Original Research Article

Correlation of aspartate aminotransferase-to-platelet ratio index with child-turcotte-pugh score and model for end stage liver disease score in patients of liver cirrhosis

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ABSTRACT

Background: Though liver biopsy is considered to be a gold standard for the diagnosis and severity of liver cirrhosis, recently many non-invasive markers have come up for the same. In the current study, we investigated the correlation of aspartate aminotransferase-to-platelet ratio index with other severity scores of liver cirrhosis namely child-turcotte-Pugh score and model for end stage liver disease score.
Methods: Fifty-one patients with cirrhosis, identified on the basis of abdomen ultrasonographic findings were enrolled in the study. APRI was calculated for every patient using the formula, (AST/upper limit of normal/platelet count;10^9/l)×100. The MELD score was calculated according to the original formula proposed by the Mayo clinic group: 3.8×loge (bilirubin; mg/dl)+11.2×loge(INR)+ 9.6×loge (creatinine; mg/dl)+6.4. CTP scoring was calculated based on the severity of hepatic encephalopathy, ascites, total bilirubin, albumin, and INR. Correlation of APRI with MELD and CTP score was established using Pearson correlation coefficient.
Results: APRI scores correlated well with the severity of the cirrhosis. With the progression of the CTP class from A to C and with increase in the MELD score, increase in the APRI index was also observed.
Conclusions: APRI showed positive correlation with CTP and MELD score.

Keywords: Liver, Cirrhosis, APRI, CTP score, MELD score

INTRODUCTION

Liver cirrhosis is among the top twenty causes of death in the world, leading to 1.03 million deaths worldwide yearly.[1] Since last few decades, many non-invasive methods of assessing the prognosis and survival in cirrhotic patients have come up, which consider various clinical and biochemical parameters. The most widely used bed-side scores are child-turcotte-Pugh score (CTP) and model for end stage liver disease (MELD) score. The recent additions to the list are aspartate aminotransferase-to-platelet ratio index (APRI) and gamma-glutamyl transpeptidase to platelet ratio index. CTP scoring is based on the severity of hepatic encephalopathy, ascites, total bilirubin, albumin, and INR.[2] The predictive accuracy of CTP scoring is limited by lack of multi-organ evaluation and subjective variables in clinical assessment. MELD is calculated using a mathematical formula based on serum creatinine, total bilirubin and international normalized ratio (INR) or prothrombin time and also used in

prioritization of candidates for liver transplantation.[3,4] At present, the CTP classification is the most widely applied system for bed-side assessment of cirrhosis and its complications.[5] An ideal non-invasive diagnostic test for hepatic cirrhosis should be simple, available, inexpensive, and accurate. Wai et al has reported a novel index for prediction of significant fibrosis and cirrhosis by combining aspartate aminotransferase (AST) and platelets in a model termed APRI which is a simple noninvasive index that can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis.[6] Hence in our study we have tried to find out the correlation of APRI with commonly used severity scores; CTP and MELD.

METHODS

The study was conducted at a tertiary care hospital in Delhi, in the department of medicine. It enrolled 51 patients of liver cirrhosis as cases and 50 healthy subjects as controls. The study was commenced after the approval from the institutional ethics committee. A written informed consent was obtained from all the patients and healthy controls. Two-hundred patients who attended the OPD or were admitted in medicine wards, from January 2009 to April 2010 with signs, symptoms and investigations suggestive of liver pathology underwent ultrasonography. Fifty-one patients satisfying the ultrasonographic criteria for cirrhosis were prospectively enrolled for the study. Healthy controls included the relatives of the patients and other volunteers.

Inclusion criteria

Inclusion criteria were age >18 years, both male and female patients of cirrhosis identified on the basis of clinical findings and ultrasonographic features.

Exclusion criteria

The exclusion criteria were liver disorders other than cirrhosis, accompanying illnesses like haematological disorders, malignancy, and chronic disorders like diabetes, hypertension, cardiac diseases, renal failure, any surgical history or patient's unwillingness to participate in the study.

Ultrasonography was done using a real time 3.5 MHz probe in fasting state in all subjects by a single observer to minimize inter observer variations. The USG criteria for the diagnosis of cirrhosis were nodular hepatic contour, enlargement of caudate and lateral segment of left lobe, atrophy of right and medial segment of left lobe, prominence of fissures and porta hepatic, increased parenchymal echogenicity, decreased ultrasound beam penetration, poor depiction of intrahepatic vessels, regenerating nodules, altered gall bladder angle, loss of normal triphasic hepatic vein Doppler tracing, increased pulsations of portal vein on Doppler tracing. Patients with presence of any 5 out of them were labelled as cirrhotic. The sensitivity and specificity of USG for diagnosing cirrhosis has shown to be 91.1% and 93.1% respectively with accuracy of 92.3%.[7,8] Liver function test comprised of parameters like SGOT, SGPT, Alkaline phosphatase, and serum bilirubin, performed using a fully automatic Hitachi-912 auto analyser. Platelet count was determined by the fully automatic Sysmex KX 21 auto analyser using the principle of optical impedance and flow cytometry. Serum creatinine was estimated using Jaffe method (kinetic) without deprotanization. In this method, creatinine forms a coloured complex with picrate in alkaline solution. The rate of complex formation is measured photometrically using BM-Hitachi-911 auto-analyser.

Prothrombin time test was performed using the Pacific hemostasis kit. The one stage PT measures the clotting time of plasma after adding a source of tissue factor (thromboplastin and calcium) the recalcification of plasma in the presence of tissue factor generates Factor Xa, which in turn activates prothrombin to thrombin, which converts fibrinogen to an insoluble fibrin clot. APRI score was calculated as follows:[6]AST/upper limit of normal/platelet count (10^9/l)×100. Child Pugh score was calculated as given by Pugh et al shown in (Table 1).[2] Meld score was calculated according to the original formula proposed by the Mayo clinic group:[3] 3.8×log$_e$ bilirubin (mg/dl)+11.2×log$_e$ (INR)+9.6×log$_e$ (creatinine (mg/dl)+6.4. MELD score was divided arbitrarily into 3 classes as shown in (Table 2).

Table 1: Child pugh scoring system.

Measure	1 point	2 points	3 points
Total bilirubin (mgdl)	< 2	2-3	>3
Serum albumin (mg/l)	>35	30-35	< 30
Prothrombin time prolongation (second)	0-4	4-6	>6
Ascites	None	Suppressed with medication	Refractory
Hepatic encephalopathy	None	Grade I-II (or suppressed with medication)	Grade III-IV (refractory)
Points	Class	Life expectancy	Peri-operative mortality (%)
5-6	A	15 -20	10
7-9	B	Candidate for Transplant	30
10-15	C	1-3 months	82

Table 2: Division of classes as per MELD.

MELD score	Class
6-19	class 1
20 - 29	class 2
>30	Class 3

Statistics analysis

Statistical analysis was done using SSPS 27 (SSPS software Inc., Chicago, USA).Student t - test was used to compare between two groups in case of quantitative data and Fischer exact test in qualitative data. Pearson correlation coefficient was used to see the correlation between APRI, CTP and MELD scores. The comparison between APRI with respect to various classes of CTP and MELD score was done by using One Way ANOVA Kruskal-Wallis test, followed by post hoc comparison, p value <0.05 was considered significant.

RESULTS

Out of total (51) patients of cirrhosis, 41 were males (80.39%) and 10 were females (19.6%) while in the control group of 50 subjects, 37 were males (74%) and 13 were females (26%); with mean age±SD of 43.08±12.3 and 37.74±12.4 respectively (Table 3).

Out of 51 patients 9 (17.64%) were Hepatitis B positive, 7 (13.72%) were hepatitis C positive and 25 (49.01%) were chronic alcoholics, rest of them were not fitting in any particular diagnosis. There were significant differences in the platelet count, SGOT/PT, INR, prothrombin time, serum creatinine, albumin and serum bilirubin of the cases as compared to controls (p<0.05) as given in (Table 3).

There was statistically significant difference in the mean APRI score of the case cohort and control cohort (p<0.001) (Table 3). Among the cases four patients (7.84 %) were in class A, twenty one (41.17 %) in class B and twenty six (50.98 %) were in class C of CTP score. Also, eight patients (15.71 %) had grade 1 whiles seven patients (13.7%) had grade 2 and 3, and two patients (3.9%) had grade 4 hepatic encephalopathy. Four patients (7.8%) had grade 1, thirty one patients (60.8%) had grade 2 and eight patients (15.7%) had grade 3 refractory ascites. While none of the patients in control cohort had either hepatic encephalopathy or ascites (Table 4). The mean MELD score of the case cohort and control cohort was 17.73±9.974 and 2.48±2.92 respectively (Table 5).

Table 3: Comparison of variables in case and control cohort.

Parameters	Case cohort (Mean±SD)	Control Cohort	P value
Age	43.08±12.3	37.74±12.4	-
Sex (M:F)	41:10	37:13	-
Platelet count (lac/mm^3)	0.97±0.49	2.56±0.8	0.001
Se. Creatinine (mg/dl)	1.28±1.28	0.74±0.19	0.004
Se. Bilirubin (mg/dl)	4±4.51	0.78±0.19	0.001
SGOT(AST) (IU)	73.38±36.93	33.8±7.48	0.001
SGPT(ALP) (IU)	44.12±17.86	36.8±6.6	0.008
Prothrombin time (seconds)	20.23±9.65	13.28±0.86	0.001
INR	1.78±0.98	1.02±0.06	0.001
APRI score	2.178±1.224	0.364±0.137	0.001

Table 4: Distribution of complications in cases.

Hepatic encephalopathy N (%)					Total N (%)	Ascites N (%)			Total N (%)
(N)	Grade 1	Grade 2	Grade 3	Grade 4		Grade 1	Grade 2	Grade 3	
Cases (51)	8 (15.7)	7 (13.7)	7 (13.7)	2 (3.9)	27 (52.9)	4 (7.8)	31 (60.8)	8 (15.7)	43 (84)
Control (50)	00	00	00	00	00	00	00	00	00

In case cohort there were thirty-four patients in class 1, ten in class 2 and seven were in class 3 of MELD score.

All the participants in controls had MELD score of 5 or less. Individual correlation of APRI with classes of CTP

score was also seen and it was found that as the severity of the score increases from A-B-C so is the value of mean APRI scores in each individual group. The correlation coefficient of APRI with CTP score was 0.742 (p=0.001) (Table 6). Similarly, it was seen that individual classes of MELD score also showed positive correlation with APRI score. As we move from MELD class 1 to 3, the mean APRI score also shows a progressive increase. The correlation coefficient of APRI with MELD score was 0.822 (p=0.001) (Table 7). Pearson correlation coefficient was applied to find out the correlation between APRI with CTP score and APRI with MELD score. It was seen that APRI had positive and statistically significant correlation with both (Table 8).

Table 5: MELD score comparison in cases and control classes.

MELD score	Cases (51)	Controls (50)
Mean	17.73	2.48
Median	15	03
Minimum	06	-07
Maximum	40	08

Table 6: Correlation of APRI score with the classes of CTP score.

| CTP class | N | Parameters | | | 5% Confidence interval for mean | | Minimum/ maximum |
		Mean APRI	SD	Std. Error	Lower bound	Upper bound	
A	04	0.94788	0.430925	0.215462	0.26318	1.63357	0.35/1.276
B	21	1.37574	0.601373	0.13123	1.102	1.64948	0.232/2.475
C	26	3.01558	1.08335	0.212462	2.578	3.45315	1.16/5.4
Total	51	2.17818	1.224255	0.17143	1.83385	2.5225	0.232

Table 7: Correlation of APRI score with the classes of MELD score.

| MELD CAT | N | Parameters | | | 5% Confidence interval for mean | | Minimum | Maximum |
		Mean APRI	Std. Deviation	Std. Error	Lower bound	Upper bound		
1	34	1.59697	0.680935	0.116779	1.35938	1.83456	0.232	2.700
2	10	2.74350	1.086759	0.343663	1.96608	3.52092	0.192	4.074
3	7	4.19357	0.9912655	0.374663	3.27680	5.11034	2.600	5.4
Total	51	2.17818	1.224255	0.17143	1.83385	2.5225	0.232	5.4

Table 8: Correlation of APRI score with CTP and MELD score.

Parameters		APRI	CTP score	MELD score
APRI	Pearson correlation	1	0.742**	0.822**
	Significance (2-tailed)		0.001	0.001
	N	51	51	51
CTP score	Pearson correlation	0.742	1	0.791
	Significance (2-tailed)	0.001		0.001
	N	51	51	51
MELD score	Pearson correlation	0.822	0.791	-
	Significance (2-tailed)	0.001	0.001	-
	N	51	51	51

DISCUSSION

Till date, multiple studies have been published regarding the non-invasive diagnosis of significant liver fibrosis and cirrhosis. In the present study, we have tried to establish a correlation between APRI and other severity scoring systems of CTP and MELD score. CTP and MELD score have been previously used successfully to predict the

severity, assess the prognosis and predict the need for liver transplantation in cirrhosis. A retrospective study by Botta et al on 129 patients of cirrhosis that aimed at evaluating the short and medium term prognostic ability of the MELD scoring system compared with the child-Pugh score stated that CTP and MELD had sensitivity of 92% and 75% and specificity of 72% and 68% respectively for six months survival of these patients. While for one year survival outcome, sensitivity was 61% and 87% and specificity were 75% and 42% respectively.[3]

Because of its empirical simplicity, intuitiveness, and good accuracy over a wide range of causes and specific situations, CTP is being used for the last three decades but MELD is believed to be more reproducible than CTP as it does not include subjective observer-based clinical variables like ascites and encephalopathy, hence it has replaced CTP score for prioritizing liver donor allocation. Both the scores have been shown to be similar in predicting in-hospital mortality by acute upper gastrointestinal bleed in cirrhotic patients.[5,9] A study by Kamath et al that included the data of 282 patients showed that there were 129 deaths out of which 59 occurred during the first 3 months, the primary outcome measure for the study. The c-statistic for prediction of 3-month survival by the MELD score was 0.87 (95% confidence interval 0.82-0.92) and for CTP score was 0.84 (95% CI, 0.78-0.90). The 3-month mortality in patients with CTP class A was 4%, for class B 14%, and class C was 51%.[10] But a systemic review by D'Amico et al has shown CTP score as the most consistent and robust predictor of death in cirrhosis. CTP score or its components (albumin, bilirubin, ascites, encephalopathy and prothrombin time) are the significant predictors of death in the absence of features of decompensation like ascites, encephalopathy and jaundice as shown from the analysis of studies that included only compensated cirrhosis patients. This review also stated that MELD score is useful in predicting mortality in decompensated cirrhotic patients.[11] In our study also, significant differences were seen in platelet count, SGOT, Se. creatinine, Se. bilirubin, prothrombin time and APRI score among cases and controls (p<0.05).

A retrospective study to compare the predictive power of CTP and MELD in assessment of short term and overall survival after TIPS placement was done by Angermayr and colleagues in Vienna, Austria. It studied 475 patients who underwent TIPS from from May 1991 to December 2001.The three-month survival rates for CTP classes A, B, and C were 88%, 89%, and 62% respectively and for three years these were 64%, 57%, and 36% respectively. 60% of patients with MELD >18 (N=17) died within three months of TIPS placement. Multivariate analysis of CTP and MELD as three month and overall survival predictors yielded MELD as a single independent predictor for overall survival (Cox analysis: parameter estimate 0.053, standard error 0.012, p<0.0001). The accuracy of both scores for one month, three months, and one year survival were compared. The discrimination powers of MELD (c statistics: 0.73, 0.72, 0.66 for one month, three month, and

one year survival) were similar to CTP score at the same time points (c statistics: 0.78, 0.70, 0.66). The sensitivity of 40%, specificity 90%, positive predictive value 46%, and negative predictive value 87% were seen for MELD score to predict the three months mortality.[12] A study by Chalasani et al that included 239 patients with acute variceal bleeding hospitalized between January 1, 1997 and June 30, 2000 at 4 large academic hospitals of the United States. In-hospital and 1-year mortality rates were 14.2% and 27%, respectively. Mean CTP and MELD scores of the cohort were 8.8 2.2 and 11 8, respectively. This study showed that MELD score was highly predictive of in-hospital mortality rate (C-index: 0.82; 95% CI: 0.72-0.92); however, its predictability was similar to CTP score (C-index: 0.85; 95% CI: 0.76-0.94). For 1-year mortality rates, the MELD score had a C-index of 0.75 (95% CI: 0.67-0.82), that was again similar to CTP score (C-index: 0.78; 95% CI: 0.70-0.86).[13] A study by Mishra et al to evaluate the utility of MELD score in predicting the prognosis of cirrhotic patients and identify its correlation with CTP score described a significant correlation between MELD score and child-Pugh Score with correlation coefficient being, r=0.813 (p=0.05). It also showed that the cases with MELD scores ≥30 had significantly high mortality rate (75%).[14]

The APRI test for bed-side prediction of liver cirrhosis was first used by Wai et al in 2003. This study has stated APRI to have 86% negative predictive value (NPV) and 88% positve predictive value (PPV) in the presence of significant fibrosis and 98% NPV and 57% PPV in predicting the presence of cirrhosis.[6] Various studies have compared different type of non-invasive biomarkers with APRI for diagnosis of liver cirrhosis.[15-17] Ucar and colleagues demonstrated APRI to have better diagnostic value in patients with significant fibrosis as compared to other serum markers.[16] A study conducted by Dr SK Sareen etal included 74 professed a significant correlation between HVPG and APRI (Spearman's rho 0.365; p¼=0.001). The ROC curve to study the performance of APRI for predicting high portal pressure (HVPG >12 mmHg) had area under curve 0.716 (95% CI 0.574-0.858). An APRI had a sensitivity 66%, specificity 73%, positive predictive value 85%, negative predictive value 47%, and diagnostic accuracy 68% for predicting HVPG >12 mmHg at the cut off of 1.09. Hence it can be used as a cost-effective bedside, non-invasive marker for diagnosis of high portal pressure in cirrhotic patients.[17]

Others researchers have also shown that APRI correlates fairly with cirrhosis in patients with HIV and Hep C coinfection as shown by Carvalho-Filho et al and is most accurate and simple marker for predicting significant fibrosis in chronic hepatitis B.[18,19] In our study, it was seen that APRI has a positive and statistically significant correlation with CTP and MELD scores, (Table 8). Individual correlation of APRI with classes of CTP score was also seen and it was found that as the severity of the score increases from A-B-C so is the value of mean APRI scores in each individual group (Table 6). Similarly, it was

seen that individual classes of MELD score (Table 7). As we move from MELD class 1 to 3, the mean APRI score also shows a progressive increase. Thus indicating that it can be helpful in predicting the severity and prognosis of the disease. A similar reterospective study was done by George and Yeshavanth in Karnataka that investigated 50 patients to calculate APRI index, child Pugh score and MELD score in liver cirrhosis patients and to see if there existed any correlation between these scores. Out of 50 only 3 were females. 2 patients were in child Pugh class A, 14 patients were in child Pugh class B and 26 patients were in child Pugh class C. Patients were also evaluated for the severity of ascites and hepatic encephalopathy. The study showed a positive correlation of MELD score and child Pugh Score, MELD score and APRI index, APRI Index and child Pugh score with significant p value. The study also showed higher APRI index, child Pugh classification and MELD score values for patients who expired in the hospital. APRI index has a median value of 12.58, MELD score of mean of 36.08±5.946 and child Pugh score of median 15.[20]

A recent cross sectional study on 100 patients of cirrhosis was conducted by Prakash and Shetty at Bangalore medical college, to see the correlation between APRI, CTP and MELD score. The results showed that APRI index had a mean value of 3.4, child Pugh had a mean score of 13.2, and MELD had a mean score of 36.08 with standard deviation of 2.0, 1.5, and 6.0 respectively. Also, the values of all three scores were higher in patients having complications of cirrhosis like hepatic encephalopathy, ascites etc and were directly proportional to their severity. The p value for Pearson correlation coefficient among these scores was statistically significant (p<0.05). This study concluded that the prognostic performance of all 3 scores was comparable and APRI index can be used as a predictor of severity and prognosis in cirrhosis of liver.[21] Angelo Zambam de Mattos did a study in Brazil that enrolled one hundred and sixty four patients with 59.76% males and mean age of the patients was 56.70 years. Esophageal varices (EV) were diagnosed in119 (72.56%) patients by endoscopy. It showed when APRI's cutoff was taken at 1.3, to predict the existence of EV, it exhibited to have a sensitivity of 64.70% (95% CI-95%=0.56-0.73) and specificity of 72.70% (95%CI=0.59-0.86), a positive predictive value of 86.50% (95%CI=0.79-0.94) and a negative predictive value of 43.20% (95%CI= 0.32-0.55). Further in the univariate analysis, APRI (p<0.001), platelet count (p=0.001), spleen diameter (p=0.015), PC/SD (p<0.001), MELD score (p=0.017) and child-Pugh classification (p=0.015) were associated with the prediction of occurrence of EV.[22] Nagraja et al undertook a retrospective study with aim of evaluating APRI and it comparing it with MELD and albumin for predicting in hospital mortality in chronic liver disease. 299 patients were studied with the mean age being 46.47±10.9 years and mortality rate of 17.7%. 53 patients died and 246 were patients who showed improvement. To predict the in hospital mortality, the area under curve (AUC) of the APRI score was 0.631 (confidence interval: 95%: 0.574 -

0.686) with the best cut-off value of -0.743, with sensitivity of 77.9%, a specificity of 46.2%, positive likelihood ratio (PLR) of 1.72 and negative likelihood ratio (NLR) 1.66. The AUC of the MELD score was 0.766 (confidence interval 95%: 0.713-0.812), with a sensitivity of 84.2%, a specificity of 75.6%, PLR of 1.7 and NLR of 1.6. This study emphasized on MELD score being the better prognostic performer compared to APRI and albumin levels but APRI was found to be an independent predictor of mortality. The prognostic performance of all 3 markers was comparable.[23] A study by Mao et al enrolled total of 193 chronic HBV patients retrospectively. This study divided cirrhotic patients into 3 groups based on APRI levels as follows: group A (APRI≤1.0), group B (>1.0, but <2.0), and group C (>2.0). There were significant differences in INR, MELD score, ALT, and total bilirubin among the 3 groups (p<0.001, p<0.001, P¼0.026, and P¼0.002, respectively). APRI was seen to be higher in patients with complications (p<0.01). Increased APRI was seen to be associated with worsened child–Pugh grade (P¼0.001). Univariate logistic regression analysis demonstrated that patients with higher APRI and MELD score and lower albumin concentrations had a significantly higher death hazard while multivariate logistic regression analysis revealed that APRI and MELD scores were 2 independent variables in predicting the mortality rate. AUC was calculated to be 0.844-0.039 for the MELD score and 0.738-0.049 for APRI (p<0.001).[24] In our study also, value of APRI increases as the severity of complications rises, as indicated by rising values of CTP and MELD scores. Many prior studies have taken into account only a single cause but in our study, inclusion of all the important causes of cirrhosis like alcohol, Hepatitis B, Hepatitis C and drugs etc. makes our study unique.

Limitations

The limitation of current study was the use ultrasonography technique instead of liver biopsy, which is the gold standard for the diagnosis and staging of cirrhosis.

CONCLUSION

A simple quantitative bedside index, APRI correlates well with existing indices like CTP and MELD for cirrhosis and can be used to predict the severity of the disease. However, further prospective studies are needed to validate APRI in a larger number of patients in other institutes.

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