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General Medicine

COMPARISON OF EFFICACY OF ASPARTATE AMINOTRANSFERASE PLATELET RATIO INDEX TO FIBROSCAN AS A MARKER OF EARLY FIBROSIS IN NON-ALCOHOLIC FATTY LIVER DISEASE

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ABSTRACT **Background:** Nonalcoholic fatty liver disease (NAFLD) is being increasingly recognized as a cause of chronic liver disease. It has also been associated with devastating outcomes such as decompensated liver cirrhosis and hepatocellular carcinoma, as well as diabetes and metabolic syndrome. **Objective:** To assess the relation between Aspartate aminotransferase and platelet count in patients with pre cirrhosis And to compare the efficacy of aspartate aminotransferase platelet ratio index to that of Fibroscan in early fibrosis. **Materials And Methods:** A cross-sectional study was conducted on NAFLD patients who underwent Fibroscan examination. Demographic data was collected, including sex, age, and nationality; serum alanine aminotransferase levels (ALT, 30 - 65 U/L), serum aspartate aminotransferase levels (AST, 15 - 37 U/L), and platelet counts (150 - 400 k/μL) were also determined. The stages of fibrosis were defined. For each patient, the AST/ALT ratio was also measured. The results of APRI were compared with the Fibroscan fibrosis scores. **Results:** Comparison of efficacy of aspartate aminotransferase platelet ratio index to fibro scan as a marker for early fibrosis in – non-alcoholic fatty liver disease" The study population consisted of 100 NAFLD patients attending General Medicine OPD as cases. After institutional ethical clearance and informed consent, various investigations about the study are done. The data were entered into Microsoft Excel sheet and statistically analysed. The most common age group of NAFLD cases were from 46-55 years of age. There is a slight male predominance in the study. The mean AST value is 41.6IU,mean platelet count was123×109 cells.APRI index was calculated based on these parameters. Fibroscan was done in those patients, There is a significant association between APRI and fibroscan by using chi-square test.

KEYWORDS : Fibroscan, NAFLD, APRI, Metabolic syndrome

INTRODUCTION:

"Non-alcoholic fatty liver disease (NAFLD) is one of the common causes of chronic liver disease. The prevalence has been increasing during the last 20 years from 5% to 25% in Asian countries, depending upon the populations studied".

"Non-alcoholic fatty liver disease is defined as when alcohol consumption is ≤20 g/day in women and ≤30 g/ day in men with the exclusion of other causes of disease such as chronic viral hepatitis, autoimmune hepatitis, steatogenic drug-induced, etc.

It comprises a clinical spectrum from steatosis (macrovesicular triglyceride accumulation in >5% of hepatocytes), fatty infiltration plus inflammation, and hepatocellular ballooning degeneration (non-alcoholic steatohepatitis [NASH]), fibrosis and cirrhosis, in the absence of excessive alcohol consumption.

Obesity, type 2 diabetes mellitus, hypertension, and dyslipidemia are the most associated factors with NAFLD. Multiple "hits", involving metabolic syndrome as a major role and inflammatory processes involving cytokines, adipokines, and oxidative stress are hypothesized to explain the complex pathogenesis and progression of NAFLD. It is widely considered a liver manifestation of metabolic syndrome, associated with some clinical conditions.

The progression of NAFLD to fibrosis is difficult to monitor. Early and accurate assessment of the degree of liver fibrosis is essential in management and prognosis. Liver biopsy has long been considered the gold standard for the assessment of liver fibrosis. However it is an invasive procedure, with 0.05% mortality, There will be sampling error and variation in histological interpretation.

Due to these limitations, non-invasive methods like Fibroscan and aspartate aminotransferase platelet ratio index (APRI) are used. Fibroscan measures liver stiffness by using ultrasound and low-frequency elastic waves. It is painless, easy to perform, less expensive, and has good patient acceptability.

It has good sensitivity, specificity and high accuracy. In the early stages of NAFLD, The liver transferases are normal, and it tends to increase the progression of fibrosis.

The main aim of this study was to evaluate and compare the APRI and fibroscan in predicting early fibrosis in patients newly diagnosed as NAFLD attending the Outpatient department in Government Rajaji Hospital, Madurai.

Non-alcoholic Fatty Liver Disease

Non-alcoholic fatty liver disease (NAFLD) is defined as "the accumulation of fat in the liver in the absence of recent or ongoing intake of a significant amount of alcohol".

The definition of NAFLD includes the exclusion of other secondary causes of hepatic steatosis including hepatitis C virus, drugs, surgical procedures, total parenteral nutrition, and inborn errors of metabolism., The steatosis liver is defined best histologically on liver biopsy as the macrovesicular steatosis occupying at least 5% of the hepatocytes.

It is usually defined on imaging with MRS being the best modality. Since MRS is not readily available, for practical purposes, the most common imaging modality to define NAFLD is ultrasound abdomen. The differentiation of the steatosis from NASH is possible only on histology rather than imaging

NASH is defined as "steatosis and inflammation associated with the presence of one of the three features: a ballooning of hepatocytes, Mallory hyaline bodies, and fibrosis on liver histology". NASH itself is a heterogeneous condition; sometimes it may improve to steatosis or normal histology, sometimes it may remain relatively stable for years, and sometimes progress to cirrhosis

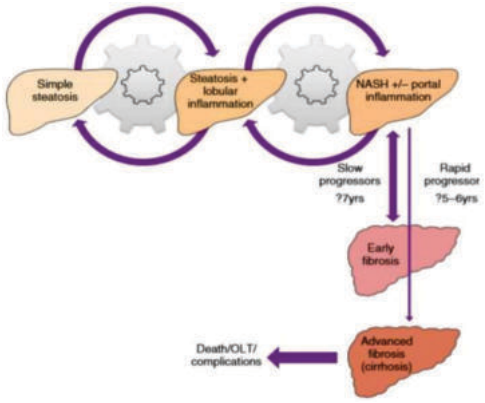
NAFLD is commonly associated with diabetes and is an important feature of metabolic syndromes and insulin resistance[1,2,3,4].

Compared with the risks of the general population, NAFLD is also associated with increased risks of mortality due to liver disease and cardiovascular disease[5,6,7,8,9].

Table 28.1. Working classification of non-alcoholic fatty liver disease

NNFL
Type 1 NAFLD: Steatosis with no inflammation or fibrosis
Type 2 NAFLD: Steatosis with non-specific lobular inflammation but absent of fibrosis or hepatocyte ballooning
NASH
Type 3 NAFLD: Steatosis with inflammation and fibrosis of variable levels (NASH)
Type 4 NAFLD: Steatosis, inflammation, hepatocyte ballooning, and fibrosis or Mallory-Denk bodies (NASH)

NNFL refers to non-NASH fatty liver and indicates the development of steatosis in the absence of significant ethanol exposure and without evidence of significant cell injury. Synonyms include simple steatosis and NAFL (non-alcoholic fatty liver). NASH, non-alcoholic steatohepatitis; NAFLD, non-alcoholic fatty liver disease.



Spectrum of Nafld:

Clinical Features And Diagnosis:
Most of the patients are asymptomatic. Diagnosis is often made by abnormal liver transaminases or features of fatty liver noted during investigations performed for other diseases. It may also be diagnosed during vague right upper quadrant abdominal pain, hepatomegaly workup, or abnormal-appearing liver at the time of abdominal surgery. Obesity is present in 50–90% of subjects.

Most patients with NAFLD will also have other features of metabolic syndrome. Some patients will have subtle stigmata of chronic liver disease such as palmar erythema, spider angioma, or splenomegaly. In a minority of patients with advanced NAFLD, complications of end-stage liver disease like jaundice, and features of portal hypertension such as ascites or variceal bleeding may be initial findings.

Mild to moderate elevation of AST and ALT levels (1.5 – 4 fold)

A pattern of aminotransferase ALT: ALT > 1 in contrast to alcoholic liver disease.

Serum alkaline phosphatase (ALP) and gamma glutaryl transferase (GGTP) levels may be elevated, but serum bilirubin level, prothrombin time, and serum albumin level will be typically normal, except in patients with cirrhosis.

Up to one-fourth of the patients with NAFLD will have ANA positivity but in low titers (<1: 320) Serum ferritin levels more than 1.5 times the upper limit of normal may be associated.

Physical examination/anthropometry including, height, weight, BMI, waist–hip ratio (WHR) and waist circumference for assessment of overweight and obesity.

These patients should be further evaluated for hypertension, impaired glucose tolerance serum triglycerides, and HDL. Screening for hepatitis B surface antigen (HBsAg) and antibodies to the hepatitis C virus should be done.

Fibroscan:
Fibroscan /transient elastography(TE) is a non-invasive ultrasound-based imaging modality for detecting liver fibrosis, its role is still being evolved in various liver diseases. Many patients with fatty liver diagnosed on conventional imaging may turn out to be having significant fibrosis on Fibroscan and they should be subjected to a liver biopsy

Principal And Procedure:
It uses shear wave velocity to assess tissue (*e.g.*, liver) stiffness. Shear waves are transverse waves which move slowly (< 50 m/s) and are rapidly attenuated by liver parenchyma. This effect depends on the elastic properties of the tissue, with the speed of shear waves inversely proportional to the tissue elasticity.

Based on the velocity and intensity attenuation of the shear wave, the acquired data are processed and displayed on the screen as the liver stiffness measurement (LSM) and controlled attenuation parameter (CAP).

Advantages Of Fibroscan:
1) Most widely used, validated non-invasive technique
2) Short duration, painless
3) Applicable for screening larger populations
4) Well-defined quality criteria
5) Good reproducibility
6) Prognostic value in cirrhosis

Limitations:
1) Ascites
2) Obesity (BMI > 30 kg/m^2) – decreased with the XL probe
3) Acute hepatitis
4) Chronic hepatitis with transaminases flare- if ALT levels are greater than 5 × the upper normal limit, there is a risk of overestimating the fibrosis stage.
5) Extrahepatic cholestasis
6) Congestive heart failure
7) Narrow intercostal spaces - failure rate decreased with the development of the S probe

APRI (aspartate aminotransferase platelet ratio index)

APRI value is calculated using the formula

$$APRI = \frac{\frac{\text{AST Level}}{\text{AST (Upper Limit of Normal)}}}{\text{Platelet Count } (10^9/L)} \times 100$$

The upper limit of normal = 40 Interpretation
<0.5 rules out significant fibrosis
>1.5 rules in significant fibrosis
> 2 cirrhosis

Aspartate aminotransferase to platelet ratio index (APRI) has been considered a noninvasive marker for detecting hepatic fibrosis in patients with chronic hepatitis B and C. APRI has been also used for predicting liver-related mortality in patients with chronic hepatitis C virus infection or alcoholic liver disease. APRI has been extensively studied in NAFLD, APRI values tend to increase with the degree of fibrosis, suggesting that it could be useful in NAFLD in predicting fibrosis.

MATERIALS AND METHODS

Source of Data:
This study includes 100 ultrasound-defined newly diagnosed NAFLD patients attending the outpatient department in Chalmeda Anand Rao institute of medical sciences, Karimnagar, Telangana and 100 age and sex-matched healthy subjects with the fulfilment of inclusion criteria and exclusion criteria.

Study Design:
Hospital-based prospective study

Conflict of Interest: NONE

Inclusion Criteria:
1) All newly diagnosed cases of ultrasound-defined NAFLD
2) Age group 25-65 years

Exclusion Criteria:
1) Alcohol consumption greater than 20gm/day in men & 10gm/day in women. HBsAg & Anti HCV positivity.
2) History of chronic liver disease.
3) Hepatocellular Carcinoma.
4) Prior liver transplantation.
5) Chronic kidney disease.
6) Coronary artery disease.

Statistical Analysis
The information collected regarding all the selected cases was recorded in a Master Chart. Data analysis was done with the help of a computer by using SPSS 16 software.

Using this software, percentages, means, and standard deviations 'p' values were calculated through the Student 't-test for raw data, Chi-square test for consolidated data and Pearson correlation for correlation coefficient to test the significance of the difference between variables.

A 'p-value less than 0.05 is taken to denote a significant relationship.

OBSERVATION AND RESULTS

Table. 1 Age distribution in NAFLD cases

AGE IN YEARS	NUMBER OF CASES
<35	7
35-45	20
46-55	43
>55	30
TOTAL	100
MEAN	50.01

Table 2. Gender distribution

GENDER	NUMBER OF CASES
MALE	60
FEMALE	40
TOTAL	100

Table 3: BMI distribution:

BMI	NUMBER OF CASES
<25	4
25.1 – 28	19
28.1 – 30	36
>30	41
TOTAL	100

Table 4: Fasting blood sugar distribution:

FBS	NUMBER OF CASES
<100	64
>100	36
TOTAL	100

Table 5: Triglyceride level distribution:

TGL	NUMBER OF CASES
<150	31
150-199	44
>200	25
TOTAL	100

Table 6: Aspartate aminotransferase (AST) distribution:

AST	NUMBER OF CASES
<30	14
31-40	30
41-50	32
>50	24
TOTAL	100

Table 7: Platelet distribution:

PLATELETS($\times 10^9$ cells/cumm)	NUMBER OF CASES
< 100	32
101 - 150	50
151 - 200	11
> 200	7
TOTAL	100

Table 8: APRI distribution:

APRI	NUMBER OF CASES
< 0.7	35
0.7 - 1.0	27
> 1.0	48
TOTAL	100

Table 9: Fibroscan:

FIBROSCAN	NUMBER OF CASES
< 7.0	42
7.0 - 8.9	35
> 9	23
TOTAL	100

Table 10: Fibroscan vs APRI:

FIBROSCAN(Kpa)	APRI		
	< 0.7	0.7 - 1.0	> 1.0
< 7.0 (42)	35	7	0
7.0 - 8.9 (35)	0	20	15
> 9 (23)	0	0	23
TOTAL	35	27	48
p VALUE	< 0.001 Significant		
CHI-SQUARE VALUE	107.426		

The Pearson correlation coefficient calculated was 0.904. showed a very good correlation.

DISCUSSION:

Non-Alcoholic Fatty Liver Disease is often considered the hepatic manifestation of metabolic syndrome with insulin resistance playing a dominant role. In NAFLD, patients are asymptomatic, the diagnosis is often made by abnormal liver aminotransferases or during the evaluation of other diseases. Early and accurate assessment of the degree of liver fibrosis is essential in management and prognosis. Cirrhosis and liver cancer are the potential outcomes of chronic NAFLD. Fibroscan measures liver stiffness by using ultrasound and low-frequency elastic waves. It has good sensitivity, specificity and high accuracy. In t early stages of NAFLD, The liver transferases are normal, and it tends to increase the progression of fibrosis.

The APRI score was calculated using the formula
APRI = {(AST level /ULN) / PLATELET COUNT(10^9/L)} * 100

The reference value of AST is 45 IU, cut off for cirrhosis in fibroscan in 14Kpa. In our study population of 100 NAFLD cases was diagnosed with the help of ultrasound and various parameters were measured. The following observations are made from this study.

In this study, the mean age was 50 years, and most patients were in the age group 45-55 years. This shows NAFLD was more prevalent in middle age groups. There was a high incidence of NAFLD in males (60%) compared to females in this study.

The mean triglyceride value was 185mg/dl. our study shows fasting triglyceride value was high in patients with NAFLD, which reflects the increased prevalence of metabolic syndrome in NAFLD cases. This observation is also seen in Shih et al.

The mean BMI in NAFLD cases in our study is 29.4. Hence our show shows an increased prevalence of obesity in NAFLD which might be a component of metabolic syndrome. This observation is consistent with the study done by Bansal et al.

The mean AST value was 41.6 IU. 34% of patients have values between 41-50 IU, and 20% of patients have >50 IU. The mean platelet count among 100 cases was 123× 10^9 cells.

APRI was calculated based on these AST and platelet values. Fibroscan was done for those patients and correlated with APRI. The mean APRI score was 1.09. 20 patients having APRI index between

0.7 to 1.0 had a fibro scan score between 7.0 to 8.9 denotes mild to moderate fibrosis according to the metavir scoring system. There is a statistically significant correlation between APRI & fibroscan in NAFLD pts ($p<0.001$). Many studies have been done in chronic Hepatitis B and C patients regarding APRI and fibroscan, so further studies need to be done in NAFLD patients to strengthen this association.

"Aspartate aminotransferase (AST) to platelet ratio index (APRI) is a cheap, blood-test based scoring system that can predict liver fibrosis."

SUMMARY:

This prospective study was conducted to study "Comparision of the efficacy of aspartate aminotransferase platelet ratio index to fibro scan as a marker for early fibrosis in – non-alcoholic fatty liver disease"

The study population consisted of 100 NAFLD patients attending General Medicine OPD as cases. After institutional ethical clearance and informed consent, various investigations about the study are done. The data were entered into Microsoft Excel sheet and statistically analysed.

The most common age group of NAFLD cases were from 46-55 years of age. There is a slight male predominance in the study. The mean AST value is 41.6 IU, mean platelet count was 123 × 10^9 cells. The APRI index was calculated based on these parameters. Fibroscan was done in those patients, There is a significant association between APRI and fibroscan by using the chi-square test. p value <0.001.

CONCLUSION:

Early and accurate assessment of the degree of liver fibrosis is essential

in the management and prevention of progression to cirrhosis in patients with NAFLD. Liver biopsy is the gold standard but being invasive, much research has been dedicated to evaluating non-invasive methods to determine liver fibrosis. This study focused on the performance of FibroScan as well as APRI to detect liver fibrosis in our hospital. This study shows a significant correlation between APRI and Fibroscan in patients with NAFLD.

Apart from the cost, the accessibility of FibroScan may be an issue in primary health care and resource-limited setting. Aspartate aminotransferase (AST) to platelet ratio index (APRI) is a very cheap, easily available biochemical test in all peripheral health care centres.
APRI and FIBROSCAN perform equally well in predicting liver fibrosis. The use of APRI ≥ 0.7 would avoid the need for a fibroscan. This index is used in a resource-limited setting where fibroscan is unavailable.

Limitations Of The Study:

1) The sample size was relatively small
2) There is no control group for this study
3) The study population involved patients who are seeking medical attention in our hospital which is a tertiary care centre. Hence, they may not represent the general population. It is a single-centre study.

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