COMPARISON OF NON-INVASIVE FIBROSIS SCORES BETWEEN ALCOHOLIC LIVER DISEASE PATIENTS AND HEALTHY NON-ALCOHOLICS IN SOUTH INDIAN POPULATION

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ABSTRACT

BACKGROUND

Alcoholic Liver Disease (ALD) is a spectrum of disorders ranging from simple steatosis to steatohepatitis and cirrhosis. Various non-invasive markers have been validated as reliable prognostic markers of fibrosis in Chronic Viral Hepatitis and Non-Alcoholic Fatty Liver Disease but their utility in ALD is least evaluated. This study aims to compare the fibrosis scores in ALD patients with non-alcoholic healthy controls.

METHODS

The non-invasive scores of fibrosis namely AST/ALT ratio, BARD score, APRI and FIB-4 were calculated in 30 ALD cases and 30 age matched controls. Alcohol drinking pattern was evaluated using the AUDIT questionnaire. The difference in the fibrosis scores between cases and controls were calculated using independent student's t test. All statistical analysis were done using SPSS software v 20.0 and p value <0.05 was considered statistically significant.

RESULTS

All the non-invasive scores of fibrosis viz. AST/ALT ratio, BARD score, APRI and FIB-4 were significantly high in ALD cases compared to controls. All the cases had AST/ALT ratio more than >1, 76% of them had BARD score >2, 97% had APRI score >1 and 73% had FIB–4 score >3.25 denoting the presence of significant fibrosis in ALD patients. AUDIT score correlates with all the non-invasive fibrosis scores except AST/ALT ratio. There is significant correlation between FIB-4 score and APRI score (r= 0.962, p=<0.001) and between FIB-4 score and AST/ALT ratio (r= 0.500 p= 0.005).

CONCLUSIONS

The non-invasive fibrosis markers are significantly high in ALD cases. APRI, FIB4 and BARD score positively correlate with alcohol drinking pattern. Hence these scores derived from routine lab investigations could be used as cost effective tools to assess the severity of fibrosis in ALD patients.

KEYWORDS

Alcoholic Liver Disease, AST/ALT Ratio, BARD Score, APRI, FIB-4 Score

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BACKGROUND

Alcoholic liver disease (ALD) is a spectrum of disorders ranging from simple steatosis to steatohepatitis, cirrhosis and hepatocellular carcinoma. Fatty liver is more common in alcoholics, of which only 30 to 35 percent of them progress to cirrhosis.[1] Hence other factors like age, body mass index (BMI), drinking pattern and genetic factors are known to play a role in the pathogenesis of cirrhosis. Early identification of those individuals at risk of progressing to cirrhosis and decompensated liver disease may prevent long term morbidity and mortality by appropriate management.

Various non-invasive markers have been used to assess the degree of fibrosis in chronic liver disease and have been proved to be useful indices of fibrosis. Serum biomarkers like transaminases and platelet count serve as indirect tests of fibrosis.[2] These are combined into score systems along with other demographic parameters like age, BMI and presence of diabetes.[3–5] The derivation of scoring systems from these non-invasive markers provide an easy and economical means of assessing and predicting liver fibrosis among alcoholics in developing country like India. Conventional methods of diagnosing fibrosis like the invasive liver biopsy, ultrasonography, computerised tomography and magnetic resonance imaging remains cumbersome and expensive in our set up. However, these non-invasive markers of fibrosis have been validated as reliable prognostic markers in chronic viral hepatitis and Non-Alcoholic Fatty Liver Disease (NAFLD) whereas its utility in ALD is uncertain. This study aims to

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estimate the fibrosis scores derived from simple biochemical tests in ALD patients in comparison with non-alcoholic healthy controls to know existing status of these biomarkers in our population and hence to identify patients with fibrosis or at risk for fibrosis. Further, assessment of their alcohol drinking pattern and its association with fibrosis scores may explain the effect of alcohol consumption on liver fibrosis.

METHODS

This case control study was conducted in the Department of Biochemistry, Mahatma Gandhi medical college and research institute, after obtaining clearance from the Ethics committee (Human studies) of the institute. Informed consent was obtained from all individual participants included in the study. 30 male patients who were diagnosed as alcoholic liver disease were recruited as cases from the department of general medicine. 30 age matched healthy male volunteers without history of liver disease and alcohol consumption who attended the master heath check-up clinic served as controls. Patients with liver diseases due to non-alcoholic causes were excluded from the study. Alcohol drinking pattern of the patients were evaluated using the AUDIT (Alcohol use Disorder Identification test) questionnaire[6–8] and the AUDIT score was recorded. A score of >8 indicates alcohol dependence. Haematological parameters like haemoglobin concentration and platelet count were estimated by Horiba 5-part autoanalyser. Biochemical parameters were analysed by Hitachi 902 autoanalyser. The following scores were calculated as non-invasive serum biomarkers of liver fibrosis from the analysed parameters: (i) AST/ALT ratio (ii) BARD score, the weighted sum of three variables (BMI>28 =1 point, AST/ALT ratio>0.8 = 2 points, diabetes = 1 point). (iii) APRI (AST to platelet ratio index) score = (AST level (/Upper Limit of Normal)/ Platelet counts (10^9/L)) × 100 (iv) FIB- 4 score = ((age (years) × AST (IU/L))/ (platelet count (10^9/L) × ALT (IU/L)).[1/2] All the parameters are expressed as mean ± S.D. The difference in the fibrosis scores between cases and controls were calculated using independent student's t test. Chi square test was used to compare the groups of cases and controls categorised based on the cut off value of the non-invasive scores. Correlation between the study parameters and AUDIT score was analysed using Spearmann rank correlation. A p value <0.05 was considered to be statistically significant.

RESULTS

The mean age of the study population was 41 yrs. and there was no significant difference in age between cases and controls. The BMI was significantly high in ALD patients and they were obese. The AUDIT score was >8 in all the cases indicating the presence of alcohol dependence. The mean levels of AST and ALT were significantly higher in cases than controls and the ALD patients had a low platelet count when compared to controls. All the non-invasive scores of fibrosis viz. AST/ALT ratio, BARD score, APRI and FIB - 4 were significantly high in ALD cases compared to controls.

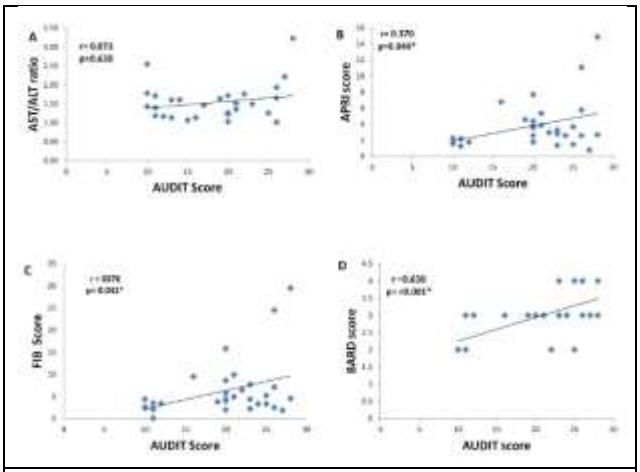

Figure 1. Correlation Between Non-Invasive Fibrosis Scores and AUDIT Score

*p <0.05

In the study population, 16.7% (5) of controls and 46.7% (14) of cases were diabetic and this difference was not statistically significant. (Table 1)

Parameter	Controls	Cases	p Value
Age (years)	41.30 ± 10.91	41.03 ± 11.83	0.928
Height (m^2)	167.43 ± 6.02	164.13 ± 5.58	0.032*
Weight (kg)	65.78 ± 9.73	72.40 ± 7.07	0.005*
BMI (Kg/m^2)	23.54 ± 3.34	26.90 ± 2.51	< 0.001*
AST (IU/L)	24.20 ± 6.0	154.70 ± 28.33	< 0.001*
ALT (IU/L)	27.37 ± 6.48	111.40 ± 29.31	< 0.001*
Platelet Count (x 10^9/L)	278.27 ± 60.77	155.43 ± 83.73	< 0.001*
AST/ALT ratio	0.90 ± 0.13	1.54± 0.47	< 0.001*
BARD score	0.53 ± 0.09	2.93± 0.64	< 0.001*
FIB score	0.72 ± 0.257	6.323 ± 6.455	< 0.001*
APRI score	0.223 ± 0.077	3.797 ± 3.032	< 0.001*

Table 1. Comparison of Study Parameters Between Alcoholic Liver Disease Cases and Healthy Controls

* p value <0.05, BMI- Body Mass Index, AST- Aspartate Transaminase, ALT- Alanine Transaminase

Non-Invasive Fibrosis Score	Values	Control	Case	p Value
AST/ALT ratio	Less than 1	25 (83.3%)	0 (0%)	0.001*
	More than 1	5 (16.7%)	30 (100%)	
APRI score	Less than 1	30 (100%)	1 (3.3%)	0.001*
	More than 1	0 (0%)	29 (96.7%)	
FIB score	0-1.45	30 (100%)	1 (23.3%)	0.001*
	1.46-3.25	0 (0%)	7 (3.3%)	
	3.26-50	0 (0%)	22 (73.4%)	
BARD score	≤ 2	29 (96.7%)	7(23.3%)	0.001 *
	>2	1 (3.3%)	23 (76.7%)	

Table 2. Distribution of Non-invasive Fibrosis Scores among ALD Cases and Controls

* p value <0.05 AST- Aspartate Transaminase, ALT- Alanine Transaminase

Table 2 shows the critical cut off values of the fibrosis markers and the distribution of cases and controls. Among the cases all of them had AST/ALT ratio more than >1, 76% of them had BARD score >2, 97% had APRI score >1 and 73% had FIB score >3.25. These cut offs denote the presence of significant fibrosis in ALD patients and all the non-invasive scores were significantly higher in cases compared to controls at these cut off values. (Table 2). There was significant positive correlation between AUDIT score and all the non-invasive fibrosis scores except AST/ALT ratio (Figure 1). There was also significant positive

correlation between FIB - 4 score and APRI score (r= 0.962 p=<0.001) and between FIB- 4 score and AST/ALT ratio (r= 0.500 p= 0.005).

DISCUSSION

Alcohol consumption remains the predominant cause for chronic liver disease which leads to morbidity and mortality due to cirrhosis and hepatocellular carcinoma. Alcoholic liver disease (ALD) is defined by anamnestic history of daily alcohol intake of at least 30 g and 20 g for men and women respectively, associated with evidence of liver injury.[9] Alcohol causes repeated inflammation and healing of hepatocytes resulting in fibrosis of liver. Hepatic stellate cells play a key role in fibrogenesis by secreting various cytokines and extracellular matrix (ECM) components. These cytokines and ECM components can serve as biomarkers of hepatic fibrosis. Simple steatosis is benign and is usually overlooked. So it is important to assess the degree of liver fibrosis in ALD patients for surveillance and prognostic purpose. Liver biopsy is considered as gold standard for diagnosis of hepatic fibrosis and various histopathological grading systems like Ishak and METAVIR scores are available for staging of viral hepatitis and cirrhosis. Nevertheless, these scores did not show direct correlation with liver fibrosis[10] and hence non-invasive assessment was preferred. Non-invasive fibrosis tests include serum biomarker panels and imaging techniques. Serum biomarkers include direct markers of fibrosis like extracellular matrix components (hyaluronic acid), fibrogenic cytokines (TGF-β) and degradation products (Procollagen IV peptide) and indirect tests of fibrosis like the transaminases, platelet count, albumin.[2] Indeed the non-invasive scores developed from these serum biomarkers namely the AST/ALT ratio, APRI, FIB- 4 and BARD score had the advantages of better patient compliance, safe, quick and inexpensive.

The non-invasive markers in spite of having low positive predictive value, were shown to have high negative predictive value that could be of clinical utility to exclude advanced fibrosis.[5] With this background this study aimed at identifying the proportion of ALD patients who were not in the advanced fibrosis zone. But unfortunately, more than 75% of the patients had their fibrosis scores above the cut off levels. And certainly, all patients had statistically significant higher cut off compared to healthy individuals. AST/ALT ratio also known as the De Ritis ratio was proposed as early as 1957 to signify cirrhosis when the ratio is greater than 1.0 in non-alcoholics. Alcohol induced liver injury causes release of both cytoplasmic and mitochondrial AST and the ratio in alcoholics is usually elevated. Additionally, the ratio has utility in non-alcoholics also as proposed by McPherson et al in his study involving Non-alcoholic fatty liver Disease (NAFLD) patients. They have showed that AST/ALT ratio of 0.8 has negative predictive value of 95% to exclude advanced fibrosis and hence liver biopsy was avoided in 69% cases.[11] In the current study, all the 30 patients had an AST/ALT ratio >1 which indicates that all the patients are vulnerable for liver fibrosis.

APRI and FIB-4 scores were originally derived in Hepatitis C virus (HCV) infection for prediction of significant fibrosis and cirrhosiss.[12,13] Considering a similar value in Chronic Hepatitis B (CHB) patients, WHO HBV guidelines have proposed a cut off for APRI and FIB-4 for use in resource limited settings.[14] Li Q et al argues that the WHO HBV guidelines for APRI and FIB-4 are higher and it underestimates the proportion of significant fibrosis and cirrhosis in HBeAg negative CHB patients.[15] APRI score has proven to be a promising marker for fibrosis more so for higher grades of fibrosis. In a retrospective analysis of 383 medical records conducted by Derbala et al has shown that APRI score showed statistically significant association with liver fibrosis and predicted severe fibrosis with odds ratio of 2.41. The APRI cut off for significant fibrosis, severe fibrosis and cirrhosis was 0.64, 1.06 and 1.11 respectively. The results of their study have concluded that APRI is a useful marker in patients with coinfection of HCV and schistosomiasis.[16] High APRI score in cirrhosis is due to increased AST levels and decreased platelet count. The decreased platelet count seen in chronic liver disease may be the result of decreased production due to bone marrow suppression caused by viruses or alcohol. Additionally, there is also decreased levels of thrombopoietin and increased platelet destruction due to shear stress in chronic inflammation.[17,18] The findings of the current study indicate that 97% of the patients have an APRI >1 which denotes the presence of underlying severe fibrosis and cirrhosis. The results of Dvorak K suggest that APRI is certainly high in biopsy proven cirrhosis in NAFLD.[19] APRI score has recently been used to determine advanced fibrosis in HIV patients and is found to be a surrogate marker of significant liver fibrosis in HIV/ HCV-coinfected patients.[20] Jackson et al has also found APRI to be a modest performer in differentiating mild and significant fibrosis with an ROC of 0.67 in paediatric NAFLD cases.[21]

FIB-4 index is found to be useful in diagnosis of advanced fibrosis and cirrhosis in HIV/HCV co infected patients, HBV and HCV patients.[22] Karic et al has found that FIB-4 has a greater AUC than APRI (0.875 vs 0.861) and is superior to APRI in identifying severe fibrosis in chronic hepatitis C infection. As per their finding none of the patients with severe fibrosis had a FIB-4 score <1.08 and had 100% sensitivity in ruling out severe fibrosis at this cut off.[23] According to the cut off values established by Sterling et al, FIB-4 <1.45 had a 90% negative predictive value and hence 23% of ALD patients can be ruled out from doing a liver biopsy.[24] In the present study, 73% of the ALD patients had a FIB-4 score > 3. 25 denoting advanced fibrosis.

77% of the cases had a BARD score >2 which classifies them under significant fibrosis category. Though BARD score was originally validated as a scoring system for identification of fibrosis in NAFLD, it is worth considering it in ALD patients because the metabolic markers like obesity, age and diabetes mellitus are additional factors to alcohol in aggravating fibrosis in ALD patients. Further significant positive correlation of BARD score with AUDIT score in the present study is noteworthy. Naveau et al has correlated

adipose tissue inflammation and visceral adiposity with liver lesions in ALD.[25] Raynard et al has quoted BMI as an independent risk factor for fibrosis in ALD.[26] Hence BMI, diabetes mellitus and alcohol can render a synergistic thrust in the acceleration of liver fibrosis.

Further, APRI, FIB4 and BARD scores had significant positive correlation with AUDIT score signifying the effect of alcohol drinking pattern on the extent of liver damage. An Indian study evaluating the patterns of alcohol use, revealed risky drinking patterns are common among men from socioeconomically disadvantaged situations and they are at increased risk for multiple adverse outcomes.[27] Added to this burden is the risk of hepatic fibrosis and cirrhosis. Various studies have confirmed that abstinence improves clinical outcome in ALD. Abstinence can prevent complications and increase survival in patients with ALD cirrhosis.[28] Powell et al followed up 283 patients with ALD cirrhosis and found that 5-year survival was 63% in abstainers and 45% in drinkers.[29] Even though liver biopsy is considered as gold standard for the diagnosis and staging of fibrosis, it cannot clearly delineate the early and intermediate stages of liver fibrosis. Similarly the serum biomarker panels can better predict advanced fibrosis and cirrhosis than early stages.[30] Germani et al suggests that non-invasive scores must be validated with proper measurement of liver fibrosis by measuring the CPA (collagen proportionate area) which correlates with HVPG(Hepatic venous pressure gradient) rather than validating the scores using liver biopsy stage scores.[10] Though the non-invasive markers are less accurate in predicting fibrosis, they can still serve as useful tools in centres with limited facilities since they are objective and readily calculated from the available laboratory variables.

CONCLUSIONS

Non-invasive fibrosis markers are significantly high in ALD cases. APRI, FIB4 and BARD scores correlate positively with alcohol drinking pattern. Hence these scores derived from routine lab investigations could be used as cost effective tools to assess the severity of fibrosis in ALD patients. Further they can be used to counsel the patients for abstinence thereby delaying the process of fibrosis in such individuals. The present study suggests that these non-invasive markers must be evaluated among drinkers well before the diagnosis of liver disease. Just like periodic monitoring of blood glucose and blood pressure in non-communicable diseases, an additional calculation of these scores from readily available parameters among those with history of alcohol consumption can serve as a means to sensitise them about their impending hazard of fibrosis and cirrhosis. Further these tests can be repeated periodically as they are less expensive and safe compared to other imaging techniques and liver biopsy.

Abbreviations

NAFLD, Non-Alcoholic Fatty Liver Disease; AUDIT, Alcohol Use Disorder Identification Test; AST, Aspartate Transaminase; ALT, Alanine Transaminase; APRI, AST to Platelet Ratio Index; FIB 4, Fibrosis 4; BARD, BMI AST/ALT ratio Diabetes mellitus.

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