of alcohol and duration of its usage are independent risk factors for liver cirrhosis and also cardiac abnormalities. Consumption of >25 g of alcohol per day in males and >12 g/day in females for 10–12 years is associated with an increased risk of liver cirrhosis.[3,4]Multiple literature researches showed evidence of cardiac abnormalities in chronic alcoholics in Western populations. For this part of Indian subcontinent especially in Northeastern state of Manipur where populations of alcoholics are high there is inherent necessity therefore we conducted this study to identify the various cardiac manifestations in spectrums of alcoholic liver disease (ALD) and to correlate them with the severity of ALD and cirrhosis.
Methods: *This cross-sectional study was conducted in Regional Institute of Medical Sciences (RIMS), Imphal, Manipur from October 2019 to September 2021. 98 alcoholic liver disease patients who attended Medicine OPD or admitted in the General Medicine wards were enrolled. Cardiac manifestation was observed by Chest X-ray, ECG and Echocardiography. Liver function tests, viral markers and other investigations as per clinical suspicion were done.*
Results: *A total of 98 alcoholic liver disease patients were included in the study. The mean age of the participants was 47.01±12.43 years with majority (28.6) of them in the age group of 41-50 years. Majority (88.8%) of the participants were males and females were 11(11.2%). Fatty liver was present in 26(26.5%), hepatitis in 25(25.5%) and majority were cirrhotics in 47(48%). Cardiomegaly on chest X-ray was present in 36.7% patients, ischemic changes was present in 23.5% of the patients, Dilated cardiomyopathy (DCM) was detected in 37.8%. subjects, hypertension in 7.2% patients, ischemic stroke in 14.3%, hemorrhagic stroke in 5.1%. Cardiomegaly, ischemic changes on ECG. DCM and incidence of stroke were significantly higher among cirrhotic patients when compared with fatty liver and hepatitis patients and their association were statistically significant (p value< 0.005). There was no significant association between liver disease grade and incidence of hypertension in this study.*
Conclusion: *Our study inferred a strong positive correlation of cirrhosis with cardiomegaly, ischemic changes on ECG, DCM and incidence of stroke. The results of this study indicate that alcoholic cardiomyopathy and cirrhosis not only may coexist, but that they often do.From these findings, we can substantiate the possibility of cardiac impairment as a secondary effect of liver cirrhosis and can conclude that liver cirrhosis has significant negative influence on the cardiovascular system.*

Keyword: *alcohol, alcoholic liver disease, cirrhosis, dilated cardiomyopathy*

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I. Introduction

Overuse of alcohol has been known to cause innumerable organ injury especially liver. However, its effect on cardiovascular system is less. According to World Health Organization (WHO), harmful use of alcohol accounts for 5.3% of all deaths worldwide. Of all deaths attributable to alcohol consumption 19% is attributed to cardiovascular diseases.[1] Excessive consumption of alcohol significantly increases morbidity and mortality from hepatic, cardiovascular, pancreatic, brain, renal and oncological diseases.[2] Consumption of >25 g of alcohol per

day in males and >12 g/day in females for 10–12 years is associated with an increased risk of liver cirrhosis.[3,4] Those amounts of alcohol can be cardioprotective, and therefore patients with liver cirrhosis may not present with alcoholic heart disease, but rather with cirrhotic cardiomyopathy.[4,5]

Recent hemodynamic, metabolic and structural studies in man and experimental animals have emphasized the deleterious effect on the heart of chronic alcohol ingestion.[6-12] .The liver is the most affected organ, since ethanol is mostly metabolized there[13,14] but gastrointestinal, central, and peripheral nervous system, the heart and vascular system, endocrine system, nutrition and musculo-skeletal system are clearly affected.[15]

Cardiomyopathy is a severe disorder of the heart muscle characterized by significant functional or electrical dysfunction of the myocardium with progressive heart failure as the most devastating complication. Cardiomyopathies can be classified as either primary or secondary. Primary cardiomyopathies are genetic in nature while secondary cardiomyopathies occur in the setting of a medical condition or due to environmental factors such as toxins or medications.[16] Alcohol is one of toxic substances frequently consumed globally.[17]Although daily intake of low to moderate amounts of alcohol improves the cardiovascular health of ischemic and non-ischemic patients, chronic and excessive consumption of alcohol could result into progressive cardiac dysfunction and heart failure (HF).[18,19]

Alcoholic cardiomyopathy is a form of dilated cardiomyopathy (DCM) and a typical example of secondary cardiomyopathy which is associated with chronic and excessive consumption of alcohol. It accounts for 40% of DCM cases.[20-23] Similar to other causes of DCM, alcoholic cardiomyopathy (ACM) is characterized by an increased left ventricular end-diastolic diameter (LVEDD) and a reduced left ventricular ejection fraction (LVEF).[24] However, the diagnosis is usually one of exclusion in a patient with a long history of heavy alcohol abuse, as no specific clinical, or histological features have been identified.[20-23] Individuals who consume more than 80 g of alcohol per day over a period of at least 5 years are at risk for the development of alcoholic cardiomyopathy and heart failure (HF).[20,25,26]

Although many risk factors like advanced age, hypertension, diabetes mellitus, obesity, valvular heart disease, and myocardial infarction have been recognized as predictors of HF,[27,28] limited data are available on the effects of modifiable lifestyle factors on the risk of HF.

Despite the evidence that links excessive alcohol ingestion with some cases of "primary" cardiomyopathy, cardiac impairment has not generally been thought to be an important factor in the deciding the management of the alcoholic patient with chronic liver disease. [6-12,]The importance of alcohol as a cause of DCM was investigated in only few studies. With this background in mind, the study was conducted to identify the various cardiovascular manifestations in alcoholic liver disease (ALD) and to correlate them with the severity of ALD.

II. Materials and Methods

This cross-sectional study was conducted in Regional Institute of Medical Sciences (RIMS), Imphal, Manipur from October 2019 to September 2021. 98 alcoholic liver disease patients who attended Medicine OPD or admitted in the General Medicine wards were enrolled following the criteria.

Inclusion Criteria

1. All previously or newly diagnosed alcoholic liver disease patients (>30g/day for more than 5 years) with deranged LFT, USG evidence of fatty liver, hepatitis, cirrhosis.
2. Those above 18 years of age giving consent for participation.

Exclusion Criteria include patients diagnosed with Viral hepatitis/cirrhosis (Hep B,Hep C related) ,drug induced hepatitis /cirrhosis, haemochromatosis ,Wilsons Disease, autoimmune steato-hepatitis and those not giving consent.

Study procedure Independent variables: Personal details including a detailed history of presenting symptoms, past history and personal history were recorded in proper proforma along with age, sex, stages of hypertension grade of chronic liver disease and cardiovascular manifestations. A complete physical examination with emphasis on the disease activity and duration of every subject was also done. Cardiac manifestation was observed by Chest X-ray, ECG and Echocardiography. Kidney function test, complete hemogram, liver function tests, viral markers, prothombin time and other investigations as per clinical suspicion were done.

Operational definitions:

Standard Alcoholic Drink: A standard alcoholic drink contains approximately 14gms of alcohol, which is equivalent to 12 ounces of beer (~5% alcohol), 8.5 ounces of malt liquor (~9% alcohol), 5 ounces of wine (~12% alcohol), 3.5 ounces of fortified wine (e.g., sherry or port), or 1.5 ounces of liquor (distilled spirits; ~40% alcohol).

Moderate Alcohol Consumption:
Men: No more than two standard alcoholic drinks/day
Women: No more than one standard alcoholic drink/day
Heavy alcohol consumption
Men: More than 14 standard alcoholic drinks/week or more than 4 standard alcoholic drinks in a day
Women: More than 7 standard alcoholic drinks/week or more than 3 standard alcoholic drinks in a day

Statistical analysis: Study variables were expressed as frequency and percentages, mean (±SD) or median (IQR), depending on the type of distribution. Frequencies & proportions for categorical variables like gender, age groups, grade of liver disease, stages of hypertension etc were summarised. Chi squared test was used to see the association between cardiovascular manifestations and grade of liver disease. A p-value of <0.05 was considered significant.
Statistical software: IBM SPSS Version 21.0 for Windows, Armonk NY: IBM Corp.were used for the analysis of the data and Microsoft word and Excel have been used to generate graphs, tables etc**.**

Approval of Research Ethics Board and Informed consent: The study was approved by Research Ethics Board Regional Institute of Medical Sciences, Imphal. (Ref No. A/206/REB-Comm (SP)/RIMS/2015/564/42/2019.)

III. Results

A total of 98 alcoholic liver disease patients were included in the study. Baseline characteristics of the study subjects were given in table 1. The mean age of the participants was 47.01±12.43 years with majority (28.6) of the patients in the age group of 41-50 years. Majority (88.8%) of the participants were males and females were 11(11.2%). Fatty liver was present in 26(26.5%), hepatitis in 25(25.5%) and majority were cirrhotic in 47(48%). Cardiomegaly on chest X-ray was present in 36.7% patients, ischemic changes were present in 23.5% of the patients, DCM on echocardiogram was detected in 37.8%. subjects, hypertension in 7.2% patients, ischemic stroke in 14.3%, hemorrhagic stroke in 5.1%.Associations of grade of liver disease with cardiomegaly, ischemic changes on ECG, DCM on echo, incidence of stroke and incidence of hypertension were shown in table 2,3,4,5,6 respectively. Cardiomegaly, ischemic changes on ECG. DCM and incidence of stroke were significantly higher among cirrhotic patients when compared with fatty liver and hepatitis patients and their association were statistically significant (p value< 0.005). There was no significant association between liver disease grade and incidence of hypertension in this study.

Table1. Baseline characteristics of the study subjects.

Parameters	**Results n(%)** **98 (100%)**
Age in years, mean (range)	47.01±12.43 years
Gender: Male Female	87(88.8%) 11(11.2%)
Grades of liver disease Fatty liver Hepatitis Cirrhosis	 26(26.5%) 25(25.5%) 47(48%)
Chest Xray findings Cardiomegaly normal	 36(36.7%) 62(63.3%)
ECG findings Ischemic changes Low voltage complexes Normal	 23(23.5%) 28(28.6%) 47(48)
Echo findings Dilated cardiomyopathy (DCM) Normal	 37(37.8%) 61(62.2%)
Hypertension stages Normal Pre hypertension Stage 1 hypertension Stage 2 hypertension	 59(60.2%) 32(32.7%) 3(3.1%) 4(4.1%)
Types of stroke No stroke Ischemic stroke	79(80.6%) 14(14.3%) 5(5.1%)

Hemorrhagic stroke	

Table 2. Association of grade of liver disease with cardiomegaly on CXR

Grade of Liver Disease	Cardiomegaly on Chest X-ray		P-value
	Present	Absent	
Fatty Liver	3 (8.3%)	23 (37.1%)	<0.05
Hepatitis	3 (8.3%)	22 (35.5%)	
Cirrhosis	30 (83.3%)	17 (27.4%)	

Table 3. Association of grade of liver disease with Ischemic changes on ECG

Grade of Liver Disease	Ischemic change on ECG		P-value
	Present	Absent	<0.05
Fatty Liver	1 (4.3%)	25 (33.3%)	
Hepatitis	3 (13.0%)	22 (29.3%)	
Cirrhosis	19 (82.6%)	28 (37.3%)	

Table4. Association of grade of liver disease with dilated cardiomyopathy on Echocardiography

Grade of Liver Disease	Dilated Cardiomyopathy on Echocardiography		P-value
	Present	Absent	
Fatty Liver	2 (5.4%)	24 (39.3%)	<0.05
Hepatitis	3 (8.1%)	22 (36.1%)	
Cirrhosis of Liver	32 (86.5%)	15 (24.6%)	

Table 5. Association of grade of liver disease with incidence of stroke

Grade of Liver Disease	Stroke		P-value
	Present	Absent	
Fatty Liver	1 (5.3%)	25 (31.6%)	<0.05
Hepatitis	2 (10.5%)	23 (29.1%)	
Cirrhosis of Liver	16 (84.2%)	31 (39.2%)	

Table6. Association of grade of liver disease with incidence of hypertension

Grade of Liver Disease	Hypertension		P-value
	Present	Absent	
Fatty Liver	17 (28.8%)	9 (23.1%)	0.635
Hepatitis	16 (27.1%)	9 (23.1%)	
Cirrhosis of Liver	26 (44.1%)	21 (53.8%)	

IV. Discussion

Amount of alcohol if taken less and in moderation is helpful in coronary artery diseases, heart failure, stroke etc. One or two drinks (1 drink =17.6ml 100% alcohol) is acceptable. Beyond this amount, it can harm the heart leading to alcoholic cardiomyopathy.[29] Cardiomyopathy is a severe disorder of the heart muscle characterized by significant functional or electrical dysfunction of the myocardium. The most devastating complication is progressive heart failure with considerable morbidity and mortality. Alcoholic cardiomyopathy is a type of dilated cardiomyopathy associated with long-term heavy alcohol intake in the absence of other known causes for myocardial disease.

In this study, a total of 98 patients were recruited consecutively for a period of two years with mean age of 47.01±12.43 years and majority of them were males (88.8%). Other studies observed similar findings.[30,31,32] We observed that almost half (48%) of study subjects had cirrhosis which is in concordance with findings by Gautam MP et al [32](56% of the alcoholics had cirrhosis).

In our study, ischemic changes on ECG were present in 23.5% of the patients. Mishra SK et al,[33] who conducted a cross sectional study to discuss the circulatory and cardiovascular dysfunction in cirrhosis and also examine the pathophysiologic and clinical implications found that Electro physiologically, 38.33% patients of cirrhotic liver patients had abnormal ECG in form of prolonged QTc interval. They found QTc prolongation more in severe degree of cirrhosis MELD score III (7 out of 10) 70%, than moderate (40%) MELD score II and mild (20%) MELD score I of cardiac QTc prolongation. Similar findings were also reported by Sharma KRD and KavyaST [34] that 59% of the patients had abnormal ECG finding. 40% of them had QT prolongation and was related to the severity of liver disease. Sharma KRD and Kavya ST,[34] concluded that chronic liver disease patient's QT prolongation is the most common ECG abnormality. Most common Echocardiographic finding was diastolic dysfunction, which had strong correlation with the severity of the liver disease. Mishra suggested that diastolic dysfunction should be a major criterion of cirrhotic cardiomyopathy.

In our study, cardiomegaly was present in 36.7% patients. Most of the cardiomegaly was apparently diagnosed on chest x-ray. It may be representing the dilated cardiomyopathy on echo which in our study was detected in 37.8%. subjects. Similarly, Estruch R et al,[35] found 50 % of its cases (10 of the 20 active alcoholics with cirrhosis) showed evidence of DCM. They recorded cirrhosis in 13 of 30patients with ACM(43%)and suggested actively drinking alcoholics with cirrhosis had a significantly lower mean ejection fraction and shortening fraction, as well as a greater mean end-diastolic diameter and left ventricular mass than abstaining alcoholics with cirrhosis. Alcoholics admitted solely for cardiomyopathy have a higher prevalence of cirrhosis than unselected alcoholics without heart disease. Actively drinking alcoholics admitted only for cirrhosis show impaired cardiac performance, whereas abstaining alcoholics with liver disease tend to manifest normal cardiac function.

Mechanism of affection of heart by alcohol was postulated by numerous researchers. Studies by J Ren [36] postulated intracellular Ca^{2+} cycling proteins, sarcoendoplasmic reticulum Ca^{2+}-ATPase, Na–Ca^{2+} exchanger and phospho-lamban disturbs the intracellular Ca^{2+} handling .Alcohol derivatives such as ethanol and acetaldehydecause impairment of heart function, hypertrophy and heart failure by increasing catecholamines and reactive oxygen species. Few suggested oxidative stress ,protein-aldehyde adduct formation accumulation of fatty acid ethyl esters or modifications of lipoprotein and apolipoprotein particles [36]

Cardiomyopathy was also found to be significantly higher among the cirrhotic patients when compared with patients who had fatty liver or hepatitis. While Gautam et al,[32] observed a higher proportion (58%) of their subjects suffering from DCM. In our study,86.5% of the cirrhotic patients had dilated cardiomyopathy which is in line with other studies and various literatures.[32,37,39] Dadhich S et al,[40] observed that cirrhosis with portal hypertension is associated with increased heart rate, ejection fraction and mean peak systolic velocity, while mean arterial pressure is decreased. All cardiac chamber dilation occurs and is mostly seen in the left atrium. They concluded that left ventricular diastolic dysfunction is commonly associated with advancement of hepatic dysfunction while systolic function is maintained till advanced hepatic failure.

Estruch R et al,[35] and others opined that in view of the substantial prevalence of cardiomyopathy in alcoholics with liver disease, the occurrence of sudden death in alcoholics with cirrhosis or fatty liver is likely to reflect an increased susceptibility to fatal arrhythmias.[41,42] Actively drinking alcoholics with cirrhosis had a significantly lower mean ejection fraction and shortening fraction, as well as a greater mean end-diastolic diameter and left ventricular mass than abstaining alcoholics with cirrhosis. They conclude that a positive correlation exists between alcoholic cardiomyopathy and cirrhosis. Actively drinking alcoholics admitted only for cirrhosis show impaired cardiac performance, whereas abstaining alcoholics with liver disease tend to manifest normal cardiac function. Hence, in light of the findings from this study we can conclude that chronic alcoholic liver disease has significant negative influence on the cardiovascular system.

V. Conclusion

Alcoholic cardiomyopathy is a type of dilated cardiomyopathy associated with long-term heavy alcohol intake in the absence of other known causes for myocardial disease.In our study, 32(86.5%) of the cirrhotic patients had dilated cardiomyopathy, 19(82.6%) had ischemic changes on ECG, 30(83.3%) had cardiomegaly, 16(84.2%) had stroke and 26(44.1%) had hypertension. These findings were also found to be significantly higher among the cirrhotic patients when compared with patients who had fatty liver or hepatitis. There were statistically significant associations of cirrhosis with cardiomegaly, ischemic changes on ECG and DCM. From these findings, we can substantiate the possibility of cardiac impairment as a secondary effect of liver cirrhosis and can conclude that liver cirrhosis has significant negative influence on the cardiovascular system. This study, employed a representative sample of chronic alcoholics, although a larger sample size inclusive of moderate drinkers and non-drinkers could have been employed for comparison findings. Thus, a prospective study with large sample size will be crucial for further clarification and thereby strengthening of the results of this study.

Declarations:
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Conflict of Interest: None declared
Approval of research ethics board**:** Taken

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