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Non-Invasive Biomarkers vs Liver Biopsy in Diagnosing & Staging NAFLD

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Abstract

Introduction: Non-alcoholic fatty liver disease (NAFLD) encompasses a spectrum of disease ranging from simple steatosis to inflammatory steatohepatitis (NASH) with increasing levels of fibrosis and ultimately cirrhosis. It has been considered the most common liver disease and the most frequent cause of elevated aminotransferases and cryptogenic cirrhosis.

Aims and Objectives: To evaluate the role of non invasive biomarkers and compare them with liver biopsy in diagnosis and staging of Non Alcoholic Fatty Liver Disease.

Material and Methods: This study was conducted at Pt. B D Sharma, PGIMS, Rohtak. A total of forty consecutive patients of nonalcoholic fatty liver disease underwent liver biopsy, in addition to non-invasive biomarkers. P value of <0.05 was taken as significant and <0.01 as highly significant whereas p value >0.05 was taken as non-significant.

Results: The patients were in age group of 22-70 years with mean age of 44-35 years. Seventy percent were females and 30% were male. Impaired fasting glucose levels were seen in 37.5% cases, obesity and hypertension was present in 35% and 45% cases respectively. Out of 40 cases, features of definite NASH were seen in 65% cases and 35% cases showed features of probable NASH. Fibrosis stage I was seen in 80% cases, while both stage II and III fibrosis cases were 10% each.

Conclusion: The simple noninvasive scoring systems have a role in assessment of fibrosis and can identify patients with NAFLD at higher risk for development of liver related complications and higher overall mortality. The major advantage of using any of these simple scoring systems is that they are derived from readily available clinical and laboratory indices. Furthermore, a combination of these simple noninvasive markers may perform better than each alone. However, this needs to be assessed in future studies with larger sample size.

Keywords: Non alcoholic liver disease; Liver biopsy; Fibrosis; Fatty liver

Abbreviations: NAFLD: Non-Alcoholic Fatty Liver Disease; AUROC: Area Under Receiver Operator Characteristic Curve

Introduction

Non-alcoholic fatty liver disease (NAFLD) encompasses a spectrum of disease ranging from simple steatosis to inflammatory steatohepatitis (NASH) with increasing levels of fibrosis and ultimately cirrhosis. NAFLD is closely associated with obesity and insulin resistance, and is now recognized to represent the hepatic manifestation of metabolic syndrome [1]. It has been considered the most common liver disease and the most frequent cause of elevated aminotransferases and cryptogenic cirrhosis [2]. Estimates of current prevalence rates range from 24% to 42% in Western countries and 5% to 40% in Asian countries. A combination of lifestyle, older age, gender, steroid hormone metabolism, genetic predisposition, environmental and metabolic factors play a role in the pathogenesis of NAFLD whereas genetic predisposition, overabundance of calorie-rich food and lack of physical activity contribute to development of obesity [3]. Diabetes is characterized by a defect in insulin secretion or a decrease in sensitivity to insulin, which results in elevated fasting blood glucose. Both obesity and elevated fasting glucose are risk factors for nonalcoholic fatty liver disease. Increased adiposity and insulin resistance contribute to the progression from NASH to fibrosis through the development of a profibrotic milieu in the liver, including increased hepatocellular death, increased reactive oxygen species generation, and an altered adipokine/cytokine balance [4]. The majority of patients with NAFLD are asymptomatic and diagnosis is suspected after finding elevated transaminases on routine testing especially in the presence of features such as obesity, diabetes, obstructive

sleep apnea, hypertension and other high risk factors after exclusion of other inflammatory and metabolic liver diseases.[1] Having made a diagnosis of NAFLD, the next step is to determine the severity, as that provides important information on prognosis. The histological spectrum of NAFLD ranges from simple steatosis through steatohepatitis to fibrosis and cirrhosis. Hepatocellular carcinoma is a well-recognized complication of NASH related cirrhosis [1]. Several systems have been proposed for the histological assessment of NAFLD, of which the Kleiner NAFLD activity score (NAS) is probably the most well established [5].

Although percutaneous liver biopsy is still considered the gold standard in diagnosing and is the only reliable tool for distinguishing NASH from simple steatosis and for grading and staging of the disease, the limitations of this technique include invasive nature of the procedure, intraobserver variation, substantial sampling variability since fibrosis is often not uniformly distributed. Development of reliable noninvasive biomarkers for the diagnosis of non-alcoholic fatty liver disease has heralded a new era in the diagnosis of this disease [5-7]. Ideal noninvasive tool would be able to distinguish NASH from simple steatosis and allow for grading and staging of disease, which would largely facilitate screening of population at risk. The various non-invasive markers of NAFLD developed so far can be broadly grouped into three categories i.e. markers of inflammation, fibrosis and apoptosis. Development of noninvasive tools would also enable monitoring of disease course and progression and evaluation of response to therapy, both in routine practice and in the setting of clinical trials, which is currently only possible with a follow-up liver biopsy. Another very important, and somewhat disregarded point, is that an efficient biomarker or set of biomarkers would accurately reflect the inflammatory and fibrotic processes on the level of the whole of liver parenchyma, thereby increasing the diagnostic accuracy and resolving the problem of sampling variability intrinsic to liver biopsy, which represents only about 1/50,000 part of the organ which is not homogeneously affected by disease features [6,7].

Material and Methods

This study was conducted at Pt. B D Sharma, PGIMS, Rohtak. A total of forty consecutive patients suspected to be suffering from nonalcoholic fatty liver disease from the gastroenterology ward/OPD were recruited in the study. Patients suspected of having nonalcoholic fatty liver disease on basis of clinical features, radiological imaging and/or laboratory investigations (transaminasemia i.e. increased AST or ALT) and after ruling out history of any ethanol intake (currently or in the past), autoimmune or infective hepatitis (B, C, HIV), any history of drug intake on a chronic basis including indigenous drugs and inherited metabolic or genetic liver diseases e.g. Wilson disease, haemochromatosis, Alpha-1 antitrypsin deficiency were included in the study. Each liver biopsy specimen was fixed in formalin, routinely processed for histology, sectioned, and stained with Haematoxylin and Eosin. The extent of steatosis was determined by Haematoxylin and eosin-stained slides and graded as the percentage of tissue occupied by fat vacuoles. Fibrosis was assessed with the Masson trichrome stain, reticulin stain, Van gieson stain. Grading and staging of NAFLD was done using NAFLD activity score (NAS) developed by Kleiner et al. [8] and sum of scores for steatosis, lobular inflammation and hepatocellular ballooning was calculated. The various serum markers and scoring systems used in the study were: AST/ALT ratio, AST/platelet ratio index (APRI), FIB-4 index, NAFLD fibrosis score, BARD Score and Neutrophil/lymphocyte ratio. Advanced fibrosis (F3-4) is associated with an elevated N/L ratio (2.0-3.9) compared with patients with fibrosis stage 1-2 in which N/L ratio is between 1.2-2.2. For each one-unit increase in N/L ratio, the likelihood of having NASH increases by 70% and the likelihood of having fibrosis increases by 50% [9-11].

Statistical Analysis

A descriptive study was carried out for all the variables included in the study. The whole data was entered in Microsoft excel master sheet and analyzed using SPSSv20 software. The results obtained were interpreted and descriptive statistics (mean, standard deviation, range, percentages) were applied wherever appropriate. Where the data was qualitative, chi square test was used to assess the association between these parameters. A value of $p < 0.05$ was taken as significant and < 0.01 as highly significant whereas p value > 0.05 was taken as non-significant. Data obtained were analyzed and correlation of risk factors with NAFLD activity score and fibrosis stage; and correlation of serum markers with fibrosis stage was done. Area under receiver operator characteristic curve (AUROC) for the various serum markers was calculated and their correlation with fibrosis was seen.

Observations

The present study was a prospective study conducted on 40 suspected cases of non alcoholic fatty liver disease that were recruited from the gastroenterology ward/OPD of PGIMS, Rohtak. The association of hypertension and NAFLD activity score was statistically not significant. The association of diabetes and NAFLD activity score was statistically significant. The association of fibrosis stage and BMI was statistically not significant. The association of fibrosis stage and hypertension was statistically not significant. The association of fibrosis stage and diabetes was statistically significant.

Correlation of serum markers with fibrosis stage

The association of AST/ALT ratio with fibrosis stage was statistically not significant. The association of AST platelet ratio index with fibrosis stage was statistically not significant. The association of FIB4 index with fibrosis stage was statistically highly significant. The association of NAFLD fibrosis score with fibrosis stage was statistically highly significant. The association of BARD score with fibrosis stage was statistically not significant.

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The association of neutrophil lymphocyte ratio with fibrosis stage was statistically not significant.

Discussion

The ideal noninvasive tool should be able to distinguish NASH from simple steatosis and allow for grading and staging of disease, which would largely facilitate screening of population at risk.

Age and sex distribution

Our study included forty cases of suspected NASH. The patients' age ranged from 22 – 70 years. Majority (42.5%) of the cases belonged to age group of 41-50 years and the mean age was 44.35±10.80 years. In the study, there were 30% males and 70% females. (M: F – 3:7).

Assessment of risk factors

In our study, 34 cases (85%) had BMI > 25 (overweight) and 14 cases had BMI > 30 (obese). Impaired fasting glucose (fasting blood glucose>110 mg/dl) was seen in 32.5% cases. Also, in our study there were 45% hypertensive's (blood pressure >140/90).

Histological grading and staging of NASH

In the study, 26 patients (65%) had NAFLD activity score >=5 (definite NASH), 14 cases (35%) had a score between 3- 4 (probable NASH). None of the biopsies showed a NAFLD activity score between 1- 2 (not NASH). 32 cases (80%) showed stage 1 fibrosis, 4 cases (10%) showed stage 2 fibrosis and 4 cases (10%) showed stage 3 fibrosis. None of the cases showed stage 4 fibrosis.

Correlation of risk factors and NAFLD activity score

In our study, 58% cases of definite NASH had a BMI >30 while all the cases of uncertain NASH had BMI <30. Association of BMI and NAFLD activity score was found to be statistically not significant. Fifty eight percent cases of definite NASH were hypertensive. Association of hypertension and NAFLD activity score was statistically not significant. In our study, fifty eight percent cases of definite NASH were diabetic while all the cases of uncertain NASH were non diabetic. Association between diabetes and NAFLD activity score was found to be statistically significant.

Correlation of risk factors and fibrosis stage

In our study, 63.9% cases of early fibrosis had BMI<30 (obesity ruled out) while the rest 36.1% cases of early fibrosis had BMI>30. Out of the four cases of advanced fibrosis, three cases had BMI <30. Association of fibrosis stage and BMI was statistically not significant. Sixty seven percent cases of early fibrosis were diabetics. Three out of four cases with advanced fibrosis were diabetics. Association of fibrosis stage and diabetes was statistically significant. Forty four percent cases of early fibrosis were hypertensive while three out of four cases with significant fibrosis were not hypertensive. The association between fibrosis stage and hypertension was not significant.

Correlation of various serum markers and fibrosis stage

Correlation between fibrosis stage and FIB4 index: In our study, 29 (80.5%) of the 36 cases which had fibrosis stage 1-2 had FIB4 index <1.45 (significant fibrosis ruled out). However, rest 7 cases (19.5%) with stage 1-2 fibrosis had FIB4 index between 1.45– 3.25 (significant fibrosis seen). All 4 cases with stage 3 fibrosis had FIB4 score between 1.45– 3.25. Association of FIB4 index with fibrosis stage was found to be statistically significant. However, FIB4 index does not distinguish between a fatty liver and steatohepatitis, and it should not be used to diagnose NASH and the potential use of FIB4 index should be restricted to subjects with suspected NAFLD to evaluate the likelihood of having advanced or no fibrosis.

Correlation between fibrosis stage and NAFLD fibrosis score (NFS)

NAFLD fibrosis score (NFS), is a composite score of age, hyperglycemia, body mass index, platelet count, albumin, and aspartate aminotransferases and alanine aminotransferases (AST/ALT) ratio and was found to independently identify NAFLD patients with and without advanced fibrosis at initial NAFLD diagnosis [12]. In the study, 31 (86.1%) of the 36 cases with stage 1-2 fibrosis histologically had NFS <-1.455 (rules out significant fibrosis). Two (5%) of these 36 cases showed NFS > 0.676. Three out of four cases with stage 3 fibrosis had NFS >0.676 (indicative of significant fibrosis). The association between fibrosis stage and NFS was statistically significant in our study with a high AUROC of 0.902 (95% C.I: 0.80- 0.98) and p value <0.001. The advantage of NFS over a similar composite score; BARD score, was that the latter does not have the capacity to differentiate the severity of liver fibrosis among patients with a higher BMI or a higher ratio of AST/ALT, whereas the NFS takes into consideration the different ranges of BMI or AST/ALT ratios. However, the drawback of this marker is the need for a calculator to produce the value because the formula is complex [12].

Correlation between fibrosis stage and AST platelet ratio index (APRI)

In our study, 16 (44.4%) of the 36 cases which showed no evidence of fibrosis had APRI<0.5 (rules out significant fibrosis and cirrhosis). However, 20 cases (55.5%) with no significant evidence of fibrosis on histology had APRI between 0.5 -1.5 (significant fibrosis seen). All the four cases with evidence of significant fibrosis (stage 3) on biopsy also had APRI between 0-1.5. The association between fibrosis stage and APRI was statistically not significant in our study with an AUROC of 0.64 (95%C.I: 0.49 - 0.78) and p value 0.64. This could be because of the small sample size of our study. Hence, the efficacy of this marker should further be validated in studies with larger sample size.

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Correlation between fibrosis stage and AST ALT ratio (AAR)

AST ALT ratio levels more than 0.8 is associated with higher risk of advanced fibrosis. Therefore, an AST/ALT ratio >0.8 can be used as a screening tool to determine which patients with NAFLD should be referred to secondary care for evaluation [12]. In our study, 34 (94.4%) of the 36 cases which did not show evidence of significant fibrosis (histologically) had AAR <1 (significant fibrosis ruled out). All the four cases with evidence of fibrosis on biopsy also had AAR<1. Also, 2 cases with no evidence of any significant fibrosis on biopsy had AAR > 1 (indicative of significant fibrosis). The association between fibrosis stage and AAR was statistically not significant in our study with an AUROC of 0.51 (95%C.I: 0.34 - 0.67) and p value 0.96.

Correlation between fibrosis stage and neutrophil lymphocyte ratio (N/L)

Neutrophil lymphocyte ratio was originally developed as marker of systemic inflammation in prevalent chronic conditions viz cardiovascular diseases and cancer. It has been recently validated for assessing fibrosis in non-alcoholic steatohepatitis.[11] In our study, 14 (38.9%) of the 36 cases which showed no evidence of fibrosis had N/L ratio between 1.2 – 2 (significant fibrosis ruled out). The rest 22 cases of these 36 cases had N/L ratio 2 -3.9 (significant fibrosis seen). All the four cases with significant fibrosis on biopsy also had N/L ratio of between 2-3.9 (indicative of significant fibrosis). The association between fibrosis stage and neutrophil lymphocyte ratio was statistically not significant in our study with an AUROC of 0.75 (95% C.I: 0.59 - 0.87) and p value 0.79. Not many studies have been conducted to validate the role of neutrophil lymphocyte ratio for ruling out advanced fibrosis in NASH. This marker hence needs validation in larger studies.

Correlation between fibrosis stage and BARD Score

BARD score is a composite score based on weighted sum of three variables: BMI>=28, AAR>= 0.8 and presence of diabetes mellitus. In our study, 9 (25%) of the 36 cases of stage 1-2 fibrosis had a BARD score of 0-1 (significant fibrosis ruled out). However, 27 (75%) of these cases had a BARD score of 2-4 (indicative of significant fibrosis). Three out of four cases with stage 3 fibrosis (significant fibrosis) had BARD score between 2- 4. The association between fibrosis stage and BARD score was statistically not significant in our study with an AUROC of 0.68 (95% C.I: 0.51 - 0.87) and p value 0.32. In most of the previous studies, BARD score proved to be an efficacious tool for ruling out advanced fibrosis. Since the two variables; AAR and diabetes did not correlate well with stage of fibrosis, BARD score in our study had a poor diagnostic accuracy (Table 1).

Table 1: Comparison between Non Invasive Serum Markers in the Present Study.

S. No	Serum marker	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	AUROC	P value
1.	FIB4 index	100	80.56	36.36	100	0.927 (95% C.I 0.798-0.985)	<0.0001
2.	NAFLD fibrosis score	100	93.93	60	100	0.902 (95% C.I 0.766-0.973)	<0.0001
3.	AST/ALT ratio	_	94.44	_	89.47	0.506 (95% C.I 0.344-0.668)	0.9621
4.	APRI	100	47.22	17.39	100	0.640 (95% C.I 0.490-0.785)	0.3444
5.	BARD score	75	25	10	90	0.084 (95% C.I 0.518-0.821)	0.3246
6.	N/L ratio	100	38.89	15.38	100	0.753 (95% C.I 0.591- 0.875)	0..791

The sensitivity, specificity, AUROC and p values for the non invasive markers were analyzed (Figure 1). While comparing the various markers, FIB4 index had the best accuracy for advanced fibrosis with an AUROC of 0.927 (95% C.I 0.798-0.985) followed by NAFLD fibrosis score which had an AUROC of 0.902 (95% C.I 0.766-0.973). AAR had an AUROC of 0.51 (95% C.I 0.34-0.67), for APRI, AUROC was 0.64 (95% C.I 0.49 - 0.79), AUROC for neutrophil lymphocyte ratio was 0.75 (95% C.I 0.59 - 0.87) and for BARD score AUROC was 0.64 (95% C.I 0.59 - 0.87) FIB4 index and NAFLD fibrosis score were found to be the best non invasive markers for diagnosis of NAFLD with high AUROC and high sensitivity, specificity, PPV and NPV. AST/ALT ratio, APRI, BARD score and N/L ratio with a low AUROC failed to prove their efficacy as diagnostic markers in our study.

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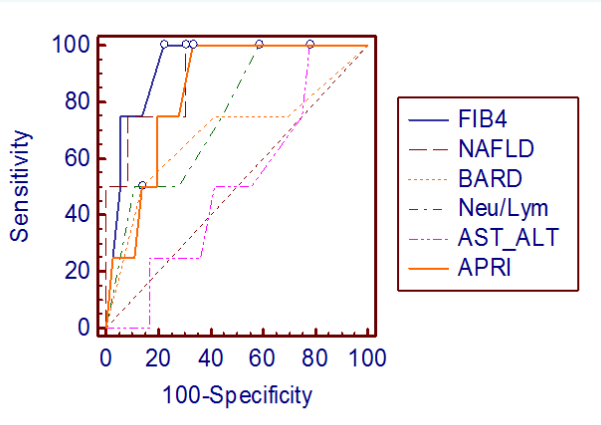

Figure 1: Receiver Operator Characteristic Curve of Non Invasive Markers.

Summary and Conclusion

The patients were in age group of 22 -70 years with Seventy percent were females. Present in 35% and 45% cases respectively. Out of 40 cases, features of definite NASH were seen in 65% cases and 35% cases showed features of probable NASH. Fibrosis stage I was seen in 80% cases, while both stage II and III fibrosis cases were 10% each. Association between diabetes and NAFLD activity score and fibrosis stage were found to be statistically significant while association of NAFLD activity score with hypertension and obesity were found to be statistically not significant. In the study, 29 out of the 36 cases which had fibrosis stage 1-2 had FIB4 index <1.45. However, rest 7 cases with stage 1-2 fibrosis had FIB4 index between 1.45–3.25 (indicative of significant fibrosis). All 4 cases with stage 3 fibrosis had FIB4 score between 1.45– 3.25. Association of FIB4 index with fibrosis stage was found to be statistically significant. Thirty one of the 36 cases with stage 1-2 fibrosis had NFS <-1.455. Two of these 36 cases showed NFS > 0.676(indicative of significant fibrosis) while 3 cases with stage 1 fibrosis had NFS in indeterminate range. Three out of four cases with stage 3 fibrosis had NFS >0.676. The association between fibrosis stage and NFS was statistically significant. Sixteen of the 36 cases with stage 1-2 fibrosis had APRI < 0.5. However, 20 cases with similar stage of fibrosis had APRI between 0.5 -1.5. All the four cases with stage 3 fibrosis had APRI between 0.5 – 1.5 indicative of significant fibrosis. No significant association between APRI and fibrosis stage was seen. In the study, 34 cases of the 36 cases with stage 1-2 fibrosis had AAR <1 while 2 cases had AAR>1. All the four cases with stage 3 fibrosis had AAR<1. The association between fibrosis stage and AST ALT ratio was not significant. In the study, 14 of the 36 cases with stage 1-2 fibrosis had N/L ratio between 1.2– 2. The rest of the 22 cases had N/L ratio 2-3.9. All the four cases with significant fibrosis on biopsy had N/L ratio of between 2- 3.9. The association between N/L ratio and fibrosis stage was not significant. Nine of the 36 cases with stage 1-2 fibrosis had a BARD score of 0-1. The rest 27 of these cases with similar stage of fibrosis had a BARD score of 2-4. Three out of four cases with stage 3 fibrosis had BARD score between 2- 4. The association between fibrosis stage and AST ALT ratio was not significant. FIB4 index had the best accuracy for ruling out advanced fibrosis with AUROC of 0.927 (95% C.I 0.798-0.985) followed by NAFLD fibrosis score which had AUROC of 0.902 (95% C.I 0.766-0.973). AAR had an AUROC of 0.51 (95% C.I 0.34-0.67), for APRI, AUROC was 0.64 (95% C.I 0.49 - 0.79), AUROC for neutrophil lymphocyte ratio was 0.75 (95% C.I 0.59 - 0.87) and for BARD score AUROC was 0.64 (95% C.I 0.59 - 0.87). Based on our results, FIB4 index and NAFLD fibrosis score were found to be the best noninvasive markers for diagnosis of NAFLD with high AUROC and high sensitivity, specificity, PPV and NPV. AST/ALT ratio, APRI, BARD score and N/L ratio with a low AUROC failed to prove their efficacy as diagnostic markers. The strength of our study, was that being a prospective study, we could record the various clinical and laboratory parameters for calculation of various non invasive markers. Also, history of alcohol intake, any metabolic or infectious cause of liver disease could be conclusively ruled out. We also made an attempt to validate the role of an array of non invasive markers rather than evaluating the role of a single marker.

However, there were few limitations to the present study.

- Number of study population in our study was less; hence the results of our study need to be validated in larger, multicentre trials.
- Our study being a cross sectional study, patients were not followed up, the development of progression of the disease and hence consequent morbidity could not be assessed.
- The simple non-invasive scoring systems evaluated in the present study have a role in the assessment of fibrosis, but are not effective in differentiating patients with simple steatosis from those with NASH. No marker indicative of inflammatory or apoptotic activity was tested which if done could have improved the overall assessment.

To conclude, the simple noninvasive scoring systems evaluated in the present study have a role in assessment of fibrosis and can identify patients with NAFLD at higher risk for development of liver related complications and higher overall mortality. The major advantage of using any of these simple scoring systems is that they are derived from readily available clinical and laboratory indices. Furthermore, a combination of these simple noninvasive markers may perform better than each alone. However, this needs to be assessed in future studies with larger sample size.

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