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Original Research Article

Serum fibroscores APRI, FIB-4 and fibroscan in assessment of liver fibrosis in alcoholic associated liver disease

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ABSTRACT

Background: Alcohol-associated liver disease includes a variety of clinical disorders which include steatosis, Alcoholic steato hepatitis, alcoholic hepatitis of varying degrees of severity, alcoholic cirrhosis, and alcohol associated cirrhosis complicated by hepatocellular carcinoma (HCC). In patients with alcoholic liver disease the presence of hepatic (liver) fibrosis and progression into cirrhosis is a prognostic variable and having impact on survival. To assess hepatic (liver) fibrosis using serum fibro scores fibrosis-4 (FIB-4) scores, AST platelet ratio index (APRI scores) and to compare these results with fibro scan to rule out severe fibrosis in patients with alcohol related disease.
Methods: A cross sectional clinical study conducted on 50 patients with alcohol associated chronic liver disease between December 2019 to December 2020 who were in follow up in outpatient department (OPD) and admitted in the Department of Medical Gastroenterology. APRI and FIB-4 scores were calculated and compared with fibro scan values.
Results: The results of 50 patients were analysed, including, males with a mean age. Among the study population, 6 (12%) participants had no significant FIB-4, 16 (32%) participants had intermediate FIB-4 and 28 (56%) participants had likely cirrhosis. 33 (66%) participants had no significant APRI, 6 (12%) participants had significant APRI and 11 (22%) participants had cirrhosis liver. Among the people with fibro scan KPA F0-F1 (<7), all of them 100% were no significant FIB-4. Among the people with fibro scan KPA F2 (7 To 9.50), 2 (50%) were no significant FIB-4 and intermediate FIB-4 for each respectively.
Conclusions: FIB-4 score correlated better than APRI score in assessing patients with and without severe fibrosis and cirrhosis in the setting of alcohol associated liver disease patients.

Keywords: APRI, FIB-4, Fibro scan, Alcoholic associated liver disease

INTRODUCTION

Alcohol associated liver disease (ALD) is the commonest cause of cirrhosis in the world and is currently one of the ten most common causes of death.[1] Cirrhosis involves replacement of the normal hepatic parenchyma with extensive thick bands of fibrous tissue and regenerative nodules, which results in the clinical manifestations of portal hypertension and liver failure.[2] Assessment of hepatic fibrosis is important for predicting the prognosis and outcomes. A liver biopsy is the gold standard for establishing a definite diagnosis of ALD. However, liver biopsy is an invasive procedure, with significant morbidity. Other non-invasive alternatives methods include the AST platelet ratio index (APRI), fibrosis index based on 4 factors (FIB-4) liver imaging techniques include fibro scan (transient elastography) or MR elastography.

The World Health Organization (WHO) estimates that alcohol is now the third highest risk factor for premature mortality, disability and loss of health worldwide.[3] Liver fibrosis caused by alcohol abuse and its end stage, cirrhosis, present enormous problems for health care worldwide. Overall, stopping drinking has been shown to improve the survival of patients with all stages of ALD.[4]

Aspartate transaminase (AST) to platelet ratio index (APRI), score was initially designed to predict fibrosis in hepatitis C and later found to be useful in other causes of liver disease.[5,6] APRI and FIB-4 have high specificity but low sensitivity for significant fibrosis and cirrhosis. WHO proposes a high cut-off for APRI and FIB-4 test greater than equal to 2 and 3.25 respectively, while a low cut-off value of less than equal to 1 and 1.45 respectively.[5]

A FIB-4 test >3.25 has been found to have a positive predictive value of 82.1% to establish the presence of significant fibrosis, while a score <1.45 is said to have a negative predictive value of 94.7%.[7]

Objectives

The objective of the study is to assess liver fibrosis using fibro scores APRI and FIB-4 and compare the results with fibro scan in alcoholic liver disease patients who were diagnosed and in follow up in Chettinad Hospital and Research Institute.

METHODS

This is a prospective, observational and cross-sectional study conducted in the Department of Medical Gastroenterology from December 2019 to 2020 after institutional human ethical committee approval. Total of 50 Patients who were diagnosed with alcoholic liver disease attending the outpatient and cases admitted in ward were included in this study. The FIB-4 and APRI scores were calculated for each patient and the values obtained were rounded to two decimal places. A cut-off value of 3.25 for FIB-4 and 2 for APRI were used to predict which patients had severe fibrosis or cirrhosis.[8,9]

$$FIB-4 = (age \times AST) \div (platelet\ count \times (sqr(ALT))$$

$$APRI = (AST \div AST\ upper\ limit\ of\ normal) \div platelet \times 100$$

Fibro scan 402 (vibration-controlled transient elastography) was used to assess liver stiffness in all patients.

Serum fibro scores FIB-4 and APRI were considered as the primary outcome variables. Transient elastography (fibro scan) primary explanatory variable.

Age, haemoglobin (Hb in gm), platelet count (n in lakhs), international normalized ratio (INR), serum total bilirubin, aspartate transaminase (AST), alanine aminotransferase (ALT), serum albumin, blood urea, creatinine, sodium levels and model for end-stage liver disease (MELD) sodium were considered as other study relevant variables.

Statistical analysis

Descriptive analysis

Descriptive analysis was carried out by mean and standard deviation for quantitative variables, frequency and proportion for categorical variables. Data was also represented using appropriate diagrams like bar diagram, pie diagram.

The association between explanatory variables and categorical outcomes was assessed by cross tabulation and comparison of percentages. Chi square test was used to test statistical significance.

Diagnostic test (sensitivity and specificity)

Fibro scan kiloPascal's (KPA) was considered as gold standard. FIB-4 score and APRI score was considered as screening test. The sensitivity, specificity, predictive values and diagnostic accuracy of the screening test along with their 95% CI were presented. P value <0.05 was considered statistically significant. IBM SPSS version 22 was used for statistical analysis.

RESULTS

A total of 50 subjects were included in the final analysis.

Among the study population, 6 (12%) participants had no significant FIB-4, 16 (32%) participants had intermediate FIB-4 and 28 (56%) participants had likely cirrhosis (Table 1).

Table 1: Descriptive analysis of FIB-4 classification in the study population (n=50).

FIB-4 classification	Frequency	Percentages
No significant (<1.45)	6	12.00
Intermediate (1.45 to 3.25)	16	32.00
Likely cirrhosis (>3.25)	28	56.00

Table 2: Descriptive analysis of APRI classification in the study population (n=50).

APRI classification	Frequency	Percentages
No significant (<1.5)	33	66.00
Significant (1.5 to 2.0)	6	12.00
Cirrhosis liver (>2)	11	22.00

Among the study population, 33 (66%) participants had no significant APRI, 6 (12%) participants had significant

APRI and 11 (22%) participants had cirrhosis liver (Table 2).

Table 3: Descriptive analysis of fibro scan KPA in the study population (n=50).

Fibro scan KPA	Frequency	Percentages
F0-F1 (<7)	1	2.00
F2 (7 to 9.50)	4	8.00
F3 (9.51 to 12.50)	6	12.00
F4 (>12.50)	39	78.00

Among the people with fibro scan KPA, only 1 (2%) participant was F0-F1 (<7), 4 (8%) participants were F2 (7 to 9.50), 6 (12%) participants were F3 (9.51 to 12.50) and 39 (78%) participants were F4 (>12.50) in the study population (Table 6 and Figure 1).

Among the people with fibro scan KPA F0-F1 (<7), all of them 100% were no significant FIB-4. Among the people with fibro scan KPA F2 (7 To 9.50), 2 (50%) were no significant fib 4 and intermediate FIB-4 for each respectively (Table 4).

The difference in FIB-4 between the fibro scan KPA is found to be significant with a P value of 0.005, with majority of 37 (94.87%) participants within significant FIB-4 in severe fibrosis group (Table 6).

When compared to fibro scan KPA, FIB-4 had sensitivity of 36.36% (95% CI 10.93% to 69.21%) in no significant FIB-4, Specificity was 94.87% (95 CI 82.68% to 99.37%), False positive rate was 5.13 (95 CI 0.63% to 17.32%), false negative rate was 63.64% (95 CI 30.79 % to 89.07%), positive predictive value was 66.67%(95 CI 22.28% to 100%), negative predictive value was 84.09% (95 CI 69.93% to 93.36%) and the total diagnostic accuracy was 82% (95 CI 68.56% to 91.42%) (Table 10).

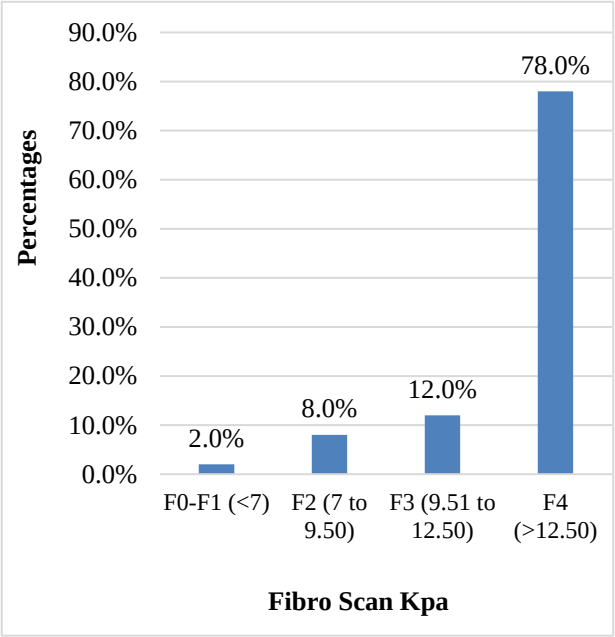

Figure 1: Bar chart of fibro scan KPA in the study population (n=50).

Table 4: Comparison of FIB-4 classification across fibro scan KPA (n=50).

Fib-4 classification	Fibro scan KPA			
	F0-F1 (<7) (N=1) %	**F2 (7 To 9.50) (N=4) %**	**F3 (9.51 To 12.50) (N=6) %**	**F4 (>12.50) (N=39) %**
No significant (<1.45)	1 (100)	2 (50)	1 (16.67)	2 (5.13)
Intermediate (1.45 To 3.25)	0 (0)	2 (50)	5 (83.33)	9 (23.08)
Likely cirrhosis (>3.25)	0 (0)	0 (0)	0 (0)	28 (71.79)

*No statistical test was applied-due to 0 subjects in the cell

Table 5: Comparison of APRI classification across fibro scan KPA (n=50).

APRI classification	Fibro scan Kpa			
	F0-F1 (<7) (N=1) %	**F2 (7 To 9.50) (N=4) %**	**F3 (9.51 To 12.50) (N=6) %**	**F4 (>12.50) (N=39) %**
No significant (<1.5)	1 (100)	4 (100)	6 (100)	22 (56.41)
Significant (1.5 to 2.0)	0 (0)	0 (0)	0 (0)	6 (15.38)
Cirrhosis liver (>2)	0 (0)	0 (0)	0 (0)	11 (28.21)

*No statistical test was applied-due to 0 subjects in the cell

Table 6: Comparison of fibro scan KPA with FIB-4 classification (n=50).

Fib-4 classification	Fibro scan KPA		Chi square	P value
	Mild to moderate (up to 12) (N=11) %	**Severe fibrosis (>12) (N=39) %**		
No significant	4 (36.36)	2 (5.13)	7.927	0.005
Significant	7 (63.64)	37 (94.87)		

Table 7: Predictive validity of FIB-4 classification in predicting fibro scan KPA (n=50).

Parameter	Value (%)	95% CI	
		Lower (%)	Upper (%)
Sensitivity	36.36	10.93	69.21
Specificity	94.87	82.68	99.37
False positive rate	5.13	0.63	17.32
False negative rate	63.64	30.79	89.07
Positive predictive value	66.67	22.28	95.67
Negative predictive value	84.09	69.93	93.36
Diagnostic accuracy	82.00	68.56	91.42

Table 8: Comparison of fibro scan KPA with APRI classification (n=50).

APRI classification	Fibro scan KPA	
	Mild to moderate (up to 12) (N=11) %	Severe fibrosis (>12) (N=39) %
No significant	11 (100)	22 (56.41)
Significant	0 (0)	17 (43.59)

*No statistical test was applied-due to 0 subjects in the cell

Table 9: Predictive validity of APRI classification in predicting Fibro scan KPA (n=50).

Parameter	Value %	95% CI	
		Lower %	Upper %
Sensitivity	100.00	71.51	100.00
Specificity	43.59	27.81	60.38
False positive rate	56.41	39.62	72.19
False negative rate	0.00	0	28.49
Positive predictive value	33.33	17.96	51.83
Negative predictive value	100.00	80.49	100.00
Diagnostic accuracy	56.00	41.25	70.01

DISCUSSION

Assessment of hepatic fibrosis is important for predicting the prognosis and outcomes in patients with ALD. Complications of ALD are the main causes of mortality related to chronic liver disease. Progressive hepatic fibrosis with the development of cirrhosis is a feature in the majority of chronic liver disease cases.[10] Therefore, liver fibrosis stage can be a significant predictive factor for mortality related to liver complications.

Liver biopsy is gold standard to assess fibrosis stage in most patients with chronic liver disease. Due to the 3 main limitations of biopsy—severe complications, sampling error, and inter observer variability, several biomarkers have been validated as non-invasive alternatives, and these biomarkers are increasingly being used in practice.

In this study, we correlated the diagnostic performance of non-invasive indices APRI and FIB-4. They are cheap, readily available, non-invasive and cost-effective than other non-invasive techniques like transient elastography fibro scan.[11] In our study, the data revealed that age was associated with more advanced stages of the disease, which is consistent with previous NAFLD studies.[12] Moreover, in our study were older on average (50.38±7.44 years old) than those from cohorts analysed by other authors in similar setting the frequencies of cardiovascular disease and chronic inflammatory diseases are higher in older populations.[13]

The specificity and sensitivity of fibro scan were highest at ≥F4. Fibro scan has also proven to be an effective method of assessing fibrosis progression for a variety of other pathologies, such as hepatic steatosis. It is also applicable in the evaluation of fibrosis progression and complications, such as portal hypertension, and in the clinical treatment of HCV and other chronic liver diseases.[14] In our study, the fibro scan showed a positive correlation with the fibrosis as 12% of F3 patients, whereas 78% of F4 patients had fibrosis. In more advanced stages of liver disease, the liver becomes small with a multinodular surface.[15]

Gara et al showed that, despite the high sensitivity and specificity of fibro scan and APRI in the diagnosis of fibrosis, due to the possibility of false-positives, it is always necessary to view the results in the context of clinical exams or an imaging exam.[16] APRI could not identify the individual stages of fibrosis, and the fibrosis of some patients remained unclassified when the initial cut-off was applied. Furthermore, the appropriate

definition of the limits of normal AST remains uncertain. Each laboratory establishes a different value for the upper limit of normal.[17]

In our study platelet count were decreased, there was a strong negative correlation between platelet count and stiffness, as thrombocytopenia in liver disease is associated with advanced fibrosis. Similarly, Siddiqui et al stated that platelet count decreases as fibrosis increases. The decrease of platelet counts is due to decreased production of thrombopoietin synthesis and direct Bone marrow toxicity from alcohol.[18]

Moreover, in our study patients with fibrosis had ALT and AST levels (44.02±18 IU/ml and 49.9±17.76). The increase of AST levels is associated with hepatocyte damage which triggers the release of AST from mitochondria and the decrease of AST clearance due to liver fibrosis.[19] ALT is an intracellular enzyme located in the cytoplasm of hepatocytes which will be released when mild hepatocytes damage occurs, in contrast to AST enzyme concentrated in hepatocytes mitochondria; thus, the release of AST generally.[20] This effect was more pronounced with AST than ALT which is to be expected with fibrosis progression since this has been associated with a reversal of the AST/ALT ratio.[21] It is only logical that the subpopulation with severe fibrosis had higher FIB-4 (2.54 versus 1.3) and APRI scores (1.49 versus 0.68). This corroborates the conclusions of studies conducted by other researchers.[22]

In our study, APRI the cut-off for fibrosis was 2 with sensitivity=100% (95% CI 71.51% to 100%) and specificity=43.59% (95% CI 27.81% to 60.38%). FIB-4 the cut-off for fibrosis was 3.25 with sensitivity=36.36% (95% CI 10.93% to 69.21%) in no significant FIB-4 and specificity=94.87% (95 CI 82.68% to 99.37%). Piecha et al found that a cut-off score for enhanced liver fibrosis of ≥9.8 had a sensitivity of 74.4% and a specificity of 92.4% for advanced fibrosis.[23] In a previous study by our group analyzing a cohort of selected patients, we found similar results for identification of significant fibrosis (F2-F4) and cirrhosis (F4).[24]

In our study, for detection of significant cirrhosis by fibroscan at the cut-off level of 12.50 kPa, sensitivity was 100%, and specificity was 43.5% which similar compared with Castera et al who reported at the cut-off level of 12.5 kPa, AUROC of 0.95, sensitivity of 97%, and specificity of 91%.[31] Soto et al who reported at a cut-off level of 17.6 kPa, sensitivity of 77% and specificity of 97%.[25]

FIB-4 had prognostic values that were significantly higher than prognostic value of APRI. These results were expected, as they were similar to the diagnostic performance previously observed in diagnostic overviews.[26] FIB-4 had higher diagnostic performance than APRI.[27]

The APRI, FIB-4 and fibro scan showed a significant correlation with the stages of fibrosis in our study. As a non-invasive method, the FIB-4 showed a better ability to differentiate the stage of liver fibrosis than did the APRI. FIB-4 may prove very useful in identifying patients without advanced liver disease in which a liver biopsy could be deferred safely. Especially in places where resource-limited settings, the application of these non-invasive methods may be reduces or replaces the need for liver biopsy in alcohol associated liver disease patients.

Limitations

The limitations of the study were: our patients were enrolled from a single referral centre, which may be have led to selection bias; the number of included patients might be small in view of the state level, but this could be compensated for by the strict inclusion criteria; and liver biopsy, the gold standard of alcohol associated liver disease diagnosis, was not used in this study.

CONCLUSION

This study has shown FIB-4 was superior to APRI when it comes to making a distinction between patients with and without severe fibrosis and cirrhosis in the setting of alcohol associated liver disease patients. Considering the risks of liver biopsy, usage of serum tests can be a helpful diagnostic tool to identify patients with higher risk of significant fibrosis taking into account overall clinical condition and additional tests like transient elastography. This can eliminate the need for liver biopsy in patients without clear indication.

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