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Study Of Association Of Liver Function Tests With Heart Failure To Assess Severity Of Heart Failure

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Abstract

Background: Heart failure (HF) is the leading cause of death globally. Elevated liver enzymes are common in patients with HF. Primary pathophysiology in hepatic dysfunction from heart failure is either chronic passive venous congestion or low cardiac output and the consequences of hypoperfusion. Elevation of liver biochemical tests in HF patients is associated with poor outcome, including increased frequency of hospitalization and increased mortality.

Objectives: Study of liver function tests in HF patients and to assess factors which influence hepatic dysfunction.

Methods: 100 patients above 18 years of age, of both genders, known and newly diagnosed with HF were studied. Detailed history, clinical examination and relevant investigations including LFT and 2D Echo were done. The patients with normal LFT and abnormal LFT were divided into two groups based on upper normal reference level and the obtained parameters were compared.

Results: Based on our observation, frequency of patients with an abnormal LFT was 53%, with male predominance. All LFT parameters were increased and 'P' value < 0.001 was obtained. Out of 53 patients with abnormal LFT, all the patients had raised total bilirubin (100%), ALT (100%) and reduced ALB (100%). Whereas, a raised AST and ALP was observed among 49 (92.45%) and 51 (96.22%) patients respectively. Abnormal LFT parameters were more frequently seen in patients with biventricular failure followed by LVF and RVF. There was significant increase in LFT as the severity of HF increased with respect to NYHA, as well as among the patients with EF <40%.

Conclusion: Liver dysfunction is common in patients with HF and the prognostic value of LFT parameters have been mentioned in various studies. In our study, we observed that all LFT parameters significantly increased as the severity of HF increased. Hence, the study of LFT parameters in all HF patients is mandatory and has got prognostic value to assess the severity of HF and for better management of patients.

Keywords: Heart failure, Liver function test, NYHA, EF

Introduction

Heart failure (HF) is a clinical syndrome characterized by the inability of systemic perfusion to meet the body's metabolic demand and is usually caused by cardiac pump dysfunction.[1] Heart Failure is the leading cause of death globally. It is responsible for 16% of the world's total deaths.[2] Since 2000, the largest increase in deaths has been for this disease, rising by more than 2 million to 8.9 million deaths in 2019.[2] The recent statistical update from AHA-2022 reported that the lifetime risk of HF remains high, with wide variation across racial as well as ethnic groups, ranging from 20% to 45% after

the age of 45 years. The worldwide prevalence and incidence rates of heart failure are approaching epidemic proportions, as evidenced by the relentless increase in the number of HF hospitalizations, the growing number of HF-attributable deaths, and the spiralling costs associated with the care of HF patients.[2,3]

HF is further subdivided into systolic and diastolic HF. Systolic failure presents as reduced cardiac contractility whereas diastolic failure exhibits impaired cardiac relaxation with abnormal ventricular filling. HF can result from several structural or functional, congenital and acquired cardiac disorders that impair the ability of the ventricle to fill with or eject blood.[4,5] Clinically, HF may present with a syndrome of decreased exercise tolerance due to dyspnoea and/or fatigue-related to impaired cardiac output or may present with a syndrome of fluid retention from elevated filling pressure.[6]

Liver, the largest gland in the body has many complex functions. For the liver to perform its primary functions, high rates of blood flow and close contact between sinusoids and hepatocytes are essential.[7] As a result of its complex vascular supply and high level of metabolic activity, the liver is uniquely vulnerable to a broad spectrum of circulatory disturbances too. Elevated liver enzymes are common in patients with HF. Primary pathophysiology in hepatic dysfunction from heart failure is either chronic passive venous congestion or low cardiac output and the consequences of hypoperfusion. The specific patterns of elevated liver tests differ between patients with chronic and acute decompensated HF and are surrogates of the type of haemodynamic alterations. Elevations of liver biochemical tests in HF patients are associated with increased frequency of hospitalization and increased mortality.[8]

A spectrum of hepatic derangements can also occur in HF particularly in the setting of right heart failure (RHF). Any cause of right ventricular dysfunction can be associated with severe hepatic congestion; patients with hepatic congestion are usually asymptomatic and this entity may be suggested only by abnormal liver function tests (LFT) during routine laboratory analysis. Bridging fibrosis or cardiac cirrhosis can result from prolonged hemodynamic abnormalities, resulting in an impaired hepatic function with impaired coagulation, decreased albumin synthesis, and alterations in the metabolism of several cardiovascular drugs, which can lead to unwanted toxicity.

The biochemical parameters of liver function in HF are found to be moderately elevated 2 to 3 times the upper normal reference level. These parameters include elevated AST, ALT, LDH, GGT, ALP, hyperbilirubinemia, increased PT, INR and decreased serum albumin.[7,8,9] We conducted this study to assess the factors responsible for LFT abnormalities in HF patients.

Methodology

We conducted a cross-sectional, observational, hospital-based study involving inpatients and out patients in the department of General Medicine, Rajarajeswari Medical College and Hospital, Bengaluru. 100 patients of both genders aged between 18 to 80 years, with their informed consent, presenting with symptoms suggestive of heart failure. Critically ill patients, pregnant females, patients with history of alcoholism, those with history suggestive of hepatocellular jaundice (present/ past), recent intake of hepatotoxic and cholestatic drugs and patients diagnosed with hepatitis and HIV were excluded from the study.

Study was initiated after obtaining the ethical committee clearance. After taking written informed consent regarding enrolment in the study and maintaining adequate privacy and confidentiality, all patients were subjected to a standardized interview. Detailed medical history was taken and complete general physical and systemic examinations was done to establish the diagnosis of heart failure and rule out close differentials such as renal failure, acute respiratory distress syndrome, acute and chronic liver disease. Patients further underwent investigations including complete hemogram (CBC), urine analysis, renal function test (RFT), liver function test (LFT), serum electrolytes, electrocardiogram (ECG), chest x-ray, 2D echocardiography and USG abdomen.

Descriptive and inferential statistical analysis was carried out using statistical software SPSS 22.0, R environment ver.3.2.2 and MS Excel.

Results

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The data was tabulated into two groups, one with normal LFT and the other with abnormal LFT. All the obtained parameters were analysed to understand the variables affecting the LFT among the patients diagnosed with HF. Out of 100, 47 patients had normal LFT whereas 53 had abnormal LFT. Out of 63 male patients, 44 were in the age group of 41-60 years. Out of 37 female patients, 23 were in the age group of 41-60 years. Mean age is 48.54±8.6 years. We observed a M:F ratio of 1.7: 1, with 63 males and 37 females. Frequency of heart failure in male patients was significantly higher than in females (Table 1, Graph 1). Out of these 63 males, 21 (33.33%) had normal LFT and the rest 42 (66.67%) had abnormal LFT. The number of male patients with abnormal LFT were significantly higher (Table 2).

Table 1: Distribution of subjects according to their age group and gender

Age	Number of study population N (%)	Male	Female
21 to 30	2	2	-
31 to 40	23	11	12
41 to 50	32	23	9
51 to 60	35	21	14
61 to 70	8	6	2
Mean	100	63	37

Graph 1: Distribution of subjects according to their age group and gender

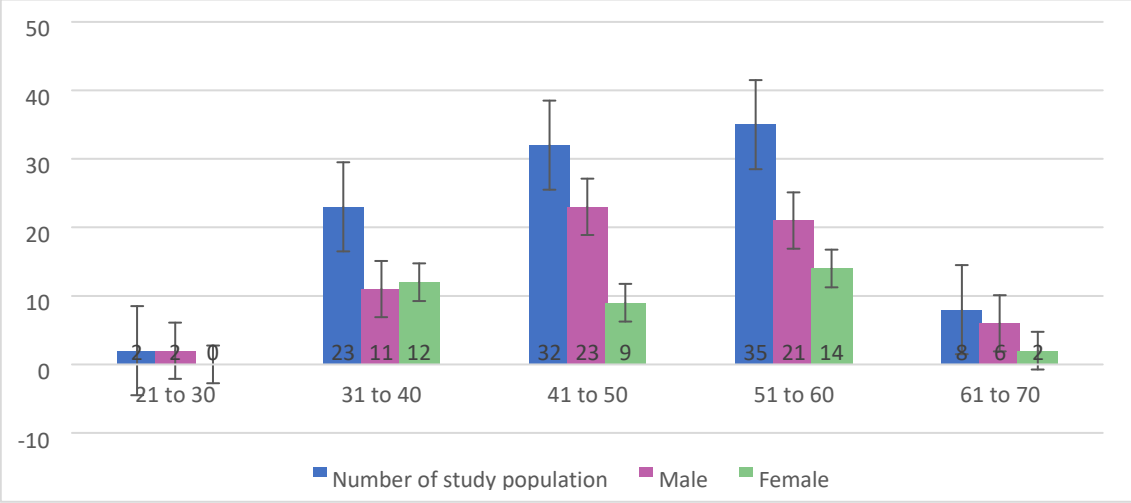

Table 2: Distribution of subjects according to their gender and LFT status

Gender	N	Normal LFT	Abnormal LFT
Male	63 (63%)	21 (33.33%)	42 (66.67%)
Female	37(37%)	26 (70.37%)	11 (29.73%)

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The mean value of Hb distributed among the NYHA 1, 2, 3 and 4 was 11.18±6.2, 11.4±3.5, 10.8±2.7 and 10.1±3 respectively. There was no clinical or statistically significant association observed between Hb and the severity of the HF. Although few patients in NYHA 4 were comparatively lesser Hb than other three groups. Average NT pro BNP were 1028±29.2, 1235±60.5, 2631.84±69.27 and 2950±82.7 among NYHA 1, 2, 3 and 4. This determined the risk among NYHA 3 and 4 patients to develop ischemic heart disease but, as the SD was huge and the number of patients with >450 NTpro BNP was widely distributed, we found statistically significant difference. (Table 3).

Table 3: Distribution of average Haemoglobin and NT pro BNP based on the NYHA classification

Parameters	NYHA 1 Mean	NYHA 2 Mean±SD	NYHA 3 Mean±SD	NYHA 4 Mean±SD	P value Mean±SD
Hb	11.18±6.2	11.4±3.5	10.8±2.7	10.1±3	0.16
NT proBNP	1028±29.2	1235±60.5	2631.84±69.27	2950±82.7	<0.01

Majority of the recruited study population were aged between 41 to 60 years with the frequency 67% of the study population. 23%, 8% and 2% of the study population were aged between 31 to 40, 61 to 70 and 21 to 30 respectively. The distribution of patients based on the age between the two groups is as tabulated above. Mean age of the patients is 48.54±8.6 years. Those with normal LFT was 46.23±5.9 years and abnormal LFT was 49.91±7.3. We did not find any significant difference with respect to age between two groups. Abnormal LFT was more in the age group of 41-60 years (37 patients). (Table 4)

Table 4: Distribution of recruited study population according to their age group and LFT status

Age	Number of study population N (%)	Normal LFT	Abnormal LFT
21 to 30	2	1 (50%)	1 (50%)
31 to 40	23	12 (52.1%)	11 (47.8%)
41 to 50	32	17 (53.1%)	15 (46.9%)
51 to 60	35	13 (37.1%)	22 (62.9%)
61 to 70	8	04 (50%)	4 (50%)
Average age	48.54±8.6 years	46.23±5.9	49.91±7.3

Out of 100 recruited study population, 51% of the study population had presented with symptoms of LVF, followed by 35% with RVF and the rest 14% of them had the symptoms of biventricular failure. Out of 35 patients with RHF, 22 (62.85%) patients had normal LFT and the rest 13 (37.14%) had abnormal LFT. Out of 51 patients with LHF, 22 (43.13%) had normal LFT and 29 (56.86%) had abnormal LFT. Whereas 03/14 (21.43%) had normal LFT and (78.57%) had abnormal LFT among those with biventricular failure. (Table 5, Graph 2).

Table 5: Distribution of subjects according to their type of heart failure and LFT status

Type	N (%)	Normal LFT	Abnormal LFT
Right heart failure	35	22 (62.85%)	13 (37.14%)
Left heart failure	51	22 (43.13%)	29 (56.86%)

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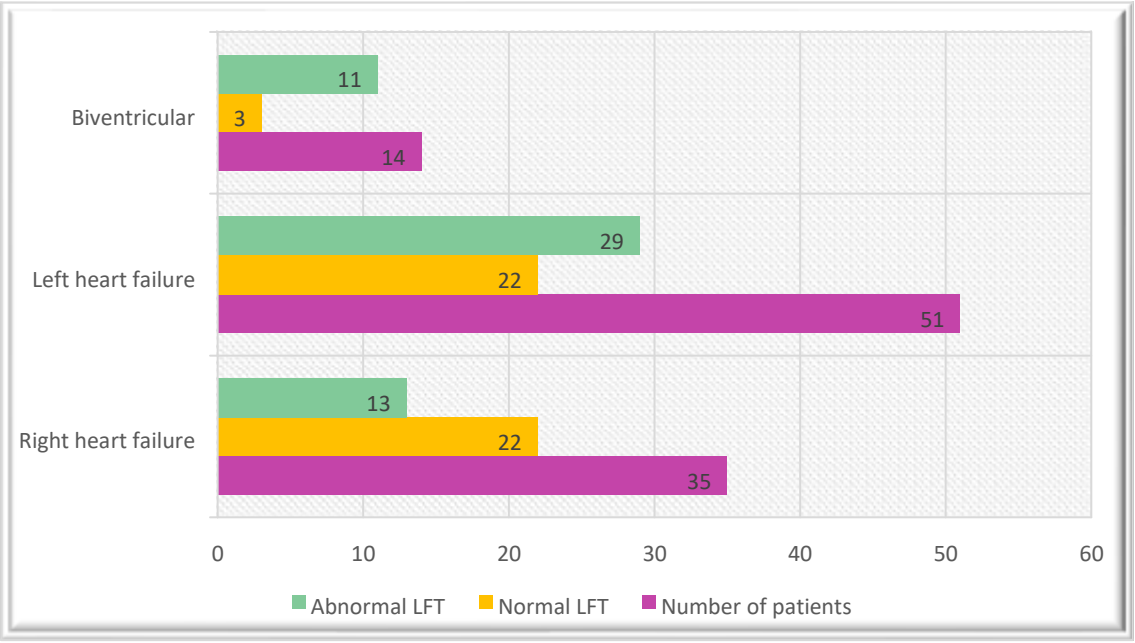
Biventricular	14	03 (21.43%)	11 (78.57%)
P value	0.778		

Graph 2: Distribution of subjects according to their type of heart failure and LFT status



We could observe that all these parameters were significantly higher among the patients with abnormal values. Also, we could observe that all the enzymes were raised above the normal reference range. This indicates that the patients with HF could also be presented with significantly raised LFT. Hence, subjecting all the patients with HF for LFT is mandatory. We found that all the patients had raised total bilirubin, ALT and ALB. Whereas the raised AST and ALP was observed among 49 (92.45%) and 51 (96.22%) of the patients respectively. (Table 6,7, Graph 3).

Table 6: Showing normal and abnormal LFT parameters

Average Parameters	Normal LFT	Abnormal LFT	P value
Total bilirubin	2.8±0.23	2.2±1.4	<0.001
ALT	39.53±23.49	329.56±38.1	<0.001
AST	33.82±18.52	675.82±112.3	<0.001
ALP	88.35±31.5	392.36±28.4	<0.001
ALB	3.4±1.2	2.3±0.2	<0.001

Table 7: Distribution of population based on the abnormal LFT parameters

Parameters	Abnormal	P value
Total bilirubin	53 (100%)	<0.001
ALT	53 (100%)	<0.001

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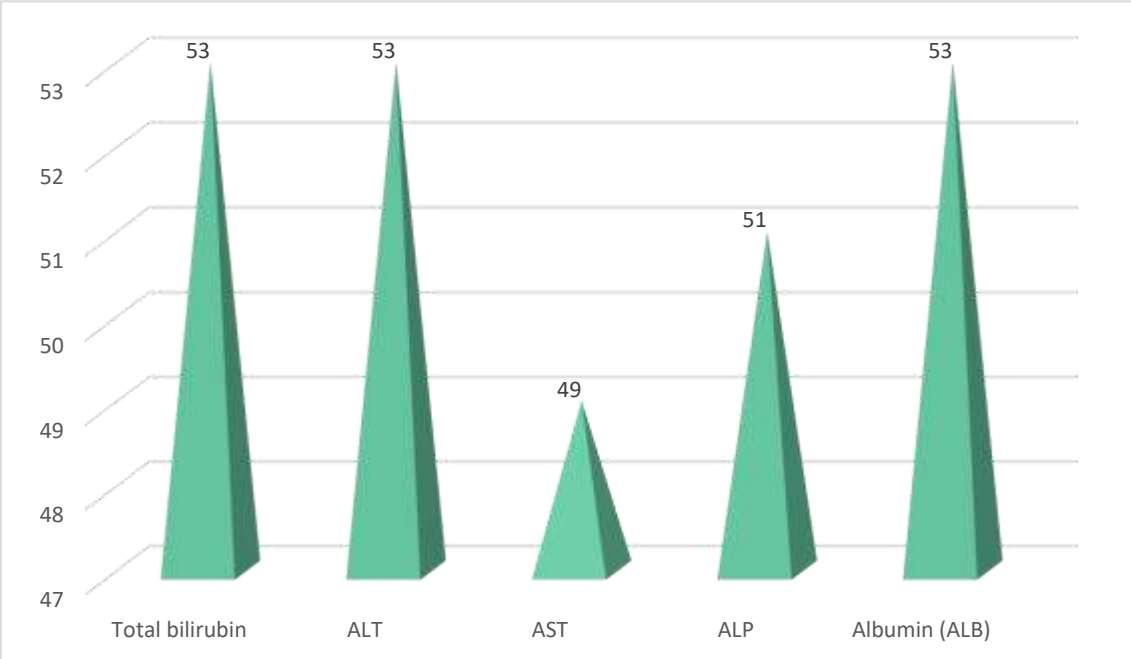
AST	49 (92.45%)	<0.001
ALP	51 (96.22%)	<0.04
ALB	53 (100%)	<0.001

Graph 3: Distribution of population with components of LFT



Out of 100 study samples,56 patients belong to NYHA class 3 and 4, among them 35 patients were having abnormal LFT which is significant.43 patients belong to NYHA 1 and 2, only 18 patients were having abnormal LFT. (Table 8) We observed that all the components of LFT were raised and had the significant positive correlation with the severity of HF. Also, the serum albumin had reduced significantly as the severity increased. (Table 9, Graph 4)

Table 8: Distribution of recruited study population according to their NYHA class and LFT status

NYHA	N (%)	Normal LFT	Abnormal LFT
1	13	9 (69.23%)	04 (30.77%)
2	31	17 (54.84%)	14 (45.16%)
3	34	15 (44.12%)	19 (55.88%)
4	22	6 (27.28%)	16 (72.72%)

Table 9: Distribution of components of liver function test (LFT) in relation with NYHA class

Parameters	NYHA 1	NYHA 2	NYHA 3	NYHA 4	P value

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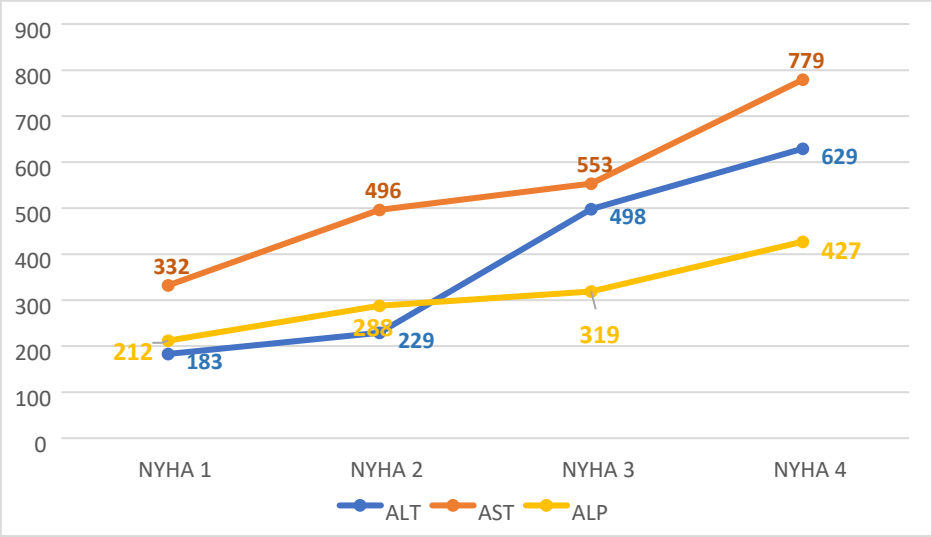
	Mean± SD	Mean± SD	Mean± SD	Mean± SD	
Total bilirubin	1.9±1.4	2.1±2.1	2.3±1.9	2.8±2.1	<0.001
ALT	183.8±66.2	229.4±82.3	498.7±34.5	629.9±112.3	<0.001
AST	332.6±43.4	496.2±68.17	553.5±38.1	779.1±107.34	<0.001
ALP	212±45.3	288.4±30.9	319.8±52.1	427.6±43.1	<0.001
ALB	4.4±2.1	2.2±1.8	2.2±2.1	2.2±1.9	<0.001

Graph 9: Distribution of Liver enzymes with respect to the severity of HF



In patients with EF< 40%, there was a significant increase in the LFT parameters in comparison to patients with EF >40-50%. (Table 10)

Table 10: Distribution of LFT based on the ejection fraction among the abnormal LFT group

	<40	40 to 50	>50	P value
Total bilirubin	2.5±1.9	2.1±1.9	2±1.5	0.81
ALT	682.4±62.1	598.7±102.5	593.5±108.3	0.53
AST	742.5±58.13	653.4±58.11	648.8±49.34	0.28
ALP	539.5±32.9	419.4±48.1	412.9±53.6	0.19
ALB	2±1.3	2.2±1.1	2.2±1.3	0.84

Discussion

A spectrum of hepatic derangements can also occur in HF especially in right heart failure (RHF). Hence, any aetiology of right ventricular dysfunction can be associated with severe hepatic congestion; patients with hepatic congestion are usually asymptomatic and this entity might be suggestive only by abnormal liver function tests (LFTs) during routine laboratory analysis. The primary pathology behind it could be either passive congestion from increased filling

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pressures or low cardiac output and the consequences of impaired perfusion.[6] We found many evidences which had reported the raised LFT among HF patients by comparing the parameters with non-HF controls. Whereas, we could not find much studies which have conducted subgroup analysis based on the NYHA classification and EF. Hence the present study was conducted to assess the fate of liver enzymes and other components of iver functions in correlation with severity of HF.

Discussion On Demographic Details

We had recruited 100 patients diagnosed with HF. In the present study, out of 100 HF patients, the frequency of abnormal LFT was found to be 53%. Similarly, Samsky MD et al,[65] mentioned that 49% of the HF patients being presented with abnormal LFT. Of which we observed that the majority of the recruited study population was aged between 41 to 60 years with a frequency of 67%. Whereas we did not find any significant difference with respect to age between the patients with HF having normal and abnormal LFT. (Table 1) Another cohort observation by Vasti E et al found that out of all the HF patients with abnormal LFT, men had comprised of 56% of the abnormal LFTs and the average age being 67 years.[14]

Comparison Of Liver Enzymes

In the present study, all the components of LFT were raised and had a significant positive correlation with the severity of HF. All the liver enzymes were significantly raised among the recruited study population compared to the upper limit of normal range of those particular enzymes and also the increased LFT was significantly associated with the severity as indicated by NYHA. (Table 8,9)

Similar to our observation, CHARM study was another evidence which had aimed at assessing the correlation between HF and LFT profile.[15] They also observed ALP, direct total bilirubin and albumin being the most predictors of HF and also significant in predicting the expected cardiovascular event in the patients with HF.

Another related clinical trial by Beigus J et al found that deranged LFTs were observed in patients with HF.[10] Of these, 46% of the patients for AST, 31% for ALT, 33% for bilirubin and 44% for albumin. Only 29% of the patients had all LFTs within the normal ranges. Similar to our study outcome, Liang W et al also had found that increased total bilirubin and ALP had significant association with HF whereas AST and ALT did not have any correlation. Hence, they had concluded that TB and ALP could be the indicators of poor outcome among the patients with HF and did not have any liver abnormalities before.[17]

As the present study, Allen LA et al, Alvarez AM et al and Yamada S et al also had reported that raise in all components of LFT and had even stated that the raised LFT among the heart failure with no previous history of liver disease could be one of the prognostic factors of the outcome of HF.[11,13] Similarly Vasti E et al included more than 5000 suspected acute decompensated heart failure (ADHF) in their cohort study. Of these, 60% had LFTs ordered whereas 34.6% was observed to be abnormal. The odds of a final cohort diagnosis assessment, of all the ADHF in the univariate analysis was 59% higher in patients with significant abnormal LFT. Hence, they concluded that LFT had been the missing investigation in their emergency department, because of which they had missed significant finding. So, they suggested LFT could be the predictive and prognostic factor of severity of HF.[14]

Also, Selen T et al was another unique study which had compared the LFT, CVD risk and the CKD outcome. In this study they had analysed that, all the liver enzymes have been the prognostic markers for CVD risk. Of these they stated that GGT could be the significant prognostic factor for indication for dialysis. Hence, there is need of assessing LFT being a prognostic factor in dialysis too.[18]

Our observation was also in consistent with Lubis IH et al., in the study total bilirubin and GGT was significantly greater than for other liver functions. SGOT, SGPT, total bilirubin, ALP and GGT had a higher mean among those with ejection fraction <= 40% compared to ejection fraction> 40%. Their strong suggestion was total bilirubin and GGT are the significant associated parameters with HF.[19]

The research conducted Samsky MD et al the “Acute Study of Clinical Effectiveness of Decreased Heart Failure (ASCEND-HF)” showed that patients with heart failure generally had elevated liver function values and EF <50% was said to have a significantly increased bilirubin ($p<0.001$) but they did not observe any correlation with aminotransferase.[12]

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Contrast to these observations, serum total bilirubin levels were significantly lower in the heart failure group compared with the control group ($P < 0.01$) in Zheng H et al. Whereas patients in the subgroup (4-severe) showed significantly ($P < 0.05$) lower levels of total bilirubin when compared with the subgroup (1-mild).[20]

Same as the present study, Sankar K et al also had found that among the patients with ejection fraction ≤40-85% there was significant increased bilirubin and 92.5% had increased serum glutamic oxaloacetic transaminase, 92.5% had increased serum glutamic pyruvic transaminase and 22.5% had increased alkaline phosphatase. In patients with ejection fraction ≤40-57.5% had increased urea and 62.5% had increased creatinine too. Hence, they concluded that the liver and renal involvement should be considered crucial among the patients diagnosed with HF particularly with less EF.[21]

Also, we observed that all the patients had raised total bilirubin, ALT and reduced ALB. Whereas the raised AST and ALP was observed among 49 (92.45%) and 51 (96.22%) of the patients respectively. (Table 7)

Similar to which, Liang W et al also mentioned that the elevated AST, ALT, TB and ALP were 12.3%, 16.8%, 11.4% and 19.1% respectively, among the patients with preserved HF. They had not analysed the patients without preserved volume.[17] Even Samsky et al had found 42% HF patients had abnormal bilirubin, 22% had abnormal ALT and 30% with abnormal AST. So, we could analyse that there might not be changes in all the parameters of LFT affected in the patients with HF, hence there is need for assessing the LFT with keen observation when the patient diagnosed with HF.[12]

The present study found that as with reduced EF, there was significant increase in the liver enzymes, bilirubin and significant reduction in the albumin levels. (Table 10) Similarly, Sankar K et al also observed that derangement in the LFT profile was significant as the EF reduced but they had divided their patients into EF with ≤40% and >40% only,[21] which also similar to the observations by Lubis IH et al and Samsky et al.[19,12]

With the above discussion, we could analyse that although there is wide variation in the demographic profile as well as in the distribution of the disease but majority of the evidences implying that the chances of deranged LFT is observed among the patients with HF. Hence, LFT could be considered as one of the crucial investigations for all the patients admitted with HF to assess the severity of HF and prognosis of the patients.

Conclusion

Liver Dysfunction is common in patients with HF and the prognostic value of LFT parameters are studied in various studies. In our study, we found that all LFT parameters are increased and 'P' value < 0.001 which is statistically significant. Abnormal LFT parameters are more frequently seen in patients with biventricular failure followed by LVF and RVF. Patients with NYHA class 3 & 4, EF< 40% were having increased frequency of abnormal LFT parameters. So, study of LFT parameters in all HF patients is mandatory and has got prognostic value, so that we can assess severity of HF at the bedside for the better management of patients.

Limitations

1. Since our study is cross sectional observational, we have not done serial estimation of LFT to assess the prognosis of the patients.
2. GGT & LDH levels are also prognostic factors to assess the severity of HF. We have not included these parameters
3. We have not included control group in our study.

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